

Iridoids from *Scrophularia* Genus

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Iridoid Gglycosides, *Scrophularia*, *Scrophularia scorodonia*

We report here an updated summary about iridoid composition of a series from the genus *Scrophularia* which have been investigated until now from a phytochemistry point of view. In addition a list is included about iridoids isolated in our laboratory from different plant parts of *Scrophularia scorodonia* L., which are compared with iridoids from some species of the *Scrophularia* genus. The present study may serve as a current information to researchers working on phytochemistry and pharmacological aspects from the *Scrophularia* genus and possibly to serve as a new starting point for future investigations.

Iridoid glycosides such as harpagoside, aucuboside and harpagide are of particular interest to botanists because of their potential value in chemosystematics to elucidate phylogenetic relationships (Bianco, 1990; Luczak and Swiatek, 1978).

The *Scrophularia* genus is represented by more than 300 species. But only a few species have been investigated from a phytochemical and pharmacological point of view. We have now examined species from genus *Scrophularia* which have been investigated from a phytochemical point of view, and report here the results of the literature search. In genus *Scrophularia* the following iridoid glycosides have been found till now: Aucuboside, 6'-cinnamoylaucuboside (scrophularioside), 10-O- β -glucosylaucuboside and scopheanoside I in: *Scrophularia canina* (Berdini *et al.*, 1991), *Scrophularia alata* Gilib (Swiatek and Broda, 1967), *Scrophularia grossheimi* (Akhmedov, 1970), *Scrophularia nodosa* (Weinges and von der Eltz, 1978), *Scrophularia ningpoensis* (Qian *et al.*, 1992), *Scrophularia lateriflora* (Swiatek *et al.*, 1981), *Scrophularia vernalis* (Swiatek and Krzacek, 1976), *Scrophularia ilwensis* (Calis *et al.*, 1993) and *Scrophularia koraiensis nakai* (Pachaly *et al.*, 1994) (Table I).

Ester derivatives of harpagide in: *Scrophularia canina* (Berdini *et al.*, 1991), *Scrophularia spicata* (Zhang *et al.*, 1992), *Scrophularia ilwensis* (Calis *et al.*, 1993), *Scrophularia buergeriana* (Kitagawa *et al.*, 1967), *Scrophularia grossheimi* (Akhmedov, 1970), *Scrophularia nodosa* (Weinges and von der Eltz, 1978), *Scrophularia variegata* (Babayan and

Mnatsakanyan, 1989), *Scrophularia chrisantha* (Babayan and Mnatsakanyan, 1989), *Scrophularia ningpoensis* (Quian *et al.*, 1992; Ming *et al.*, 1999), *Scrophularia leucoclada* (Saatov and Abdullaev, 1996), *Scrophularia vernalis* (Swiatek and Krzacek, 1976) and *Scrophularia koraiensis nakai* (Pachaly *et al.*, 1994) (Table II). Acylated 6-O- α -L-rhamnopyranosylcatalpol are common in genus *Scrophularia*: *Scrophularia scopolii* var. *scopolii* (Calis *et al.*, 1988), *Scrophularia nodosa* (Weinges and von der Eltz, 1978), *Scrophularia spicata* (Zhang *et al.*, 1992), *Scrophularia ilwensis* (Calis *et al.*, 1993), *Scrophularia auriculata* (Giner *et al.*, 1991; 1998), *Scrophularia koelzii* (Bhandari *et al.*, 1992) and *Scrophularia koraiensis nakai* (Pachaly *et al.*, 1994) (Table III). Catalpol, methylcatalpol, ajugol and laterioside were found only in some species: *Scrophularia ningpoensis* (Qian *et al.*, 1992), *Scrophularia vernalis* (Swiatek and Krzacek, 1976), *Scrophularia lateriflora* (Swiatek *et al.*, 1981), *Scrophularia ilwensis* (Calis *et al.*, 1993).

The presence of picroside I was detected only in one species, *Scrophularia lateriflora* (Swiatek *et al.*, 1981) (Tables IV, V).

In the course of a search for biologically active substances in *S. scorodonia* we have isolated several iridoids from leaves and stems, flowers and roots from this species.

