Pharmaceutical Biology

ISSN: 1388-0209 (Print) 1744-5116 (Online) Journal homepage: informahealthcare.com/journals/iphb20

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To cite this article: J. de Santos Galíndez, A.M.a Díaz Lanza & L. Fernández Matellano (2002) Biologically Active Substances from the Genus Scrophularia, Pharmaceutical Biology, 40:1, 45-59, DOI: 10.1076/phbi.40.1.45.5864

To link to this article: https://doi.org/10.1076/phbi.40.1.45.5864

Pharmaceutical Biology
2002, Vol. 40, No. 1, pp. 45–59

1388-0209/02/4001-045$16.00

Review

Biologically Active Substances from the Genus *Scrophularia*

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Abstract

Scrophularia species have been used since ancient times as folk remedies for some medical treatments including scrophula, scabies, tumours and inflammatory affections. Some compounds isolated from these species, such as iridoids and phenylpropanoids, are considered responsibles for these activities. This review summarizes mainly the biological activity associated with this genus.

Keywords: Biologically active substances, iridoids, phenylpropanoids, *Scrophularia*, Scrophulariaceae.

Introduction

The genus *Scrophularia*, consisting of about 300 species, is one of the most important genera belonging to the Scrophulariaceae. Many species belonging to this genus have been used since ancient times as folk remedies for some medical treatments (scrophulas, scabies, tumours, eczema, psoriasis, inflammatory affections, etc.) (Heather & Henderson, 1994; Paris & Moyse, 1976). One species, *Scrophularia ningpoensis* (officially indexed drug in the Chinese Pharmacopoeia), is even cultivated as a medicinal plant in China. It has been used for the treatment of fever, swelling, constipation, pharyngitis, neuritis, and laryngitis in traditional Chinese medicine (Miyazawa et al., 1998). *S. grossheimi* and *S. nodosa* have been used as diuretic plants in traditional medicine (Akhmedov et al., 1969; Schaunbenger & Paris, 1977) and *S. oldhamii* has been used as an antipyretic and for the treatment of inflammation (Won Sick Woo, 1963). Others species have been used as antiinflammatory, antihypertensive, and antihypercholesterolemic agents (Kajimoto et al., 1989).

According to the literature, many *Scrophularia* species have been investigated and found to contain many classes of secondary metabolites including iridoids, phenylpropanoids, phenolic acids, flavonoids and saponins. Some of these compounds were shown to have antiinflammatory, antibacterial, hepatoprotective, immuno-modulator, cardiovascular, diuretic, protozoocidal, fungicidal, molluscicidal, cytotoxic, cytostatic, antitumour activities (Ghisalberti, 1998; Bermejo Benito et al., 1998; Emam et al., 1997; Nishibe, 1994; Lacaille-Dubois & Wagner, 1996).

A survey of the presently available chemical and biological data suggests that the iridoid glycosides are the main classes of substances of interest to pharmacologists, and it was suggested that the therapeutic action of these plants depends on the presence of iridoids (Ghisalberti, 1998). A number of reports have been published which demonstrate that iridoids possess a number of biological properties, such as choleretic, vasoconstrictor, hepatoprotective, antiviral and antimicrobial activities, and these compounds could act synergically with other active substances (Tables 1 and 2).

Antiinflammation

Most species belonging to the *Scrophularia* genus have been used as antiinflammatory drugs by folk medicine. Iridoids and phenylpropanoids are considered to be the active principles of these drugs (García et al., 1996; Fernández et al., 1998).

