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Review

Chemotaxonomy of the Oleaceae: iridoids as taxonomic markers

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Abstract

The distribution and biosynthesis of iridoid glucosides in the Oleaceae is reviewed and five distinct biosynthetic pathways to iridoids have been identified in the family, deoxyloganic acid apparently being a common intermediate. Likewise, the distributions of caffeoyl phenylethanoid glycosides (CPGs), i.e. verbascoside and its analogues, as well as cornoside are listed. Iridoid glucoside data exist for 17 genera of Oleaceae and the occurrence of iridoids from the different biosynthetic pathways correlate extremely well with the phylogenetic classification inferred from recent chloroplast DNA sequence data. Thus the tribe Fontanesieae (*Fontanesia*) contains "normal" secoiridoids, Forsythieae (*Abeliophyllum*, *Forsythia*) contains cornoside and/or iridoids from the forsythide pathway, Myxopyreae (*Myxopyrum*, *Nyctanthes*) have iridoids from the myxopyroside pathway, and finally, the two tribes Jasmineae and Oleeae (the remaining genera) both contain iridoids from the oleoside pathway. Within Jasmineae, one group of *Jasminum* sp. is characterized by the presence of jasminin or similar compounds, while another group of *Jasminum* species and *Menodora* display derivatives of 10-hydroxyoleoside, compounds not present in the other group. CPGs are reported from about half of the species investigated. With regard to taxonomy at the order level, the chemical data might support a position within or close to Lamiales due to the common presence of CPGs, the iridoids being of less significance since they are of a type that are barely found elsewhere. © 2002 Elsevier Science Ltd. All rights reserved.

Keywords: Oleaceae; Taxonomy; Phylogeny; Iridoid glucosides; Biosynthesis; Verbascoside; Cornoside; *Menodora*; *Forestiera*; *Nestegis*

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1. Introduction

The Oleaceae is a family of medium size with 25 genera and about 600 species. With regard to chemical constituents, it has been quite extensively investigated. It is mainly characterized by the presence of iridoid glucosides and phenylethanoid derivatives in the form of esters and glycosides of tyrosol (*p*-hydroxyphenyl-ethanol) and in particular the closely related dopaol (3,4-dihydroxyphenyl-ethanol). Coumarins and lignan glucosides are also common in the family, but they appear to have a more limited distribution (Hegnauer, 1969, 1990). The presence of iridoids is linking Oleaceae both to Lamiales and to Gentianales, and since most of the iridoids are formally of the seco-type, a closer relationship with Gentianales is indicated. This fact was among others adopted by Dahlgren (Dahlgren et al., 1981; Dahlgren, 1989) to place Oleales as a sister group to Gentianales. However, the presence of tyrosol/dopaol-derivatives in Oleaceae, both as iridoid esters and (mainly) as verbascoside and its analogues (caffeoyl phenylethanoid glycosides = CPGs) could conversely indicate a closer relationship with Lamiales since such compounds are widespread in this order and are hardly found anywhere else (Jensen, 1992).

Within Oleaceae several subdivisions have been suggested, but recent results from chloroplast DNA sequencing have provided an alternative basis for a phylogenetic classification (Wallander and Albert, 2000). In view of the diversity and an almost universal occurrence of iridoids in the family, we decided to investigate what correlations between iridoid distribution and classification might be found.

The benefit of iridoid glucosides for the plants is not obvious, although the bitterness of many of the compounds has been considered to be a deterrent for herbivores. Recently, however, it has been demonstrated that oleuropein, which is the main iridoid in *Ligustrum obtusifolium* and in many other species from Oleaceae including *Olea europaea*, is a strong protein denaturant when hydrolyzed by the enzymes in the plant (Konno et al., 1998, 1999). Thus, the glucoside is compartmentalized in the cells of the intact plant, but when the tissue is damaged by insect chewing, the compound is hydrolyzed to the aglucone which react irreversibly with the proteins and renders these more or less indigestible and thus useless, especially with regard to the essential amino acid lysine.

2. Biosynthesis of iridoids

The iridoids are of terpenoid origin and their biosynthesis has been fairly well investigated (Inouye and Uesato, 1986; Jensen, 1991, 1992), thus it is known that two main routes exist. One main route (*route I*; Fig. 1) is leading from iridodial (**1**) via iridotrial (**2**) to deoxyloganic acid (**3**) which is the known precursor of many carbocyclic iridoids having the 8β-stereochemistry including loganin (**6**) and loganic acid (**10**), secologanin and secologanic acid (**11**) as well as the derived secoiridoids and complex indole alkaloids. Compounds from this route are found mainly in Cornales, Gentianales and Oleaceae.

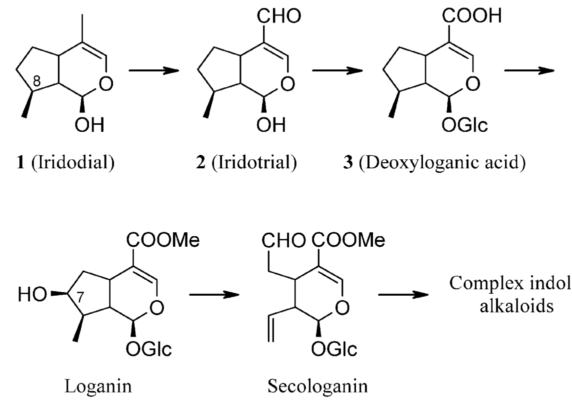
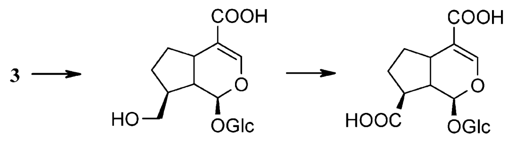


Fig. 1. Biosynthetic pathway (*route I*) to the common precursor deoxyloganic acid (**3**) and to the complex indole alkaloids.



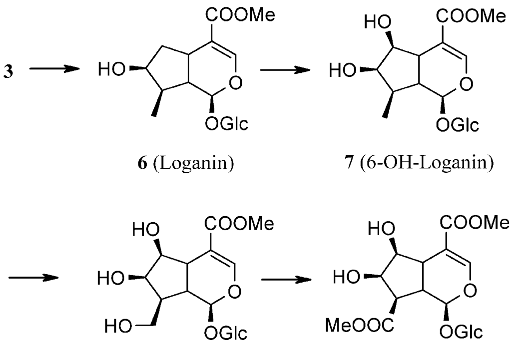
4 (Adoxosidic acid) **5** (Forsythide)

Fig. 2. Biosynthetic pathway (*route Ia*) to *Forsythia* iridoids.

Another main biosynthetic pathway (*route II*) involves 8-*epi*-iridodial, 8-*epi*-iridotrial and 8-*epi*-deoxyloganic acid; these are precursors for the decarboxylated carbocyclic iridoids such as aucubin and catalpol. These compounds are almost exclusively found in Lamiales families and never in Gentianales or Oleaceae (Jensen, 1992). A few unusual secoiridoids are known to be formed by this route (Damtoft et al., 1992a; Otsuka, 1993) but they are different in structure from those derived from *route I*.

The Oleaceae is characterized by the presence of iridoids from *route I* only. However, compounds from at least five distinctive subroutes, all branching out from deoxyloganic acid (**3**), are present in the family. What appears to be the most simple route (*Ia*, Fig. 2) in Oleaceae is found in *Forsythia* only. Feeding experiments (Damtoft et al. 1994a) have shown that in *F. viridissima* and *F. europaea*, **3** is oxidized at C-10 to adoxosidic acid (**4**) followed by further oxidation of C-10 to the carboxylic acid stage present in forsythide (**5**).

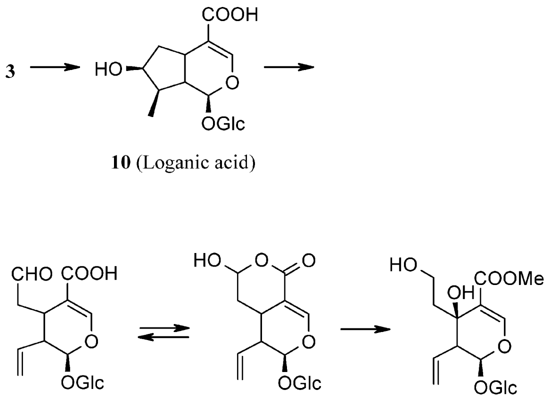
The second route (*Ib*, Fig. 3) leading to nyctanthoside (**8**) and myxopyroside (**9**) is hypothetical, but it is based on the structural similarity of the compounds found in the tribe and also on the similarity to *route Ia*. Esters of the glucosides present, namely of loganin (**6**), 6-hydroxy-loganin (**7**) and nyctanthoside (**8**) have all been isolated from *Nyctanthes arbor-tristis*, while **9** and its esters are found in *Myxopyrum smilacifolium*, both assigned to tribe Myxopyreae. It seems natural to assume that we have a pathway like that shown in Fig. 3 with an initial oxidation at C-7 followed by consecutive oxidative introductions of hydroxyl groups at C-6 and C-10 in *Nycthantes*, while in *Myxopyrum* a full oxidation of C-10 to the carboxyl stage takes place, and finally esterification to the methyl ester. This is another difference from *route Ia* where the iridoid glucosides in *Forsythia* mainly are found as the acids.