For leaves and stems we have reported, bartsioside, aucuboside, harpagoside, 8-O-*cis*-cinnamoyl-harpagide, 8-O-acetyl-harpagide and one new iridoid 6-O- α -L-(3"-O-acetyl-2"-O-*trans*-cinnamoyl)-



rhamnopyranosylcatalpol (scorodioside) (Fernández Matellano *et al.*, 1995a; Fernández Matellano *et al.*, 1995b).

Different catalpol derivates have been isolated in this species: 6-O- α -L-(3''-O-*trans* and *cis* *p*-coumaroyl)-rhamnopyranosylcatalpol and 6-O- α -L-(2''-O-*trans*-*p*-coumaroyl)-rhamnopyranosylcatalpol (saccatoside) have been reported in flowers; 6-O- α -L-(2''-O-acetyl-3'',4''-O-di-*trans*-cinnamoyl)-rhamnopyranosylcatalpol (scropolioside B) and 6-O-methylcatalpol in roots from *S. scorodonia* (De Santos *et al.*, 1998).

It is of interest to compare the presence and distribution of some of these iridoids in different plant parts, because a different composition has been found in leaves, stems, flowers and roots (Table VI). We have detected the presence of harpagide for the first time in leaves, stems and roots from *S. scorodonia*. In roots, we have isolated and identified different iridoids: bartsioside, aucuboside,

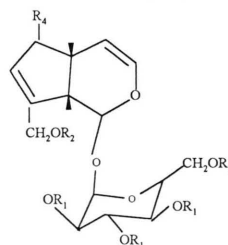
side, harpagoside and 8-O-acetyl-harpagide. These compounds have also been isolated from flowers of this species, except aucuboside. Scorodioside, the new iridoid glycoside isolated from leaves and stems, has also been identified in flowers. As shown in Table VI there is a different distribution between all plant parts.

Identification and assignment of the isolated compounds were performed on the basis of UV spectral data, ^1H and ^{13}C NMR.

Results and Discussion

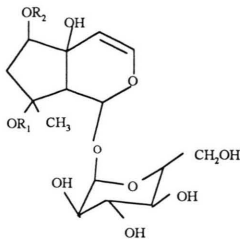
We have compiled a first listing of iridoids occurrence in *Scrophularia* genus (Table VII). From the distribution of iridoids listed it can be concluded that the presence of aucuboside (52.9%), harpagide (47.05%), harpagoside (47.05%) and 8-O-acetylharpagide (41.17%) is not rare in species of the genus, and we have also isolated these compounds from *Scrophularia scorodonia*.

Table I. Aucuboside, scrophularioside, bartsioside and 10-O- β -glucosylaucuboside.



Compound	R	Species	Reference
Aucuboside	R1=R2=R3= H R4=OH	<i>S. nodosa</i> <i>S. grossheimi</i> <i>S. lateriflora</i> <i>S. canina</i> <i>S. ningpoensis</i> <i>S. ilwensis</i> <i>S. scorodonia</i> <i>S. alata</i> <i>S. vernalis</i>	(Weinges and von der Eltz, 1978) (Akhmedov, 1970) (Swiatek <i>et al.</i> , 1981) (Berdini <i>et al.</i> , 1991) (Quian <i>et al.</i> , 1992) (Calis <i>et al.</i> , 1993) (Fernandez <i>et al.</i> , 1995 a) (Swiatek and Broda, 1967) (Swiatek and Krzaczek, 1976)
Scrophularioside	R1=R2=H R3=C ₆ H ₅ CH=CH-CO R4=OH	<i>S. lateriflora</i>	(Swiatek <i>et al.</i> , 1981)
10-O- β -Glucosylaucuboside	R1=R3=H R2= β -D-GLUCOSA R4=OH	<i>S. canina</i>	(Berdini <i>et al.</i> , 1991)
Bartsioside	R1=R2=R3=R4=H	<i>S. scorodonia</i>	(Fernandez <i>et al.</i> , 1995 a)
Scorpheanoside I	R1=R2=R3=H R4 = 4''-O-(<i>p</i> -OCH ₃ - <i>m</i> -OH-C ₆ H ₃ -CH=CH-CO) - β -D-RHAMNOSA	<i>S. koraiensis</i>	(Pachaly <i>et al.</i> , 1994)

Table II. Derivatives of harpagide.