The roots of *Scrophularia ningpoensis* have been used for the treatment of inflammation in Chinese traditional medicine (Kajimoto et al., 1989). This plant has also been prescribed as an antipyretic and antiiflammatory in diseases causing heat or fever, dry cough and pulmonary tuberculosis. This antiinflammatory effect has been demonstrated in animals (Qian et al., 1991). The hydrophilic extract of the roots from *S. ningpoensis* had intense antiinflammatory activity with the carrageenin-induced rat paw model for edema. From this species were isolated harpagide (**1**), harpagoside (**2**), aucuboside (**3**), 6-*O*-methylcatalpol (**4**), ningpogenin (**5**), ningpogoside A (**6**), ningpogoside B (**7**),

Accepted: August 15, 2001

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Table 1. Activities of some species from the *Scrophularia* genus.

	S. auriculata	*S. frutescens*	*S. ningpoensis*	*S. scorodonia*	*S. nodosa*
ANTIINFLAMMATORY	(Giner et al., 1991, 2000; Cuellar et al., 1998)	(Garcia et al., 1996; Fernandez et al., 1996, 1998)	(Kajimoto et al., 1989; Quian et al., 1991, 1992; Zhang et al., 1194)	(Bermejo Benito et al., 1998, 2000)	(Paris & Moyse, 1976; Schaunbenger & Paris, 1977;
ANTIBACTERIAL	(Swiatek, 1970, 1973; Paris & Moyse, 1976; Van Hellemont, 1986)	(Fernandez et al., 1996)			Vigneau, 1985) (Paris & Moyse, 1976; Schaunbenger & Paris, 1977; Rombouts and Links, 1956; Swiatek, 1970)
HEPATOPROTECTIVE					(Swiatek, 1970)
IMMUNOMODULATOR					
CARDIOVASCULAR			(Kajimoto et al., 1989; Ody, 1993)		(Karimova et al., 1966)
DIURETIC		(Fernandez Arche et al., 1993)			(Akhmedov et al., 1969; Schaunbenger & Paris, 1977)
PROTOZOOCIDAL FUNGICIDAL AND MOLLUSCICIDAL				(Martin et al., 1998; Emam et al., 1997)	
ANTITUMOR CYTOTOXIC AND CYTOSTATIC		(Garcia et al., 1998)	(Miyazawa et al., 1998; Pinkas et al., 1994; Liu & Wu, 1993)		
NEUROPROTECTIVE					
ANTIPRURITIC			(Tohda et al., 2000)		
OTHERS					(Karimova et al., 1996)

verbascoside (**8**), angoroside A (**9**) and angoroside C (**10**) (Kajimoto et al., 1989; Zhang et al., 1994; Qian et al., 1992). Pharmacological investigations are necessary for evaluating their potential as antiinflammatory agents.

S. auriculata is a medicinal plant used in traditional medicine against inflammatory skin diseases. Its aqueous alcohol extract showed a marked effect on both acute and chronic models of inflammation (Cúellar et al., 1998).

Two catalpol derivates [6-*O*-α-L-(2″-*O*-acetyl-3″,4″-*O*-di-*p*-methoxycinnamoyl-rhamnopyranosyl)-catalpol (**11**) and 6-*O*-α-L-(4″-*O*-acetyl 2″,3″-*O*-di-*p*-methoxycinnamoyl)-rhamnopyranosyl-catalpol (**12**)], isolated from *S. auriculata* L., exert high antiinflammatory activity on mouse ear edema induced by tetradecanoylphorbol acetate (TPA). When these products were assayed at the same dose as indomethacin (0.5 mg/ear), they exhibited nearly the same effect as this reference drug with an edema percentage inhibition of 73.4% (Giner et al., 1991).