6 (Loganin) **7** (6-OH-Loganin)

8 (Nyctanthoside) **9** (Myxopyroside)

Fig. 3. Probable biosynthetic pathway (*route Ib*) to iridoids found in Myxopyreae.



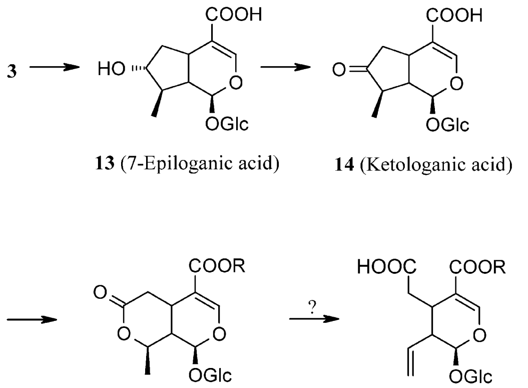
10 (Loganic acid)

11 (Secologanic acid) **12** (5-Hydroxysecologanol)

Fig. 4. Pathway (*route Ic*) leading to *Fontanesia* secoiridoids.

Most of the iridoids reported from Oleaceae formally belong to the secoiridoids, but it has been shown that their biosynthesis is different from that of the 'normal' secoiridoids from the Gentianales which are usually derived from secologanin or secologanic acid (**11**) (*route I*, Fig. 1). Only the genus *Fontanesia* exhibits compounds derived from the latter compound (Damtoft et al., 1994b, 1995a), but even so, the end-products—esters of 5-hydroxysecologanol (**12**)—are not found elsewhere and therefore this route deserves its own designation: *route Ic* (Fig. 4).

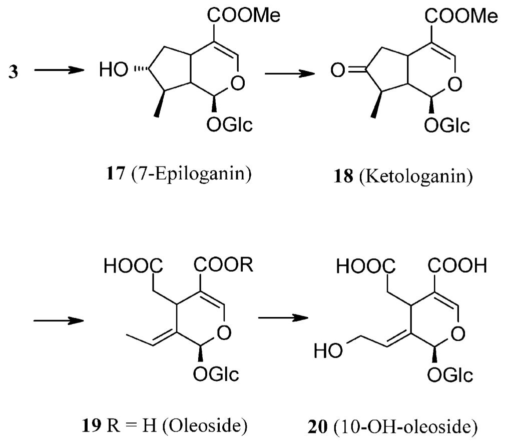
While loganin/loganic acid (**6**/**10**) are the common intermediates in the biosynthesis of normal secoiridoids, this is not the case in most species of Oleaceae. We have found that 7-epiloganin/7-epiloganic acid (**17**/**13**) are the intermediates in the biosynthesis of most of the oleoside-type secoiridoids present in *Syringa* and *Fraxinus* (Damtoft et al., 1993a, 1995b,c). Two subroutes can be distinguished, one pathway (*route Id*, Fig. 5)



13 (7-Epiloganic acid) **14** (Ketologanic acid)

15 R = H (Epikingisidic acid)
15a R = Me (Epikingiside)
16 R = H (Secologanoside)
16a R = Me (Secoxyloganin)

Fig. 5. Pathway (*route Id*) leading to epikingisidic acid and secologanoside and their derivatives.



17 (7-Epiloganin) **18** (Ketologanin)

19 R = H (Oleoside) **20** (10-OH-oleoside)
19a R = Me (Oleoside 11-methylester)

Fig. 6. Biosynthetic pathway (*route Ie*) leading to oleoside derivatives (**19** and **20**).

from 7-epiloganic acid (**13**), which in *S. josikaea* has been established to be the precursor for epikingisidic acid (**15**) and probably also secologanoside (**16**), and thus also their derivatives.

The second pathway (*route Ie*, Fig. 6) from 7-epiloganin (**17**) to the oleoside ester (**19a**) and 10-hydroxyoleoside (**20**) derivatives has been demonstrated in *Fraxinus excelsior*, *Syringa josikaea* and *S. vulgaris*. The initial steps are similar to those of *route Id*, but in this case methyl esters seem to be utilized instead of the acids. It is difficult, however, to distinguish between these two routes since **15** and **16** in some species also occur as their methyl esters.

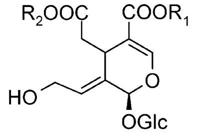
In an early (Inouye et al., 1974) and a more recent work (Kuwajima et al., 1999) Inouye and co-workers have investigated the biosynthesis of oleside-type glucosides in *Jasminum*, *Olea*, *Osmanthus* and *Ligustrum*. The experiments were interpreted as pointing to secologanin as a possible intermediate in the formation of the oleoside-type glucosides despite the fact that incorporations lower than 0.4% were obtained in all cases. In our works cited above, secologanin was found to give similarly low incorporations while the intermediates shown in Figs. 5 and 6 gave much better results (incorporations above 5%).

3. Iridoids and CPGs in Oleaceae

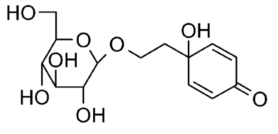
We have reviewed the available literature dealing with iridoids and CPGs in the family. About 240 different iridoid glucosides have so far been reported from the family. However, due to the diversity of oleoside derivatives reported from many species, only a representative number of these compounds have been selected in order to show the biosynthetic ability for each species and genus. Each type of compounds found in the species have been listed in Table 1, using the classification of Wallander and Albert (2000).

3.1. *Abeliophyllum*

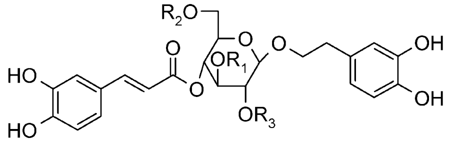
The monotypic *Abeliophyllum distichum* Nakai was found (Kuwajima et al., 1993) not to contain any iridoid glucosides but instead the taxonomically interesting cornoside (**21**) which was previously known from among others, *Forsythia* (see below). In addition verbascoside (**22**) and two hydroxycinnamoyl esters of **21** were found. Cell cultures of this plant were later shown to produce **21** and **22** (Yamamoto et al., 1998).



20a R_1 = H, R_2 = Me
(10-OH-oleoside 7-methylester)
20b R_1 = R_2 = Me
(10-OH-oleoside dimethylester)



21 (Cornoside)



22 R_1 = Rha, R_2 = H, R_3 = H (Verbascoside)
22a R_1 = H, R_2 = Rha, R_3 = H (Forsythiaside)
22b R_1 = H, R_2 = Xyl, R_3 = H Calceolarioside C)
22c R_1 = Rha, R_2 = H, R_3 = Oleosyl (Oleoacteoside)

Formulae 1.

3.2. *Forsythia*

From this genus with 11 species only the carbocyclic type of iridoids are known. Initially, forsythide (**5**) and its methyl ester were isolated from the leaves of *F. viridissima* Lindl. (Inouye and Nishioka, 1973). In the same work, forsythide was also detected by chromatography in *F. japonica* Makino and *F. europaea* Degen & Baldacci, but seemed to lack in two other species, *F. suspensa* (Thunb.) Vahl and *F. koreana* (Rehd.) Nakai. Adoxosidic acid (**4**) and the 11-glucosyl ester of **5** were later found in both *F. viridissima* and *F. europaea* (Damtoft et al., 1994a), and a small amount of cornoside (**21**) was found to be present in the latter.