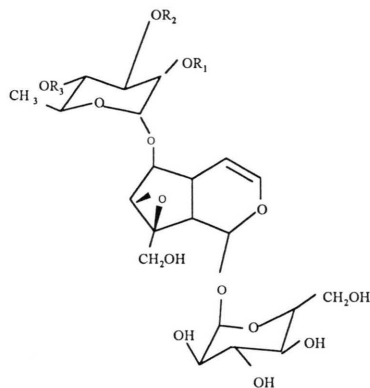


Compound	R	Species	Reference
Harpagide	R1=H R2=H	<i>S. nodosa</i>	(Weinges and von der Eltz, 1978)
		<i>S. grossheimi</i>	(Akhmedov, 1970)
		<i>S. variegata</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. chrisantha</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. ningpoensis</i>	(Quian <i>et al.</i> , 1992)
		<i>S. ilwensis</i>	(Calis <i>et al.</i> , 1993)
		<i>S. koraiensis</i>	(Pachaly <i>et al.</i> , 1994)
		<i>S. leucoclada</i>	(Saatov <i>et al.</i> , 1996)
		<i>S. scorodonia</i>	
8-O-Acetyl-harpagide	R1=CH ₃ -CO- R2=H	<i>S. nodosa</i>	(Weinges and von der Eltz, 1978)
		<i>S. vernalis</i>	(Swiatek and Krzaczek, 1976)
		<i>S. variegata</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. chrisantha</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. canina</i>	(Berdini <i>et al.</i> , 1991)
		<i>S. ilwensis</i>	(Calis <i>et al.</i> , 1993)
		<i>S. scorodonia</i>	(Fernandez <i>et al.</i> , 1995 a)
		<i>S. leucoclada</i>	(Saatov <i>et al.</i> , 1996)
8-O-(<i>p</i> -Methoxycinnamoyl)- harpagide	R1=CH ₃ O-C ₆ H ₄ CH=CH-CO R2=H	<i>S. buergeriana</i>	(Kitagawa <i>et al.</i> , 1967)
		<i>S. variegata</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. chrisantha</i>	(Babayan and Mnatsakanyan, 1989)
8-O- <i>trans</i> -cinnamoylharpagide (harpagoside)	R1=C ₆ H ₅ -CH=CH-CO R2=H	<i>S. buergeriana</i>	(Kitagawa <i>et al.</i> , 1967)
		<i>S. vernalis</i>	(Swiatek and Krzaczek, 1976)
		<i>S. variegata</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. chrisantha</i>	(Babayan and Mnatsakanyan, 1989)
		<i>S. ningpoensis</i>	(Quian <i>et al.</i> , 1992)
		<i>S. spicata</i>	(Zhang <i>et al.</i> , 1992)
		<i>S. koraiensis</i>	(Pachaly <i>et al.</i> , 1994)
		<i>S. scorodonia</i>	(Fernandez <i>et al.</i> , 1995 a)
		<i>S. scorodonia</i>	(Fernandez <i>et al.</i> , 1995 b)
8-O- <i>cis</i> -cinnamoyl-harpagide	R1=C ₆ H ₅ -CH=CH-CO- R2=H		
8-O- <i>cis</i> -feruloyl-harpagide	R1=Feruloyl- R2=H	<i>S. ningpoensis</i>	(Ming <i>et al.</i> , 1999)
8-O-(2-hydroxy-cinnamoyl)- harpagide	R1=C ₆ H ₅ -CH=C-CO- R2=H	<i>S. ningpoensis</i>	(Ming <i>et al.</i> , 1999)
6-O- α -D-galactopyranosyl- harpagide	R1=H R2=d-galactopyranosyl	<i>S. ningpoensis</i>	(Ming <i>et al.</i> , 1999)

On the other hand, iridoids derived from aucuboside are rarer in the genus *Scrophularia*, they appear only in some species, such as scrophularioside in *S. lateriflora*, 10-O- β -glucosylaucuboside in *S. canina* and scropheanoside I in *S. koraiensis* (Table I).