Two saponins, verbascosaponin A (**13**) and verbascosaponin (**14**), and two iridoids, scropolioside A (**15**) and

Table 1 (continued)

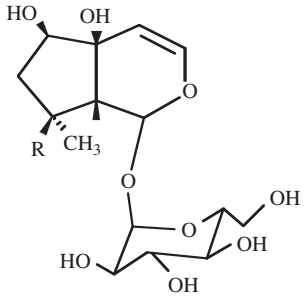
S. canina	*S. sambucifolia*	*S. koelzii*	*S. grosheimi*	*S. buergeriana*	*S. oldhamii*	*S. scopolii*
					(Won Sick Woo, 1963)	
(Swiatek, 1970, 1973; Paris & Moyse, 1976; Van Hellemont, 1986)	(Fernandez et al., 1996)				(Won Sick Woo, 1963)	
		(Garg et al., 1994) (Garg et al., 1994)	(Akhmedov et al., 1969)			
			(Akhmedov et al., 1969)			
	(Fernandez Arche et al., 1993)		(Akhmedov et al., 1969; Schaunbenger & Paris, 1977)			
						(Saracoglu et al., 1997)
				(Kim & Kim, 2000)		
		(Bhandari et al., 1992)				

scrovalentinoside (**16**), isolated from *S. auriculata* ssp. *pseudoauriculata*, assayed with various acute and chronic experimental models, showed antiinflammatory activity against all the inducers with the exception of arachidonic acid (Giner et al., 2000). Both saponins significantly inhibited mouse paw edema induced by single and multiple doses of 12-*O*-tetradecanoylphorbol 13-acetate (TPA). Verbascosaponin A (**13**) showed a potency twice as high as that of indomethacin in the acute TPA model. Verbascosaponin A (**13**) and scropolioside A (**15**) were active after a long latency period against ethyl phenylpropiolate edema, as are glucocorticoids. When the putative corticoid-like mechanism of the two compounds was studied, verbascosaponin A (**13**) activity was notably reduced by the mRNA synthesis inhibitor, actinomycin D, while the effect of scropolioside A (**15**) was partially blocked by the anti-glucocorticoid drugs used. Both iridoids were active on the delayed-type hypersensitivity reaction. They significantly reduced the inflammatory lesion and suppressed cellular infiltration.

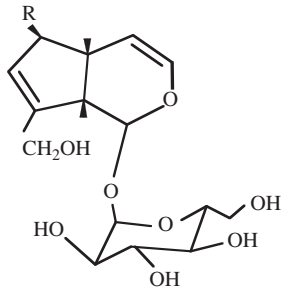
The aqueous extract and harpagoside (**2**) isolated from *S. frutescens* L. were tested for antiinflammatory activity on rat paw edema. The results obtained showed that the aqueous

Table 2. Bioactive compounds, parts or fractions and activities derived from *Scrophularia* species.