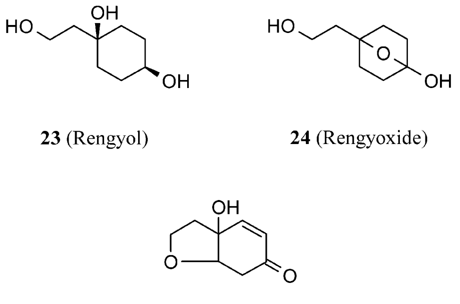
From fruits of *F. suspensa* were isolated rengyol (**23**), rengyoxide (**24**), halleridone (= rengyolone; **25**) together with **21** (Endo and Hikino, 1984). More recently, also a trace of adoxosidic acid (**4**) was isolated from this source (Ming et al., 1998), and it has been shown that cell cultures of *F. suspensa*, *F. viridissima* and *F. koreana* all can produce **21** as well as verbascoside (**22**) and

Table 1
Iridoid derivatives, cornoside, and CPGs reported from Oleaceae

Genus species	Carbocyclic iridoids	Seco-iridoids	Oleoside	10-Hydroxy oleoside	Others[a]
Abeliophyllum distichum Nakai					**21**, **22**
Forsythia europaea Degen & Baldacci	**4**, **5**				**21**, **22a**
japonica Makino	**5**				**22**
koreana (Rehd.) Nakai					**21**, **22**
suspensa (Thunb.) Vahl	**4**				**21**, **22a**
viridissima Lindl.	**4**, **5**				**22**
Nyctanthes arbor-tristis L.	**6**, **7**, **8**				**22b**
Myxopyrum smilacifolium Blume	**9**				
Fontanesia fortunei Carr.	**10**	**11**, **12**, **16**			**22**
phillyreoides Labill.	**10**	**11**, **12**, **16**			**22**
Menodora robusta (Benth.) A. Gray	**14**	**15**, **16**		**20**	
Jasminum amplexicaule Buch.-Ham.				**20**	**22**
giraldii Diels				**20**	
hemsleyi Yamamoto	**6**, **18**			**20**	
humile L.				**20**	
lanceolarium Roxb.				**20**	
multiflorum (Burm. f.) Andr.			**19**	**20**	
odoratissimum L.	**18**	**15**		**20**	
polyanthum Franch.		**15**	**19**	**20**	**22**, **22c**
azoricum L.			**19**		**‘30’**
mesnyi Hance			**19**		**‘30’**, **22**
nudiflorum Lindl.			**19**		**‘30’**, **22**
sambac (L.) Ait.			**19**		**‘30’**
urophyllum Hemsl.			**19**	**20**	**‘30’**
nitidum Skan		**15**			
officinale L.			**19**		
Syringa josikaea Jacq. f.		**15**, **16**	**19**		**22c**
pubescens Turcz.			**19**		
reticulata (Blume) Hara	**14**		**19**		**22**
vulgaris L.	**14**	**15**, **16**	**19**		**22**
Ligustrum japonicum Thunb.		**15**	**19**	**20**	
lucidum Ait.	(**18**)	**15**	**19**	**20**	
obtusifolium Sieb. et Zucc.		**15**	**19**	**20**	**22**
ovalifolium Hassk.	**13**	**15**, **16**		**20**	
pedunculare Rehd.					
robustum (Roxb.) Bl.					
vulgare L.			**19**	?	
Fraxinus americana L.			**19**		**22**
angustifolia Vahl			**19**		
chinensis Roxb.		**16**	**19**		
excelsior L.			**19**	**20**	**22**
floribunda Wall.			**19**		
griffithii C. B. Clarke		**15**	**19**		**22**
japonica Blume			**19**		
malacophylla Hemsl.			**19**		**22**
ornus L.			**19**	**20**	**22**
oxycarpa Willd.			**19**	**20**	**22**
pallisiae Wilmott			**19**	**20?**	
uhdei (Wenzig) Lingelsh.			**19**	**20**	**22**
Chionanthus retusus Lindl. & Paxton			**19**		
Forestiera acuminata (Michx.) Poir.			**19**		
Olea capensis L.			**19**		
europaea L.		**16**	**19**		**21**
verrucosa L.			**19**		
tsoongii (Merr.) P.S. Green			**19**	**20**	
Nestegis sandwicensis (Gray) O. & I. Deg. & L. Johnson			**19**		
Phillyrea latifolia L.	**13**	**15**, **16**	**19**		
Picconia excelsa (Aiton) DC.	**3**, **6**, **10**, **14**, **18**	**15**, **16**	**19**		**22c**
Osmanthus austrocaledonicus (Vieill.) Knobl.	**6**, **10**, **18**	**16**	**19**		**22**
x fortunei Carr.			**19**	**20**	
fragrans (Thunb.) Lour.		**15**, **16**	**19**	**20**	**22**
heterophyllus (G. Don) P.S. Green			**19**	**20**	**22**

[a] Cornoside (**21**), CPGs (**22**–**22c**) and oleoside derivatives of iridane polyol (‘**30**’).

similar compounds (Yamamoto et al., 1998). Leaves of seven species of *Forsythia* investigated have been shown to contain CPGs (Kitagawa et al., 1988). Some contain verbascoside (**22**), some forsythiaside (**22a**) and one species, *F. koreana* contains both.



23 (Rengyol) **24** (Rengyoxide)

25 (Halleridone)

Formulae 2.

3.3. *Nyctanthes*

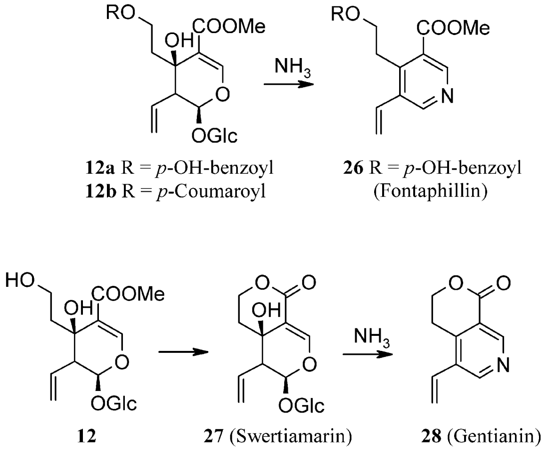
One of the two species has been investigated. Leaves or seeds of *N. arbor-tristis* L. are used in Ayurvedic medicine and much work has been done on this species. Rimpler and Junghans (1975) were the first to report the presence of an iridoid from the plant, namely nyctanthoside (**8**), obtained after hydrolysis of a crude extract. Later, 6β-hydroxyloganin (**7**) was isolated together with a number of benzoyl and substituted cinnamoyl esters of **7** and **8** (Purushothaman et al., 1985; Rathore et al., 1989; 1990; Venkatanarasimhan et al., 1991; Stuppner et al., 1993; Singh et al., 1995). One report also describes a benzoyl ester of loganin (**6**), namely arborside B (Shrivastava et al., 1990). A single CPG has been isolated from *N. arbor-tristis* (Mathuram et al., 1997) and named nyctoside. We have, however, by an inspection of the data given for nyctoside, discovered that the compound is identical to the known calceolarioside C (**22b**) (Nicoletti et al., 1988) and the name nyctoside is thus redundant.

3.4. *Myxopyrum*

A small genus with four species. During this project, we have investigated a single leaf of *M. smilacifolium* Blume and were able to isolate myxopyroside (**9**) and two esters of **9**, each with an acetyl and a methoxycinnamoyl group (Franzyk et al., 2001). No CPGs could be detected in this small amount of plant material.

3.5. *Fontanesia*

The presence of iridoids in this genus with two species was first perceived when Budzikiewicz et al. (1967) after treatment of a crude extract of *F. phillyreoides* Labill. with ammonia were able to isolate three monoterpene alkaloids, fontaphillin (**26**), gentianin (**28**) and 4-aminonicotinic acid. The authors realized that the two former compounds were artifacts formed by the ammonia treatment of iridoids present in the plant. We could confirm this when we reinvestigated the plant (Damtoft et al., 1994b) since we found the three compounds (**10**–**12**) together with secologanoside (**16**), fontanesioside (**12a**) and the artifact swertiamarin (**27**). It is well known that **27** by treatment with acid followed by ammonia gives rise to **28** (Budzikiewicz et al., 1967; Frederiksen and Stermitz, 1996), and in our hands **12** was very easily converted to **27** simply by standing. Likewise, **12a** would probably be converted to fontaphillin (**26**). *F. fortunei* Carr. was found to contain mainly the same compounds and also the ester **12b** (Damtoft et al., 1995a). Verbascoside (**22**) was present in both species.



12a R = *p*-OH-benzoyl
12b R = *p*-Coumaroyl

26 R = *p*-OH-benzoyl
(Fontaphillin)

12 **27** (Swertiamarin) **28** (Gentianin)

Formulae 3.

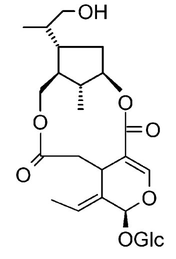
3.6. *Menodora*

Since this genus with 24 species had not previously been investigated for iridoids, we undertook an examination of *M. robusta* (Benth.) A. Gray. The main compound present was jasminoside (**37**), while minor constituents were epikingisidic acid (**15**), secoxyloganin (**16a**), ketologanin (**18**), and mono- and dimethyl esters of 10-hydroxyoleoside (**20**). No CPGs could be detected in this species.