Moreover it is well known that species of *Scrophularia* contain catalpol derivates (Table III), but

some of this iridoids have been reported only in one species: koelzioside in *S. koelzii*, scropoliosides A and B in *S. scopolii* and *S. auriculata*, scropsioside B in *S. spicata*, scropheanoside II and 6-O- α -L-(2"-O-acetyl-3",4"-O-di-*p*-methoxycinnamoyl) rhamnopyranosylcatalpol in *S. koraiensis* and *S. auriculata*, respectively. Picroside I has been detected only in *S. lateriflora* and 6-O-(β -D-xylo-

Table III. Acylated derivates of 6-O- α -L-rhamnopyranosylcatalpol.

Compound	R	Species	Reference
6- α -L-rhamnopyranosyl-catalpol	R1=R2=R3=H	<i>S. nodosa</i>	(Weinges and von der Eltz, 1978)
6-0- α -L-(4"-O-acetyl-2", 3"-di-O-cinnamoyl)-rhamnopyranosyl-catalpol (koelzioside)	R1=R2=C ₆ H ₅ -CH=CH-CO- R3=CH ₃ -CO-	<i>S. koelzii</i>	(Bhandari <i>et al.</i> , 1992)
6-0- α -L-(2", 4"-di-O-acetyl-3"-O- <i>p</i> -methoxy- <i>trans</i> -cinnamoyl)-rhamnopyranosyl-catalpol (scropolioside A)	R1=R3=CH ₃ -CO- R2=CH ₃ O-C ₆ H ₄ -CH=CH-CO-	<i>S. scopolii</i> var. <i>scopolii</i> <i>S. auriculata</i>	(Calis <i>et al.</i> , 1988) (Giner <i>et al.</i> , 1988)
6-0- α -L-(2"-O-acetyl-3"-4"-O-di- <i>trans</i> -cinnamoyl)-rhamnopyranosyl-catalpol (scropolioside B)	R1=CH ₃ -CO- R2=R3=C ₆ H ₅ -CH=CH-CO-	<i>S. scopolii</i> var. <i>Scopolii</i> . <i>S. scorodonia</i>	(Calis <i>et al.</i> , 1988) (De Santos <i>et al.</i> , 1998)
6-0- α -L-(2", 4"-di-O-acetyl-3"-O- <i>trans</i> -cinnamoyl)-rhamnopyranosyl-catalpol (scropolioside D)	R1=R3=CH ₃ -CO- R2=C ₆ H ₅ -CH=CH-CO-	<i>S. ilwensis</i> <i>S. spicata</i> <i>S. koraiensis</i>	(Calis <i>et al.</i> , 1993) (Zhang <i>et al.</i> , 1992) (Pachaly <i>et al.</i> , 1994)
6-0- α -L-(2"-O-acetyl-3"-O- <i>trans</i> -cinnamoyl)-rhamnopyranosyl-catalpol (scropolioside B)	R1=CH ₃ -CO- R2=C ₆ H ₅ -CH=CH-CO- R3=H	<i>S. spicata</i>	(Zhang <i>et al.</i> , 1992)
Scorpheanaside II	R1=R2=H R3= <i>p</i> -OCH ₃ - <i>m</i> -OH-C ₆ H ₃ -CH=CH-CO-	<i>S. koraiensis</i>	(Pachaly <i>et al.</i> , 1994)
6-0- α -L-(2"-O-acetyl-3", 4"-O-di- <i>p</i> -methoxycinnamoyl)-rhamnopyranosyl)-catalpol	R1=CH ₃ -CO- R2=R3= <i>p</i> -CH ₃ O-C ₆ H ₄ -CH=CH-CO-	<i>S. auriculata</i>	(Giner <i>et al.</i> , 1991)
6-0- α -L-(3"-O-acetyl-2"- <i>trans</i> -cinnamoyl)-rhamnopyranosyl-catalpol (scorodioside)	R1=C ₆ H ₅ -CH=CH-CO- R2=CH ₃ -CO- R3=H	<i>S. Scorodonia</i>	(Fernandez <i>et al.</i> , 1995 b)
6-0- α -L-(2"-O- <i>trans</i> - <i>p</i> -coumaroyl)-rhamnopyranosyl-catalpol (saccatoside)	R1=HO-C ₆ H ₄ -CH=CH-CO- R2=R3=H	<i>S. scorodonia</i>	(De Santos <i>et al.</i> , 1998)
6-0- α -L-(3"-O- <i>trans</i> and <i>cis</i> - <i>p</i> -coumaroyl)-rhamnopyranosyl-catalpol	R1=R3=H R2=HO-C ₆ H ₄ -CH=CH-CO-	<i>S. scorodonia</i>	(De Santos <i>et al.</i> , 1998)
6-0- α -L-(2", 3"-di-O-acetyl-4"-O- <i>p</i> -methoxy-cinnamoyl)-rhamnopyranosyl-catalpol (scrovalentinoside)	R1=R3=CH ₃ -CO- R2=CH ₃ O-C ₆ H ₄ -CH=CH-CO-	<i>S. auriculata</i>	(Giner <i>et al.</i> , 1988)