Plant sources	Bioactive compound, parts or fraction and activites	References
S. auriculata	Plant, phenolic acids (antibacterial)	(Swiatek, 1970, 1973; Paris & Moyse, 1976; Van Hellemont, 1986)
	(**11**–**16**) Iridoids and saponins (antiinflammatory), Plant, hidroalcoholic extract	(Giner et al., 1991, 2000; Cuellar et al., 1998)
S. buergeriana	(**17**–**19**, **33**, **38**, **41**–**45**) Chloroform methanol extract from roots, phenylpropanoids (neuroprotective)	(Kim & Kim, 2000)
S. canina	Plant, phenolic acids (antibacterial)	(Swiatek, 1970, 1973; Paris & Moyse, 1976; Van Hellemont, 1986)
S. frutescens	(**2**, **17**–**23**) Aqueous extract, phenolic acids, iridoid (antiinflammatory)	(Garcia et al., 1996; Fernandez et al., 1996, 1998)
	Aqueous extract of the aerial parts (ashes), flavonoids and saponins (diuretic)	(Fernandez Arche et al., 1993)
	(**17**–**23**) Phenolic acids (antitumor, cytotoxic and cytostatic)	(Garcia et al., 1998)
	(**17**–**23**, **31**, **32**) Aerial part, phenolic acids (antibacterial)	(Fernandez et al., 1996)
S. grossheimi	Plant (diuretic)	(Akhmedov et al., 1969; Schaunbenger & Paris, 1977)
	(**36**) Extract, flavonoids (cardiovascular)	(Akhmedov et al., 1969)
	Flavonoid fraction (hepatoprotective)	(Akhmedov et al., 1969)
S. koelzii	(**2**, **15**, **34**, **35**) Alcoholic extract, chloroform fraction from alcoholic extract of the aerial parts, iridoids (hepatoprotective and immunomodulator)	(Garg et al., 1994)
	(**34**) Alcoholic extract of the whole plant, iridoid (CNS depressant)	(Bhandari et al., 1992)
S. nodosa	(**3**, **19**, **29**, **30**) Iridoids and phenolic acid (antiinflammatory)	(Paris & Moyse, 1976; Schaunbenger & Paris, 1977; Vigneau, 1985)
	(**1**, **3**, **19**, **29**, **30**) Plant, iridoids and phenolic acids (antibacterial)	(Paris & Moyse, 1976; Schaunbenger & Paris, 1977; Rombouts and Links, 1956; Swiatek, 1970)
	(**19**) Phenolic acid (hepatoprotective)	(Swiatek, 1970)
	Infusion, saponin (cardiovascular)	(Karimova et al., 1966)
	Infusion (inhibited of motor activity)	(Karimova et al., 1966)
	Plant (diuretic)	(Akhmedov et al., 1969; Schaunbenger & Paris, 1977)
S. ningpoensis	(**1**–**10**) Roots, hydrophilic extract, iridoids and phenolic acids (antiinflammatory)	(Kajimoto et al., 1989; Quian et al., 1991, 1992; Zhang et al., 1194)
	Methanol extract from roots (antipruritic)	(Tohda et al., 2000)
	Aqueous extract (cardiovascular)	(Kajimoto et al., 1989; Ody, 1993)
	(**33**, **38**–**40**) Plant, methanol extract from roots and phenolic acids (antitumoral, cytotoxic and cytostatic)	(Miyazawa et al., 1998; Pinkas et al., 1994; Liu & Wu, 1993)
S. oldhamii	(**33**) Ethanol extract from roots, phenolic acid (antibacterial)	(Won Sick Woo, 1963)
	Plant (antiinflammatory)	(Won Sick Woo, 1963)
S. sambucifolia	(**17**–**23**, **31**, **32**) Aerial part, phenolic acids (antibacterial)	(Fernandez et al., 1996)
	Aqueous extract of the aerial parts (ashes), flavonoids and saponins (diuretic)	(Fernandez Arche et al., 1993)
S. scopolii	(**9**) Phenylpropanoid glycoside (antitumor, cytotoxic and cytostatic)	(Saracoglu et al., 1997)
S. scorodonia	(**24**) Methanol extract from flowers, Buddlejasaponin I (protozoocidal, fungicidal and molluscicidal)	(Martin et al., 1998; Emam et al., 1997)
	(**1**–**3**, **24**–**28**) Iridoids, Buddlejasaponin I (antiinflammatory)	(Bermejo Benito et al., 1998, 2000)



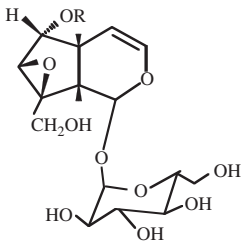
	COMPOUND	R	SPECIES	REFERENCES
(1)	**Harpagide**	R = OH	*S. scorodonia*	(Bermejo Benito et al., 2000)
			S. ningpoensis	(Zhang et al., 1994)
				(Kajimoto et al., 1989)
(2)	**8-*O*-*trans*-Cinnamoylharpagide (Harpagoside)**	R = C_6H_5-CH = CH-CO-O-	*S. scorodonia*	(Bermejo Benito et al., 2000)
			S. ningpoensis	(Kajimoto et al., 1989)
				(Zhang et al., 1994)
			S. koelzii	(Garg et al., 1994)
			S. frutescens	(Garcia et al., 1996)
(26)	**8-*O*-Acetylharpagide**	R = CH_3-CO-O-	*S. scorodonia*	(Bermejo Benito et al., 2000)