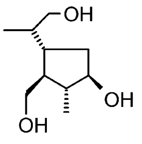
3.7. *Jasminum*

The largest genus with more than 200 species. Since many species of *Jasminum* are used medicinally, particularly in Asian medicine, a fair number of these have been chemically investigated. The first report on iridoids in the genus was a work on *J. primulinum* Hemsl. (= *J. mesnyi* Hance) published by Kamikawa et al. (1970) which described the structure of jasminin (**29**), an ester between oleoside (**19**) and the substituted iridane triol (**30**). A number of additional compounds of similar structure were later isolated from this species by Inoue et al. (1985, 1991), Tanahashi et al. (1989) and by He and Yang (1989).

Also *J. sambac* (L.) Ait. was shown to contain this type of iridoid glucosides as first demonstrated by Ross et al. (1982). In more recent reports on this species by Tanahashi et al. (1987, 1988) and Zhang et al. (1995) a number of very complicated structures were found; these had one iridane and one to three oleoside moieties such as sambacoside A (**31**). Also present was sambacolignoside (**32**), consisting of an oleoside moiety esterified to a lignan glucoside. Chemically, *J. azoricum* L. was similar to the above, containing jasminin (**29**) and some analogues (Ross and Abdel-Hafiz, 1984; Ross et al., 1986) together with **31** and other oligomeric glucosides (Somanadhan et al., 1998).



29 (Jasminin)



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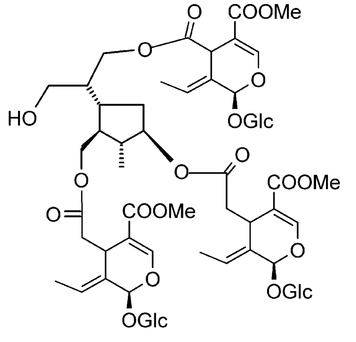
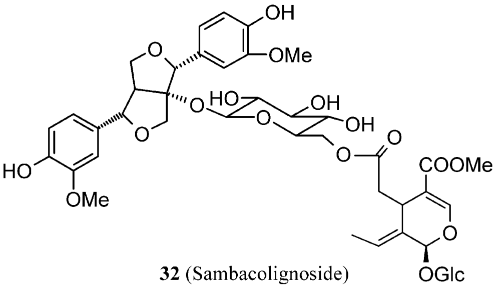


31 (Sambacoside A)



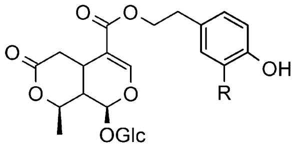
32 (Sambacolignoside)

Formulae 4.

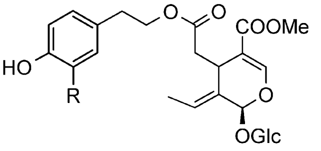
Shen and Hsieh (1997a,b) have reported a number of jasminin-like compounds from *J. urophyllum* Hemsl. This species also contains a number of oligomeric glucosides like **31** (the stereochemistry in the iridane moiety may vary) together with an oleosyl lignan named jasurolignoside (Shen et al., 1998). This species also have two derivatives of 10-hydroxyoleoside (**20**), although as minor constituents.

Like the former species, *J. nudiflorum* Lindl. contains a number of oligomeric compounds, in this case oleosyl esters of two iridane analogues different from those found in the above species (Tanahashi et al., 1999a, 2000).

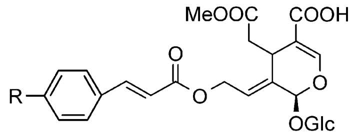
Thus, oleosyl iridane esters were present in all the five species reviewed above. Notably, the remaining species chemically investigated seem not to contain such compounds. Among these, *J. nitidum* Skan appear to be unique in apparently not having oleoside derivatives present at all. In an investigation of this plant Shen et al. (2000) only found two phenylethyl esters of epikingisidic acid (**15**), namely fliederoside and lilacoside (= syringalactone A and B; **33** and **34**, respectively). Conversely, *J. grandiflorum* L. (= *J. officinale* L.) contains mainly esters of oleoside, namely ligstroside (**35**) and oleuropein (**36**), compounds which are present in most genera of the family (Somanadhan et al., 1998; Tanahashi et al., 1999b).



33 R = H (Lilacoside)
34 R = OH (Fliederoside)



35 R = H (Ligstroside)
36 R = OH (Oleuropein)



37 R = H (Jasminoside)
38 R = OH (Jaslanceoside B)

Formulae 5.

In a work on the distribution of verbascoside (**22**) and similar CPGs, Andary et al. (1992) reported that these were present in the yellow-flowered *J. nudiflorum* and *J. mesnyi*, but absent from the white-flowered *J. sambac*, *J. azoricum* and *J. officinale*.

The remaining eight species investigated are all characteristic by containing compounds derived from 10-hydroxyoleoside (**20**). Thus, jasminoside (**37**), a cinnamic ester of **20**, was first encountered in *J. humile* L. by Inoue et al. (1982a). Jasminoside and the coumaroyl analogue jaslanceoside B (**38**) were also found in *J. giraldii* Diels by Shen et al. (2000) and in *J. lanceolarium* Roxb. (Shen and Lin, 1996; Shen et al., 1997). Such compounds were also present in *J. odoratissimum* L. (Trujillo et al., 1996) together with some esters of epikingisidic acid (**15**) (López et al., 1997) and the aglucone of ketologanin

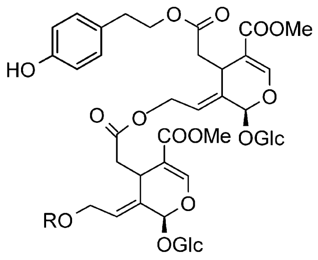
(**18**) (Pérez et al., 1999). Likewise, derivatives of **20** were encountered in *J. amplexicaule* Buch.-Ham. (Shen et al., 1999), which also contained some di- and trimeric iridoids like jasamplexoside A (**39**) and B (**40**), respectively, as well as verbascoside (**22**) (Tanahashi et al., 1992a). From *J. hemsleyi* Yamamoto jasminoside (**37**), ketologanin (**18**) and loganin (**6**), together with a number of terpenoid esters of the latter were isolated. Jashemsloside A (**41**) and C (**42**) are examples of these (Tanahashi et al., 1995, 1996a).

J. polyanthum Franch. has been very thoroughly investigated. From a locally collected unspecified plant material, Shen's Taiwanese group isolated epikingiside (**15a**) and methyl esters of **19** and **20** as well as ligstroside (**35**) and oleuropein (**36**). Also present were verbascoside (**22**) and oleoacteoside (**22c**), an ester of **22** with oleoside 11-methylester (**19a**) (Shen et al., 1996a,b). On the other hand, Tanahashi's group from Japan examined the dried flowers—known as "Ye su xin" in Chinese medicine—which were obtained from a commercial source. The flowers gave a wealth of different compounds which were reported in five papers (Tanahashi et al., 1996b, 1997a,b; Takenaka et al., 1998a,b). Besides the common ligstroside and oleuropein, this plant contained many di- and trimeric secoiridoids similar to the jasamplexosides (**39** and **40**), and in addition to these several oleoside esters of linear terpenoids: jaspogeranoside A (**43**) is such a compound. It is notable that the two plant samples are so different in content, and it seems questionable that they are indeed from the same species.

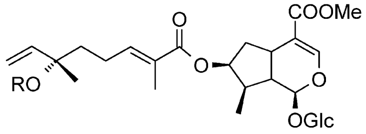
The last species investigated, *J. multiflorum* (Burm. f.) Andr., contains mainly derivatives of 10-hydroxyoleoside (**20**) (Chen et al., 1991; Shen et al., 1990) but in addition a unique series of seven-membered lactones exemplified by jasmolactone C and D (**44** and **45**) (Shen and Chen, 1989, 1994).

3.8. *Syringa*

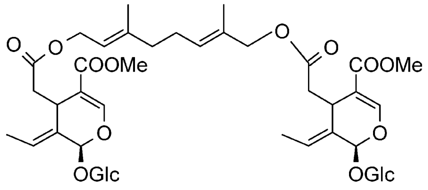
Only four of the about 20 species from this genus with many ornamentals have been investigated. Early work was concentrated on *S. vulgaris* L. from which Birkofer et al. (1968) reported a compound which they named acteosid. However, this compound had previously been isolated from *Verbascum sinuatum* and named verbascoside (**22**) by Scarpati and Delle Monache (1963). Asaka et al. (1970) isolated syringopicroside (**46**) while Popov (1975) and Popov et al. (1975) reported the presence of two compounds named syringoxide (**47**) and syringenone, but the evidence given for the structures is not convincing, and none of these two compounds has been encountered in later works. Sticher et al. (1982) presented the structures of fliederoside (**33**) and lilacoside (**34**) from this species, but gave no experimental data. Later, Kikuchi et al. (1987, 1988) reported the presence of oleuropein (**36**) together with a number of other esters of oleoside as well as epikingiside (**15a**) and the previously reported esters **33** and **34** (which here were named syringalactone A and B). Recently, also the minor constituents epikingisidic acid (**15**) and secologanoside (**16**) were reported (Damtoft et al., 1995c).