pyranosyl) methylcatalpol is unique in *S. ilwensis* (Table IV).

In *S. scorodonia* we have isolated three 6-O- α -L-rhamnopyranosylcatalpol derivates as saccatoside,

and 6-O- α -L-(3"-O-*trans* and *cis* *p*-coumaroyl)-rhamnopyranosylcatalpol which have not been reported previously in this genus. Also, bartsioside and 8-O-*cis*-cinnamoyl-harpagide are not present

Table IV. Catalpol, methylcatalpol and picroside I.

Compound	R	Species	Reference
Catalpol	R1=R2=R3=R4=H	<i>S. lateriflora</i>	(Swiatek <i>et al.</i> , 1981)
Picroside I	R1=R3=R4=H R2=C6H5CH=CH-CO-	<i>S. lateriflora</i>	(Swiatek <i>et al.</i> , 1981)
6-Methylcatalpol	R1=R2=R4=H R3=CH3-	<i>S. vernalis</i> <i>S. lateriflora</i> <i>S. ningpoensis</i> <i>S. scorodonia</i>	(Swiatek and Krzaczek, 1976) (Swiatek <i>et al.</i> , 1981) (Quian <i>et al.</i> , 1992) (De Santos <i>et al.</i> , 1998)
6-O-(β-D-xylopiranosyl)-methylcatalpol	R1=R2=H R3= CH3- R4=O-β-xylopiranosyl	<i>S. ilwensis</i>	(Calis <i>et al.</i> , 1993)

Table V. Ajugol and laterioside.

Compound	R	Species	Reference
Ajugol	R=H	<i>S. lateriflora</i> <i>S. ilwensis</i>	(Swiatek and Broda, 1967) (Weinges and von der Eltz, 1978)
Laterioside	R=C6H5-CH=CH-CO-	<i>S. lateriflora</i>	(Swiatek and Broda, 1967)

in *Scrophularia* genus, but we have isolated these compounds in *S. scorodonia*.

Of special interest is scorodioside, a new catalpol analog until now not reported as present in nature and which we have isolated from *S. scorodonia*.

Remarkably, catalpol, one of the most common iridoids, has not been found in the present investigation. This compound has been isolated in the genus *Scrophularia* only in *S. lateriflora* (Table IV).

With regard to the widespread occurrence of iridoids in members of genus *Scrophularia*, *Scrophularia scorodonia* fits well into the genus, but the iridoid patterns were some different between this species and others species from this genus. As shown in Table VII *S. scorodonia* is the species which contains the major variety of iridoids, with 11 iridoids among 31 found until now in this genus and with an unequal distribution in different plant parts as shown in Table VI.

Table VI. Iridoids from *Scrophularia scorodonia*.

Iridoids	<i>Scrophularia scorodonia</i>		
	Flowers	Leaves and stems	Roots
Aucuboside		*	*
Bartsioside	*	*	*
Harpagide	*	*	*
8-O-acetyl-harpagide	*	*	*
Harpagoside	*	*	*
8-O-cis-cinnamoyl-harpagide		*	
Scropolioside B			*
Scorodioside	*	*	
Saccatoside	*		
6-O- α -L-(3''O-trans and cis- <i>p</i> -coumaroyl)-rhamnopyranosyl-catalpol	*		
6-Methylcatalpol			*

So, bartsioside, harpagide, 8-O-acetyl-harpagide and harpagoside, are present in all plant parts. Catalpol derivatives are predominant in roots and flowers. Although scorodioside, the new iridoid isolated from *S. scorodonia*, is present in leaves, stems and flowers, it has not been detected in roots. Aucuboside, a common iridoid, was not found in flowers from this species, but it is present in leaves, stems and roots.