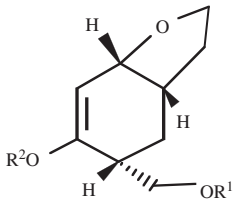
	COMPOUND	R	SPECIES	REFERENCES
(3)	**Aucuboside**	R = OH	*S. nodosa*	(Paris & Moyse, 1976)
				(Schaunbenger & Paris, 1977)
				(Vigneau, 1985)
				(Rombouts & Links, 1956)
			S. ningpoensis	(Qian et al., 1992)
			S. scorodonia	(Bermejo Benito et al., 2000)
(25)	**Bartsioside**	R = H	*S. scorodonia*	(Bermejo Benito et al., 2000)

Figure 1. Structures and sources of compounds from *Scrophulania* ssp.

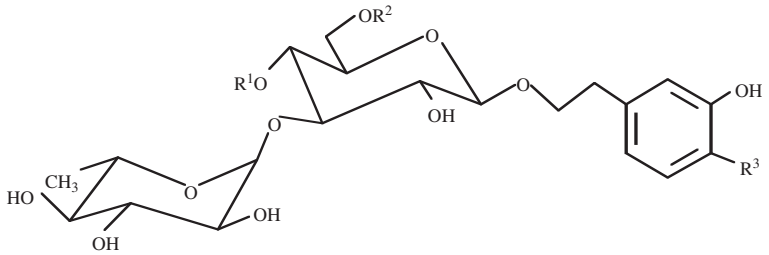
extract from this species can be considered as a potential mild antiinflammatory agent on an acute inflammation process, although harpagoside is not considered the principal responsible of the antiinflammatory effect (García et al., 1996). Probably, other bioactive substances are involved, such as phenolics acids, previously isolated from the aqueous extract of this species (Fernández et al., 1996), since it has been reported already that some of these compounds have antiinflammatory action (Fernández et al., 1998). These authors showed that *p*-coumaric (**17**), caffeic (**18**), ferulic (**19**), gentisic (**20**), protocatechuic (**21**), syringic (**22**) and isovanillic (**23**) acids isolated from *S. frutescens* are moderate systemic antiinflammatory agents but have a strong antiinflammatory effect when applied locally at the site of



	COMPOUND	R	SPECIES	REFERENCES
(4)	**6-*O*-Methylcatalpol**	R = CH_3	*S. ningpoensis*	(Qian et al., 1992) (Zhang et al., 1994)
(29)	**Catalpol**	R = H	*S. nodosa*	(Paris & Moyse, 1976) (Schaunbenger & Paris, 1977) (Vigneau, 1985)
(30)	**Catalposide**	R = *p*-hidroxybenzoyl	*S. nodosa*	(Paris & Moyse, 1976) (Schaunbenger & Paris, 1977) (Vigneau, 1985)

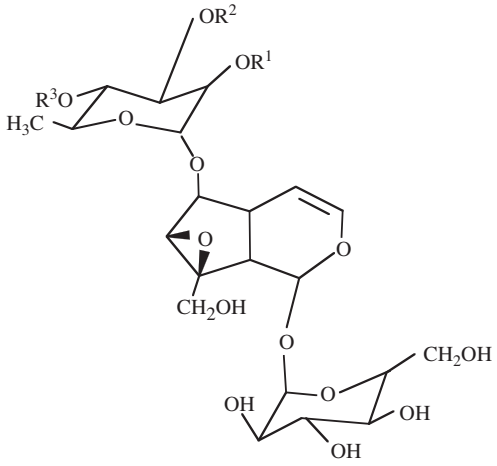


	COMPOUND	R	SPECIES	REFERENCES
(5)	**Ningpogenin**	$R^1 = R^2 = H$	*S. ningpoensis*	(Qian et al., 1992)
(6)	**Ningpogoside A**	R^1 = GLC R^2 = H	*S. ningpoensis*	(Qian et al., 1992)
(7)	**Ningpogoside B**	R^1 = H R^2 = GLC	*S. ningpoensis*	(Qian et al., 1992)