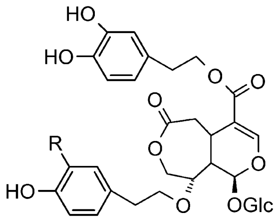
39 R = H (Jasamplexoside A)
40 R = 7-OH-oleosyl (Jasamplexoside B)



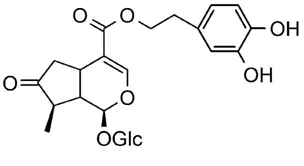
41 R = H (Jashemsloside A)
42 R = Glc (Jashemsloside C)



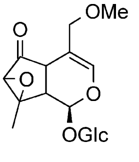
43 (Jaspogeranoside A)



44 R = H (Jasmolactone C)
45 R = OH (Jasmolactone D)



46 (Syringopicroside)



47 (Syringoxide)

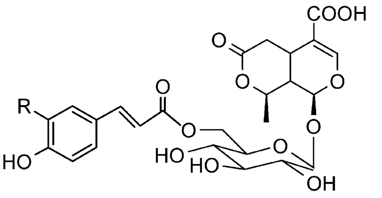
Formulae 6.

From *S. reticulata* (Blume) Hara several phenylethyl esters of ketologanic acid (**14**) were isolated together with three esters of oleoside (**19a**, **35**, **36**) (Kikuchi and Yamauchi, 1987). Later, Kikuchi and Yamauchi's group (Kikuchi et al., 1989a) also isolated oleoacteoside (**22c**) and oleoechinacoside, both being CPGs esterified with oleoside 11-methyl ester (**19a**). The bark of *S. amurensis* Rupr. [=*S. reticulata* (Blume) Hara *subsp. amurensis* (Rupr.) P. S. Green & M. C. Chang] also gave three esters of oleoside (**35**, **36**, **50**) as well as verbascoside (**22**) (Kurkin et al., 1992). Recently, *S. josikaea* Jacq. f. (Damtoft et al., 1993a,1995c) was found to contain oleoside esters similar to those reported from the former species as well as epikingiside (**15a**) and secologanoside (**16**). Finally, stem bark of *S. velutina* Kom. (=*S. pubescens* Turcz.) was found to contain **35** and **36** (Park et al., 1999).

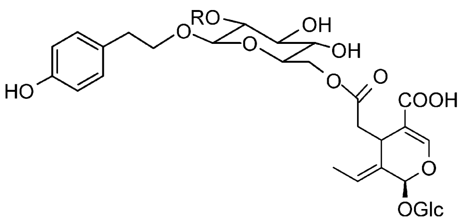
3.9. *Ligustrum*

This is a genus with about 45 species, and seven of these have been investigated chemically. The compound ligstroside (**35**) was first reported from *L. obtusifolium* Sieb. et Zucc. (Asaka et al., 1972). Later, 10-hydroxy-ligstroside and verbascoside (**22**) (Kikuchi and Yamauchi, 1984) as well as ibotalactone A, B and oleonüzhenide (**48**, **49** and **51**, respectively) were found in this species (Kikuchi et al., 1989b).

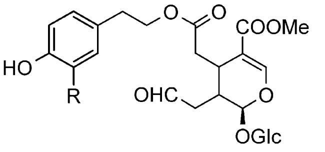
The iridoids nüzhenide (**50**) and oleuropein (**36**) were the first compounds reported from the fruits of *L. japonicum* Thunb. and *L. lucidum* Ait. (Inouye and Nishioka, 1972), the two species apparently being very similar in iridoid content. Later, the leaves of both plants gave the 10-hydroxy-analogue of oleuropein together with the aldehydes ligustaloside A and B (**52** and **53**) (Inoue et al., 1982b). Kikuchi and Yamauchi (1985a) also found the corresponding pair of compounds ligstrosidic acid and oleuropeinic acid (**54** and **55**). The esterglucoside **51** as well as epikingiside (**15a**) and some oleoside esters were reported from *L. japonicum* (Fukuyama et al., 1987; Kuwajima et al., 1989). Recently, in an investigation of the leaves of *L. lucidum* (Kikuchi and Kakuda, 1999), **52** and **53** were found to be the main constituents together with small amounts of epikingiside (**15a**), its isomer kingiside, and two new compounds, namely the abnormal *iso*-epikingiside (**56**) and 8-demethyl-ketologanin. The fruits were also reinvestigated by He et al. (2001a,b) and from this source ligstroside (**35**) was the main glucoside, accompanied by some minor constituents. Among these were lucidumoside A and B, analogues of **35** and **36**, respectively, with a saturated 8,9-bond.



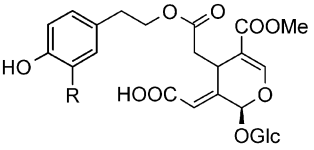
48 R = H (Ibotalactone A)
49 R = OH (Ibotalactone B)



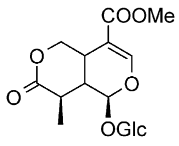
50 R = H (Nüzhenide)
51 R =7- oleosyl (Oleonüzhenide)



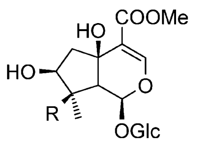
52 R = OH (Ligustaloside A)
53 R = H (Ligustaloside B)



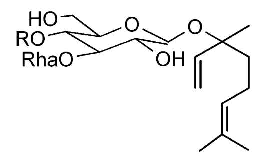
54 R = H (Ligstrosidic acid)
55 R = OH (Oleuropeinic acid)



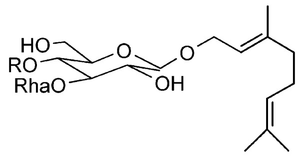
56 *iso*-Epikingiside



57 R = H (Auroside)
58 R = OH (Lamiide)



59 R = H (Lipedoside B-1)
60 R = *p*-coumaroyl (Lipedoside B-4)



61 R = H (Ligurobustoside A)
62 R = *p*-coumaroyl (Kudingoside A)

Formulae 7.

From the foliage of *L. ovalifolium* Hassk. two iridoid glucosides auroside (**57**) and lamiide (**58**) were reported by Salama et al. (1990). As also noted by the authors, this finding was somewhat surprising since this type of compounds was unexpected in Oleaceae (Jensen, 1991). Consequently, we reinvestigated this species (Damtoft et al., 1993a). However, we could only find compounds earlier reported from the family, ligustaloside B (**53**) being the main constituent, accompanied by minor amounts of **13**, **15** and **16**. In a chromatographic investigation of *L. vulgare* L., ligustaloside B (**53**) was again found to be the main secoiridoid glucoside together with **35**, **36** and **52** in smaller amounts (Romani et al., 2000).

Two species, apparently without iridoids present, are known, namely *L. pedunculare* Rehd. and *L. robustum* (Roxb.) Bl. Other terpenoid glycosides are found in these plants, which in China are used as a tea (Ku-Ding-Cha). In the former several rhamnosylglucosides with or without a *p*-coumaroyl moiety attached were found (He et al., 1994b). The examples given here with linalool as the aglucone are lipedoside B-1 and B-4 (**59** and **60**). Later, several geraniol glycosides like kudingoside A (**62**) and also CPG-like compounds like osmanthuside B and D, which are similar in structure to verbascoside (**22**), were isolated from this source (Fukuda et al., 1996). A series of monoterpenoid glycosides (ligurobustosides A–C and E–K), mainly rhamnoglucosides of geraniol, were isolated from *L. robustum* (Tian et al., 1998). Examples are **61** and **62**, the latter already known from *L. pedunculare*.