Iridoids are present in a number of folk medicines used as bitter tonics, sedatives, antipyretics, cough medicines, remedies for wounds, skin disorders and as hypotensives. Recently, intensive investigations on their bioactivity in general, and on their potential pharmacological activity in particular, have revealed that these compounds exhibit a wide range of bioactivity: cardiovascular, antihepatotoxic, choleric, hypoglycemic and hypolipidemic, antiinflammatory, antispasmodic, antitumor, antiviral, immunomodulator and purgative activities (Ghisalberti, 1998).

Although *S. scorodonia* has not been used in folk medicine, possible therapeutical properties of this species depend probably on a number of its constituents. Among them harpagoside and aucuboside should be mentioned as these compounds, they possess analgesic and antiinflammatory activ-

ities (Recio *et al.*, 1994). In addition, aucuboside is reported to exhibit antihepatotoxic, antispasmodic and antitumoral activities (Ghisalberti, 1998). The presence of 8-O-acetyl-harpagide may also be important, as the compound has shown antispasmodic and vasoconstrictor activities (Breschi *et al.*, 1992). Catalpol derivatives have shown to possess a lot of pharmacological properties, these type of compounds also exhibit antiinflammatory activity. Studies on antiinflammatory activity of these catalpol derivatives and other iridoids isolated from *S. scorodonia* have exhibited an interesting activity (Bermejo *et al.*, 1999).

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Table VII. Iridoids of the Scrophularia genus.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31
<i>S. nodosa</i>	*					*	*							*																	
<i>S. grossheimi</i>	*					*																									
<i>S. lateriflora</i>	*	*																								*	*	*		*	*
<i>S. canina</i>	*		*				*																								
<i>S. ningpoensis</i>	*					*			*		*	*	*																*		
<i>S. silwensis</i>	*					*	*												*										*	*	
<i>S. scorodonia</i>	*			*		*	*		*	*							*					*	*	*				*			
<i>S. alata</i>	*																														
<i>S. vernalis</i>	*						*		*																				*		
<i>S. variegata</i>						*	*	*	*																						
<i>S. chrisanta</i>						*	*	*	*																						
<i>S. koraiensis</i>				*	*				*										*		*										
<i>S. buergeriana</i>								*	*																						
<i>S. spicata</i>									*										*	*											
<i>S. koelzii</i>															*																
<i>S. scopoli</i> var. <i>scopoli</i>																*	*														
<i>S. leucoclada</i>						*	*																								
<i>S. auriculata</i>																*					*				*						

- | | | |
|---|--|--|
| (1) Aucuboside | (13) 6-O- α -L-galactopyranosyl-harpagide | (23) Saccatoside |
| (2) Scrophularioside | (14) 6- α -L-Rhamnopyranosyl-catalpol | (24) 6-O- α -L-(3''O- <i>trans</i> and <i>cis</i> - <i>p</i> -coumaroyl)-rhamnopyranosyl-catalpol |
| (3) 10-O- β -glucosylaucuboside | (15) Koelzioside | (25) Screoalentiniside |
| (4) Bartsioside | (16) Scropolioside A | (26) Catalpol |
| (5) Scropheanoside I | (17) Scropolioside B | (27) Picroside I |
| (6) Harpagide | (18) Scropolioside D | (28) 6-Methylcatalpol |
| (7) 8-O-acetyl-harpagide | (19) Scropioside B | (29) 6-O-(β -D-xylopiranosyl)-methylcatalpol |
| (8) (<i>p</i> -Methoxycinnamoyl)-harpagide | (20) Scropheanoside II | (30) Ajugol |
| (9) Harpagoside | (21) 6-O- α -L-(2''-O-acetyl-3'', 4''-O-di- <i>p</i> -methoxycinnamoyl-rhamno-pyranosyl)-catalpol | (31) Laterioside |
| (10) 8-O- <i>cis</i> -cinnamoyl-harpagide | (22) Scorodioside | |
| (11) 8-O-feruloyl-harpagide | | |
| (12) 8-O-(2-hydroxy-cinnamoyl)-harpagide | | |

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