	COMPOUND	R	SPECIES	REFERENCES
(8)	**Verbascoside**	R^1 = caffeoyl R^2 = H R^3 = OH	*S. ningpoensis*	(Kajimoto et al., 1989)
(8)	**Angoroside A**	R^1 = caffeoyl R^2 = arabinose R^3 = OH	*S. scopolii* *S. ningpoensis*	(Saracoglu et al., 1997) (Kajimoto et al., 1989)
(10)	**Angoroside C**	R^1 = (E)feruroyl R^2 = arabinose R^3 = OCH_3	*S. scopolii* *S. ningpoensis*	(Saracoglu et al., 1997) (Zhang et al., 1994)
(10)	**Angoroside C**	R^1 = caffeoyl R^2 = arabinose R^3 = OCH_3	*S. scopolii*	(Saracoglu et al., 1997)

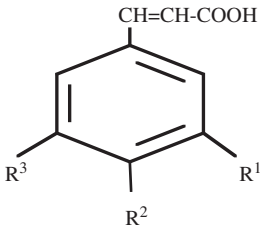
Figure 2. Structures and sources of compounds from *Scrophulania* ssp.



COMPOUND	R	SPECIES	REFERENCES
(11) **6-*O*-α–L-(2″-*O*-acetyl-3″, 4″-*O*-di-*p*-methoxy-cinnamoyl-rhamnopyranosyl)-catalpol**	$R^1 = CH_3\text{-CO-}$ $R^2 = R^3 = p\text{-}CH_3O\text{-}C_6H_4\text{-}CH = CH\text{-CO-}$	*S. auriculata*	(Giner et al., 1991)
(12) **6-*O*-α–L-(4″-*O*-acetyl 2″, 3″-di-*p*–methoxycinnamoyl)-rhamnopyranosyl-catalpol**	$R^1 = R^2 = p\text{-}CH_3O\text{-}C_6H_4\text{-}CH = CH\text{-CO-}$ $R^3 = CH_3\text{-CO-}$	*S. auriculata*	(Giner et al., 1991)
(27) **6-*O*-α–L-(3″-*O*-acetyl–2″-*trans*-*O*-cinnamoyl)-rhamnopyranosyl-catalpol (Scorodioside)**	$R^1 = C_6H_5\text{-}CH = CH\text{-CO-}$ $R^2 = CH_3\text{-CO-}$ $R^3 = H$	*S. scorodonia*	(Bermejo Benito et al., 2000)
(28) **6-*O*-α–L-(2″-*O*-acetyl–3″, 4″-di-*O*-*trans*-cinnamoyl)-rhamnopyranosyl-catalpol (Scropolioside B)**	$R^1 = CH_3\text{-CO-}$ $R^2 = R^3 = C_6H_5\text{-}CH = CH\text{-CO-}$	*S. scorodonia*	(Bermejo Benito et al., 2000)
(15) **6-*O*-α–L-(2″, 4″-di-*O*-acetyl-3″-*O*-*p*-methoxy-*trans*-cinnamoyl)-rhamnopyranosyl-catalpol (Scropolioside A)**	$R^1 = R^3 = CH_3\text{-CO-}$ $R^2 = CH_3O\text{-}C_6H_4\text{-}CH = CH\text{-CO-}$	*S. auriculata* *S.koelzii*	(Giner et al., 2000) (Garg et al., 1994)
(16) **6-*O*-α–L-(2″, 3″-di-*O*-acetyl-4″-*O*-*p*-methoxy-cinnamoyl)-rhamnopyranosyl-catalpol (Scrovalentinoside)**	$R_1 = R_3 = CH_3\text{-CO-}$ $R_2 = CH_3O\text{-}C_6H_4\text{-}CH = CH\text{-CO-}$	*S. auriculata*	(Giner et al., 2000)
(34) **6-*O*-α–L-(4″-*O*-acetyl–2″, 3″-di-*O*-cinnamoyl)-rhamnopyranosyl-catalpol (Koelzioside)**	$R^1 = R^2 = C_6H_5\text{-}CH = CH\text{-CO-}$ $R^3 = CH_3\text{-CO-}$	*S. koelzii*	(Garg et al., 1994) (Bhandari et al., 1992)
(35) **6-*O*-α–L-(3″-*O*-*p*-methoxcinnamoyl)-rhamnopyranosyl-catalpol**	$R^1 = R^2 = H$ $R^3 = p\text{-}CH_3O\text{-}C_6H_4\text{-}CH = CH\text{-CO-}$	*S. koelzii*	(Garg et al., 1991)