3.10. *Fraxinus*

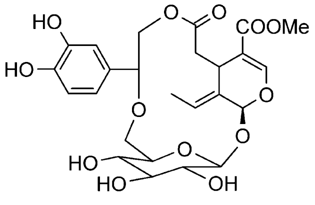
From this genus 12 of the about 40 species have been investigated. Early work on leaves of *F. japonica* Blume ex K. Koch proved that oleuropein (**36**) was present in this species (Inouye et al., 1975a). Likewise, the bark of *F. excelsior* L. was shown to contain 10-hydroxyligstroside (Jensen and Nielsen, 1976), while more extensive work on the foliage (Damtoft et al., 1992b) gave, among others, oleoside 11-methylester (**19a**), ligstroside (**35**) and verbascoside (**22**). From embryos of *F. americana* L. nüzhenide (**50**) and "Gl-3," a positional isomer of oleonüzhenide (**51**), as well as "Gl-5," a glucoside of **50**, were isolated (LaLonde et al., 1976). In a recent work on the foliage by Takenaka et al. (2000), a large number of compounds including the methyl esters of **19** as well as **35** and **22** were isolated. Also the unique compounds fraxamoside (**63**) and frameroside (**64**) were found in this species. The bark of *F. formosana* Hayata (= *F. griffithii* Clarke) gave ligstroside (**35**) (Sutarjadi et al., 1978), while leaves of this species also provided its positional isomer isoligustroside, as well as fraxiformoside (**65**) and verbascoside (**22**) (Tanahashi et al., 1992b). Continued work by Tanahashi et al. (1993a) furnished more compounds of the same type, one of which was framoside (**66**), an isomer of **65**. Leaves of *F. malacophylla* Hemsl. gave among others **65** and fraximalacoside (**68**) together with verbascoside (**22**) (He et al., 1994a). From the leaves of *F. chinensis* Roxb. were obtained oleuropein (**36**), neooleuropein (**67**) and the unique frachinoside (**69**), an oleosyl ester of the coumarin cichoriin (Kuwajima et al., 1992). Foliage of *F. angustifolia* Vahl gave the compound ligstral (**70**), probably a rearrangement product of ligstroside (**35**), a major component in the plant (Limiroli et al., 1995). Also found were angustifoliosides A–C, glucosyl derivatives of **35**, **36** and **67** as well as a number of more common iridoids (Calis et al., 1993, 1996). The taxon *F. oxycarpa* Willd. is usually considered a subspecies of *F. angustifolia*, but the chemistry is apparently different. Thus, the former taxon is reported to contain verbascoside together with a number of derivatives of **20** (Hosny, 1998), a type of compounds not reported from *F. angustifolia*.

The remaining three species investigated are all characterized by the presence of insularoside (**72**), probably formed by an oxidative cyclization of **66**. Insularoside was first isolated from *F. insularis* Hemsl. (= *F. floribunda* Wall.) by Tanahashi et al. (1993b), where it was the main iridoid constituent, together with oleayunnanoside (**73**) (Tanahashi et al., 1993c), which had earlier been found in *Olea tsoongii*, but then had been assigned an incorrect structure (see below). Oleuropein (**36**) and desrhamnosylacteoside, an analogue of **22**, were also isolated. In a later investigation (Tanahashi et al., 1998), two more glucosyl derivatives of insularoside (**72**) were discovered together with desrhamnosyloleoacteoside, an analogue of **22c**. The Central American *F. uhdei* (Wenzig) Lingelsh. was originally considered a subspecies of *F. americana* L. but the chemistry is apparently quite different. Thus, insularoside (**72**), oleayunnanoside (**73**), 10-hydroxyligstroside and verbascoside (**22**) were found in this taxon (Shen et al., 1993). Later, uhdoside B (the 10-hydroxy-derivative of **72**), ligstroside (**35**) and 10-hydroxyoleuropein were found (Shen and Chen, 1993, 1995). Insularoside has also been isolated from the bark of *F. ornus* L. (Iossifova et al., 1993), together with $2''$-hydroxyornoside, a hydroxy-derivative of **72** different from uhdoside B. Finally, some additional compounds similar to **66** and **67** together with verbascoside (**22**) and some homologues were found (Iossifova et al., 1995, 1998, 1999). A review on the constituents of *F. ornus* has also been published (Kostova, 2001).

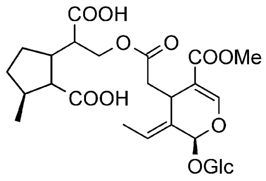
In a comparative work on *F. ornus*, *F .excelsior*, *F. oxycarpa* and *F. pallisiae*, the last three taxa were almost identical in iridoid and coumarin content, whereas *F. ornus* was the only one to contain insularoside (**72**) (Iossifova et al., 1997).

3.11. *Chionanthus*

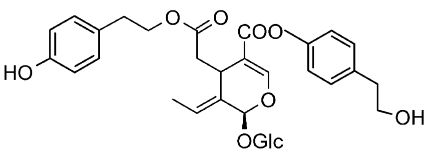
This is a large, mainly tropical genus with 80–100 species, but only a single report has dealt with *C. retusus* Lindl. and Paxton from SE Asia and the sole iridoid



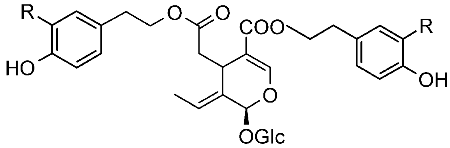
63 (Fraxamoside)



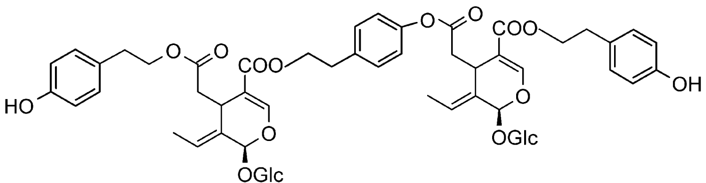
64 (Frameroside)



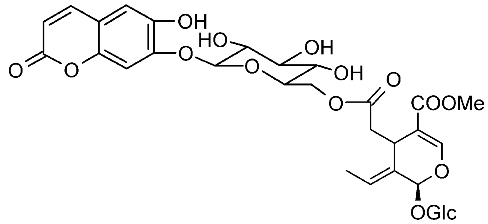
65 (Fraxiformoside)



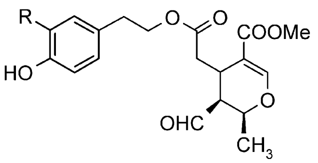
66 R = H (Framoside)
67 R = OH (Neooleuropein)



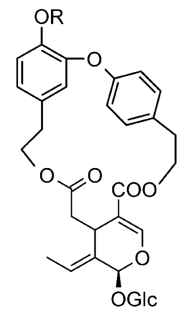
68 (Fraximalacoside)



69 (Frachinoside)



70 R = H (Ligstral)
71 R = OH



72 R = H (Insularoside)
73 R = Glc (Oleayunnanoside)

Formulae 8.

glucoside found was ligstroside (**35**) (Iwagawa et al., 1985).

3.12. *Forestiera*

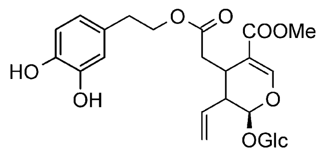
No relevant chemical data have been published on this New World genus with 10–15 species. An investigation of small sample of freshly dried leaves of *Forestiera acuminata* (Michx.) Poir. was therefore undertaken (see Experimental). Only oleuropein (**36**) could be isolated.

3.13. *Olea*

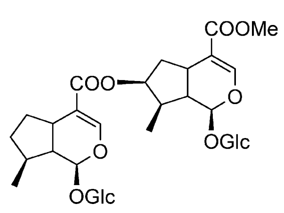
The genus comprises about 40 Old World species. The compound oleuropein (**36**) was first isolated from leaves of olive (*O. europaea* L.) by Scarpati's group in Rome (Panizzi et al., 1960). In later work (Gariboldi et al., 1986), also the dimethyl ester of oleoside (**19**), ligstroside (**35**), as well as the rearranged aglucone **71**, an analogue of ligstral were found—these are minor constituents of the plant and **71** is an artifact formed during isolation work (Limiroli et al., 1995). Also the secoxyloganin analogue of oleuropein (**36**) which was named oleuroside (**74**) has been reported from this species (Kuwajima et al., 1988). From olive fruits was again isolated a large amount of **36** accompanied by **35** and surprisingly, also a small amount of cornoside (**21**) was present (Bianco et al., 1993). Oleuropein (**35**) has also been isolated from bark of *O. europaea* L. subsp. *africana* (Mill.) Green and of *O. capensis* L. (Tsukamoto et al., 1985) as well as from leaves of *O. verrucosa* L. (Movsumov, 1994). Finally, from *O. yuennanensis* Hand.-Mazz. [= *O. tsoongii* (Merr.) P.S. Green] the presence of 10-hydroxyligstroside and 10-hydroxyoleuropein together with oleayunnanoside (**73**) (He et al., 1990) has been reported.

3.14. *Nestegis*

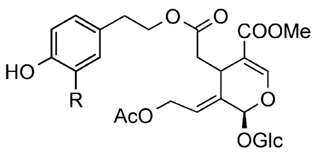
This is a small Pacific genus with five species and none of these have apparently been investigated for iridoids. Leaves from a herbarium sample of *Nestegis sandwicensis* (Gray) O. & I. Deg. & L. Johnson, gave oleuropein (**36**) and ligstroside (**35**) as the main components (see Experimental).