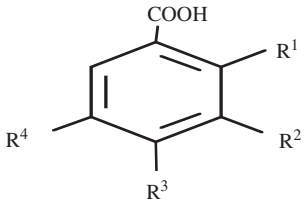
Figure 3. Structures and sources of compounds from *Scrophulania* ssp.

inflammation. In the topical model, the best antiinflammatory activity might be afforded by compounds related to benzoic acid derivates, compounds with methoxy group substitution at C-3 or C-5, or both. After topical administration, the compounds, especially syringic (**22**), protocatechuic (**21**) and ferulic (**19**) acids, showed good antiinflammatory activity. Their effect on leukocyte migration to the inflamed site might be an important aspect of their mechanism of action. It seems that the phenolic acids that are the active principles of some orally administered medicinal plants might merely



COMPOUND	R	SPECIES	REFERENCES
(17) *p*-coumaric	R^1 = CH = CHCOOH $R^2 = R^4$ = H R^3 = OH	*S. sambucifolia* *S. frutescens*	(Fernandez et al., 1996) (Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998) (Kim & Kim, 2000)
(18) Caffeic	R^1 = CH = CHCOOH $R^2 = R^3$ = OH R^4 = H	*S. buergeriana* *S. sambucifolia* *S. frutescens* *S. buergeriana*	(Fernandez et al., 1996) (Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998) (Kim & Kim, 2000)
(19) Ferulic	R^1 = CH = CHCOOH R^2 = OCH_3 R^3 = OH R^4 = H	*S. sambucifolia* *S. frutescens* *S. nodosa* *S. buergeriana*	(Fernandez et al., 1996) (Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998) (Paris & Moyse, 1976) (Schaunbenger & Paris, 1977) (Vigneau, 1985) (Swiatek, 1970) (Rombouts & Links, 1956) (Kim & Kim, 2000)
(22) Syringic	R^1 = CH = CHCOOH $R^2 = R^4$ = OCH_3 R^3 = *O*-glucose	*S. sambucifolia* *S. frutescens*	(Fernandez et al., 1996) (Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998)
(33) Methoxycinnamic	R^1 = CH = CHCOOH $R^2 = R^4$ = H R^3 = OCH_3	*S. ningpoensis* *S. oldhamii* *S. buergeriana*	(Miyazawa et al., 1998) (Won Sick Woo, 1963) (Kim & Kim, 2000)
(38) *Trans*-cinnamic	R^1 = CH = CHCOOH $R^2 = R^3 = R^4$ = H	*S. ningpoensis* *S. buergeriana*	(Miyazawa et al., 1998) (Kim & Kim, 2000)
(39) 3,4-dimethoxycinnamic	R^1 = CH = CHCOOH $R^2 = R^3$ = OCH_3 R^4 = H	*S. ningpoensis*	(Miyazawa et al., 1998)
(40) 4-hydroxy-3-methoxycinnamic	R^1 = CH = CHCOOH R^2 = OCH_3 R^3 = OH R^4 = H	*S. ningpoensis*	(Miyazawa et al., 1998)
(45) *p*-methoxycinnamic methylester	R^1 = CH = $CHCOOCH_3$ $R^2 = R^4$ = H R^3 = OCH_3	*S. buergeriana*	(Kim & Kim, 2000)

Figure 4. Structures and sources of compounds from *Scrophulania* ssp.