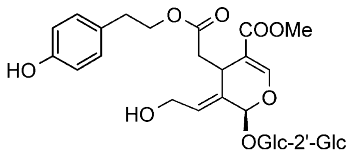
74 (Oleuroside)



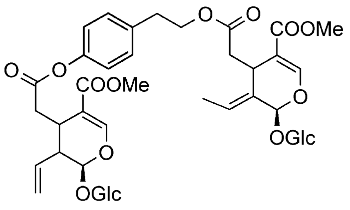
75 (Picconioside I)



76 R = H (10-Acetoxyligstroside)
77 R = OH (10-Acetoxyoleuropein)



78 (Hiiragilide)



79 (Austromoside)

Formulae 9.

3.15. *Phillyrea*

One of the two known species has been investigated and oleuropein (**36**) was found to be the main constituent with minor amounts of ligstroside (**35**) in *P. latifolia* L. (Popov et al., 1975; Damtoft et al., 1993a; Díaz et al., 2000). Other minor constituents were 7-epiloganic acid (**13**), epikingisidic acid (**15**), secologanoside (**16**) as well as secoxyloganin (**16a**) (Damtoft et al., 1993a).

3.16. *Picconia*

The single species *P. excelsa* (Aiton) DC. has been investigated (Damtoft et al., 1997) and a number of compounds were found, the main ones being loganin (**6**), ketologanin (**18**), oleoacteoside (**22c**) and the bisiridoid picconioside I (**75**), the latter consisting of a molecule of deoxyloganic acid (**3**) esterified with a molecule of loganin (**6**). Minor constituents were among others the picconiosides II–V [monoterpenoid esters of loganin similar to jashemsloside A (**41**)], epikingisidic acid (**15**) and ligstroside (**35**).

3.17. *Osmanthus*

Of the approximately 30 species, four have been investigated. In *O. fragrans* (Thunb.) Lour. Inouye's group found two derivatives of **20**, namely 10-acetoxyligstroside (**76**) and 10-acetoxyoleuropein (**77**) together with verbascoside (**22**) (Inouye et al., 1975b). Under the synonym *O. asiaticus* Nakai, this species was later reported to contain also several phenylethanoid esters similar to **22** (Sugiyama and Kikuchi, 1990a, 1991). More iridoids were also found, namely epikingiside (**15a**), secologanoside 7-methylester (an isomer of **16a**), the dimethyl ester of oleoside (**19**), as well as **35**/**36** and the corresponding 10-hydroxyligstroside and 10-hydroxyoleuropein (Sugiyama and Kikuchi, 1990b; Sugiyama et al., 1993). *O. ilicifolius* (Hassk.) Mouillefert [=*O. heterophyllus* (G. Don) P.S. Green] was found to be very similar to the previous species in iridoid content with **35**/**36**, **76**/**77** and **22** present in addition to the unique hiiragilide (**78**) with an extra glucopyranosyl moiety present (Kikuchi and Yamauchi, 1985b). Except for **78**, *O. x fortunei* Carr. was reported to contain the same compounds (Kikuchi and Yamauchi, 1985c). In contrast to the previous species, *O. austrocaledonicus* (Vieill.) Knobl. contained no derivatives of 10-hydroxyoleoside (**20**), but had ligstroside (**35**) and oleuropein (**36**) as the main constituents. Minor iridoids in this species were loganin (**6**), loganic acid (**10**), secoxyloganin (**16a**), ketologanin (**18**) and austromoside (**79**), a compound with both a secologanosyl and an oleosyl (**16a** and **19a**) moiety present; verbascoside (**22**) and 6′-cinnamoyl verbascoside were also isolated (Benkrief et al., 1998).

4. Discussion

In order to classify the large number of compounds reviewed in Section 3, we have for each plant species listed the compounds under the simple parent iridoid glucosides **3**–**20** in Table 1. Furthermore, we have listed the findings of cornoside (**21**) and the CPGs, i.e. verbascoside and some analogues (**22**–**22c**) as well as an additional group of compounds seemingly of taxonomic interest, namely the glucoside esters from *Jasminum* containing the iridane polyol (**30**) or its isomers; in the table these are designated '**30**'.

Considering first the distribution of the CPGs, we see that these are widespread in the family, having been recorded from about half of the species investigated.

However, they are not universal in Oleaceae as earlier believed (Damtoft et al., 1995b). Cornoside (**21**) has a much more limited distribution, being present only in *Abeliophyllum*, some *Forsythia* species and in fruits of *Olea europaea*.

Iridoid glucosides are present in almost all genera and species of Oleaceae investigated for them, sometimes in considerable amounts. The only exceptions we are aware of are *Abeliophyllum distichum* and the two species of *Ligustrum* listed in Section 4 together with an insufficient sample from a herbarium specimen of *Dimetra craibiana* Kerr (Franzyk et al., 2001); a fresh sample may prove different.

Inspection of the iridoid distribution patterns (Table 1) reveals some interesting correlations with the tribal divisions of Wallander and Albert (2000) shown in Fig. 7. In the tribe Forsythieae, all the species of *Forsythia* contain only carbocyclic iridoids from *route Ia* (Fig. 2) while the single species of *Abeliophyllum* appear not to contain iridoids at all. On the other hand, the rare cornoside (**21**) is present in both genera and thus complement the iridoids as a taxonomic marker for this tribe.

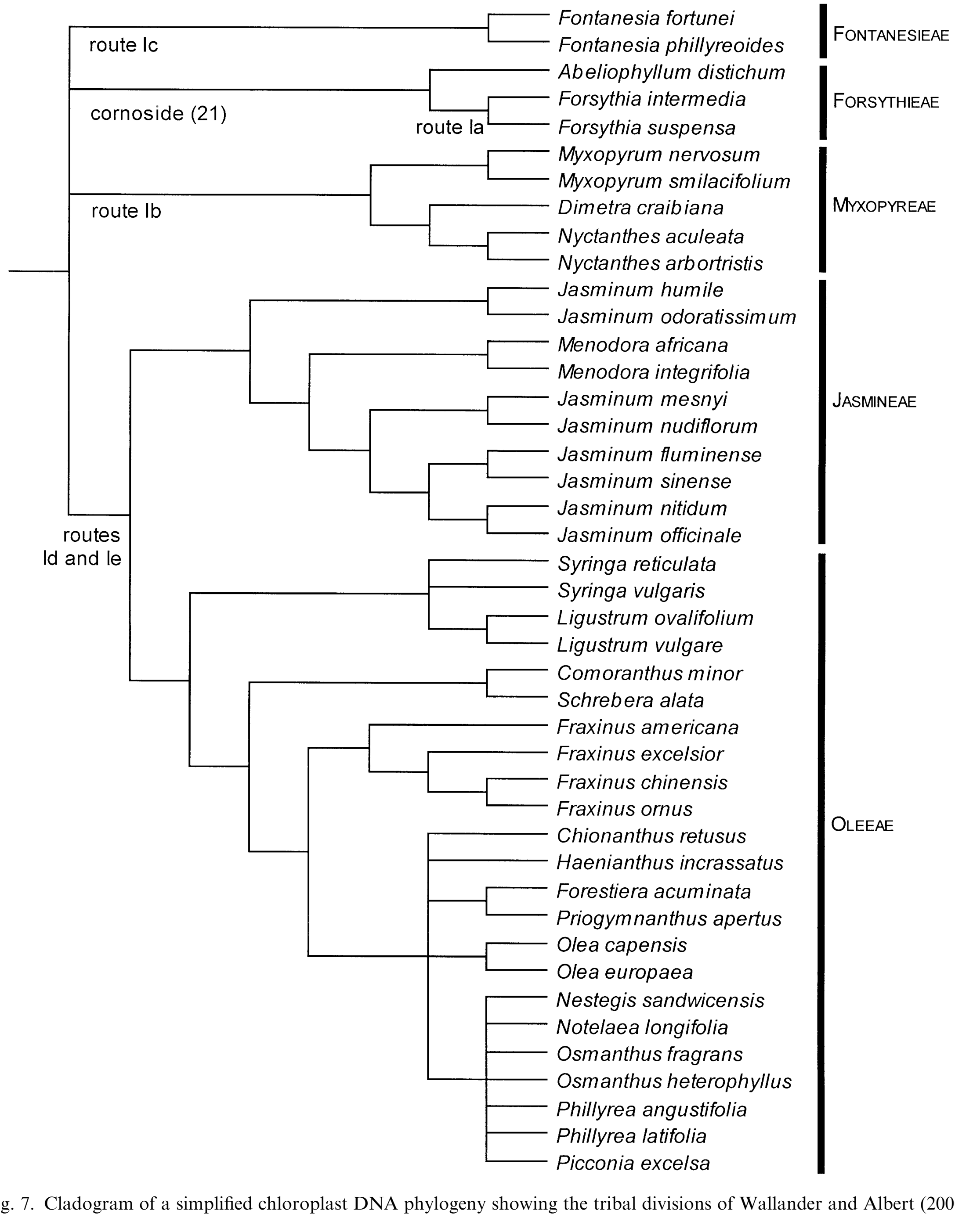


Fig. 7. Cladogram of a simplified chloroplast DNA phylogeny showing the tribal divisions of Wallander and Albert (2000).

In the next tribe, Myxopyreae, only two of the three genera have been properly investigated, namely one species each of *Myxopyrum* and *Nyctanthes*, the limited material available from *Dimetra* probably being insufficient for this purpose. However, a series of unique carbocyclic iridoids were present in the two first genera. Although the biosynthesis has not been investigated, the oxidation patterns of the compounds allow to speculate that they are on the same biosynthetic pathway, namely that designated as *route Ib* above (Fig. 3). Another common feature of most of the iridoid glucosides isolated from Myxopyreae is that they are commonly acylated with one or more acid moieties, aliphatic or aromatic, at the hydroxyl groups of the aglucone.

The smallest tribe, Fontanesieae, is monogeneric and with only two species, which have both been investigated thoroughly. The iridoids found all belong to *route Ic* (Fig. 4) which in part is identical to the secoiridoid route (Fig. 1) found in most parts of Gentianales and in many taxa within Cornales. These compounds have not been encountered elsewhere in Oleaceae, so in this regard *Fontanesia* is the taxon of this family that is most reminiscent of Gentianales. However, the CPG verbascoside (**22**) is present in *Fontanesia*, and this type of compound has never been reported from Gentianales. In fact, the presence of CPGs are also a characteristic of the Lamiales families in which true secoiridoids are extremely rare [only a single occurrence has been reported in *Lippia graveolens* HBK. from Verbenaceae (Rastrelli et al., 1998)]. In *Fontanesia*, the finding of 5-hydroxylated secologanol derivatives like **12** and its esters **12a** and **12b** is also notable, since such compounds elsewhere is more or less limited to Gentianaceae where they are so far solely found as derivatives of the cyclized analogue swertiamarin (**27**) (Rodriguez et al., 1998; Jensen and Schripsema, 2002).

The remaining tribes all contain iridoids derived from *route Id* and *Ie* (Figs. 5 and 6) although compounds (**15** and **16**) from *route Id* are less common than those (**19** and **20**) from *route Ie*. In fact, except for the two species of *Ligustrum* without iridoids at all, derivatives of **19** and/or **20** seem to be obligatory in the remaining tribes.

Within tribe Jasmineae with *Menodora* and *Jasminum* we find that the single species of *Menodora* investigated is chemically similar to the largest group (eight species in Table 1) of *Jasminum* which all contain derivatives of 10-hydroxyoleoside (**20**); many of these, including *Menodora*, contain cinnamoyl esters of **20**, e.g. jasminoside (**37**). Derivatives of **20** are virtually absent from the remaining species of *Jasminum* investigated, except for *J. urophyllum* with two derivatives of **20** isolated in trace amounts. Another group of five species [four of which belongs to sect. Trifoliolata (De Candolle, 1844)] including *J. urophyllum* all contain oleoside esters of the iridane polyol **30** or its isomers. Finally, the two remaining species, namely *J. nitidum* (sect. Unifoliolata) and *J. officinale* (sect. Pinnatifolia) seem to lack derivatives of both **20** and **30**; on the other hand, they do not seem to be chemically related as the former contains esters of **15**, the latter similar esters of **19**.

When comparing the chemical results with the cladogram based on the cDNA sequences (Fig. 7), we find that *Menodora* is nested within the group of *Jasminum*, which is in accordance with the chemical results. And fortunately, we have some overlap in the species examined in the two investigations. Thus, in the cladogram *J. humile* and *J. odoratissimum* (sect. Alternifolia) appear to be as much related to *Menodora* as to the other species of *Jasminum* sequenced, and this fits extremely well with the chemical results, where the two species above and *Menodora robusta* belong to the (larger) group (Table 1) which is characterized by the presence of derivatives of **20**. Next in the cladogram we find a branch with *J. mesnyi* and *J. nudiflorum* (sect. Trifoliolata) and these are the only representatives with known cDNA sequences of the group of species containing derivatives of **30**. Finally, we see a clade with *J. nitidum* and *J. officinale* which (although they are not chemically similar at all) are characterized by lacking derivatives of both **20** and **30**. Thus, the chemical results show an unexpectedly good correlation with the cladogram regarding this tribe.

The remaining taxa in the cladogram constituting tribe Oleaceae are remarkably close to each other and this is reflected in the chemistry. Thus all species, for which chemical data are available, within the last 10 genera (*Syringa* to *Osmanthus*) almost consistently contain esters of oleoside (**19**) and 3 of them also have esters of 10-hydroxyoleoside (**20**). The only exceptions to this are *Jasminum nitidum* with derivatives of **15**, and the above-mentioned (Section 3.9) two species of *Ligustrum* with no iridoids at all.

Regarding the relationships to other orders, the chemistry of Oleeae could be consistent with a position next to or within Lamiales due to the common presence of CPGs, which otherwise have only been reported sporadically from other taxa (Jensen, 1992). The secoiridoids in Oleaceae are, except for those found in *Fontanesia*, mainly of the oleoside type, an unusual kind of compounds not known from Gentianales. In fact, Loasaceae is the only other source from which such iridoids have been reported; thus, derivatives of 10-hydroxyoleoside (**20**) appear to be characteristic for *Cajophora* (Nicoletti et al, 1996; Müller et al., 1999, Weigend et al., 2000) but they are not found elsewhere at all. As stated above (Section 2), Lamiales are mainly characterized by containing decarboxylated iridoids (aucubin, catalpol, etc.) which are derived from epi-deoxyloganic acid (*route II*), but many exceptions are found. Thus, some *Verbena* species (Jensen et al., 1989), *Nuxia*, Stilbaceae (Jensen et al., 1998), and *Thunbergia* (Frederiksen et al., 1999) are known to produce iridoids biosynthetically derived from deoxyloganic acid (**3**). Therefore, Oleaceae can well be accomodated within Lamiales, but they are definitely not central in the order.

5. Experimental

5.1. *Menodora robusta (Benth. A) Grey*

This was collected in the East of Telsen City, Chubut, Argentina in November 1998 by Dr. J.M. Quiroga and dried (voucher no. 8 was identified by Dr. A.M. Beeskow and deposited at The Botanical Garden of CENPAT, Puerto Madryn). *Work-up*: dry twigs (57 g) were homogenized with EtOH (200 ml) and left for 4 days. Evaporation and partitioning between Et_2O and H_2O gave a crude aq. extract (2.92 g). In order to increase retention for acid constituents this was dissolved in 10% aq HOAc before chromatography on a Merck Lobar RP18 column (size C), eluting with H_2O–MeOH mixtures (4:1 to 1:1). After the polar front, a fraction (70 mg) containing epikingisidic acid (**15**) and 10-hydroxyoleoside 7-methyl ester (**20a**) in 1:1 proportion was eluted. This was followed by 10-hydroxyoleoside dimethyl ester (**20b**, 240 mg), 7-ketologanin (**18**, 20 mg), secoxyloganin (**16a**, ca. 25 mg), a fraction (560 mg) containing a complex mixture of phenylethanoid esters of 10-hydroxyoleoside 7-methyl ester, and finally the main component jasminoside (**37**, 860 mg) was obtained. The known compounds were identified by their ^1H and ^{13}C NMR spectra and by comparison with published data; **15**: Damtoft et al. (1993b), **20b**: Trujillo et al. (1996), **18**: Damtoft et al. (1995c), **16a**: Damtoft et al. (1995b), **37**: Inoue et al. (1982a). The compound **20a** has not so far been described in the literature, but we have isolated it earlier from *Cajophora cernua* (Loasaceae) (Rodriguez and Jensen, in preparation).

5.2. *Forestiera acuminata (Michx.) Poir.*

This was collected from a greenhouse specimen originating from Cape Girardeu Co., MO, USA [voucher: "E. Wallander 106" in Göteborg Herbarium (GB)]. Dry leaves (0.7 g) were extracted with EtOH as above to give a crude extract (60 mg). A ^1H NMR spectrum of this was dominated by the signals of oleuropein (**36**). Chromatography as above gave only **36** (20 mg), identified by the ^1H and ^{13}C NMR spectrum.

5.3. *Nestegis sandwicensis (Gray) O. & I. Deg. & L. Johnson*

This was collected at Hawaii Loa Ridge, Oahu, Hawaii, USA in September 1998 [voucher: "A. Yoshinaga s.n." in Herbarium of Honolulu (HLA)]. Dry leaves (4.35 g) treated as above gave a crude extract (350 mg), from which oleuropein (**36**; 20 mg) and impure ligstroside (**35**; 80 mg) were isolated and identified as above.

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