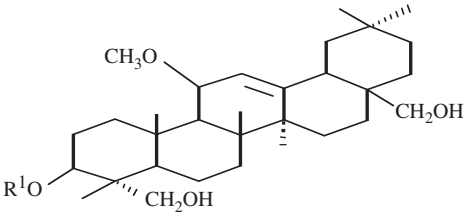
COMPOUND		R	SPECIES	REFERENCES
(20)	**Gentisic**	$R^1 = R_4 = OH$ $R^2 = R^3 = H$	*S. frutescens* *S. sambucifolia*	(Fernandez et al., 1996) (Fernandez et al., 1998) (Fernandez et al., 1996)
(21)	**Protocatechuic**	$R^1 = R_4 = H$ $R^2 = R^3 = OH$	*S. frutescens* *S. sambucifolia*	(Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998) (Fernandez et al., 1996)
(23)	**Isovanillic**	$R^1 = R_4 = H$ $R^2 = OCH_3$ $R^3 = OH$	*S. frutescens* *S. sambucifolia*	(Fernandez et al., 1996) (Fernandez et al., 1998) (Garcia et al., 1996) (Garcia et al., 1998) (Fernandez et al., 1996)
(31)	***p*-Hydroxybenzoic**	$R^1 = R^2 = R_4 = H$ $R^3 = OH$	*S. frutescens* *S. sambucifolia*	(Fernandez et al., 1996) (Fernandez et al., 1996)
(32)	**Vanillic**	$R^1 = R_4 = H$ $R^2 = OCH_3$ $R^3 = OH$	*S. frutescens* *S. sambucifolia*	(Fernandez et al., 1996) (Fernandez et al., 1996)

Figure 5. Structures and sources of compounds from *Scrophulania* ssp.

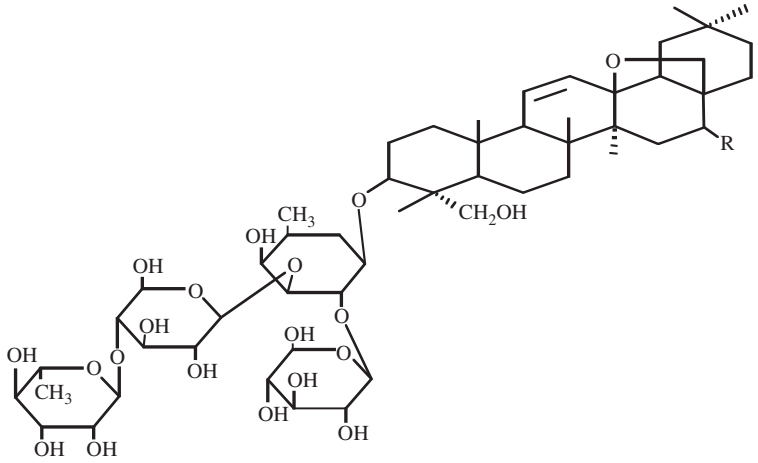
act synergistically with other active substances, for example, harpagoside (**2**), isolated from *S. frutescens*, might be another bioactive compound involved in its action (Fernández et al., 1998).

Buddlejasaponin I (**24**), a biologically active compound from *S. scorodonia* L., exerts potent *in vivo* antiinflammatory effects on mouse ear edema induced by phorbol myristate acetate (PMA). The screening for *in vitro* effects of this saikosaponin on cellular systems generating cyclooxygenase (COX) and lipoxygenase (LOX) metabolites showed a significant effect. These data support the inhibition of arachidonic acid metabolism as one of the biochemical mechanisms that might be the rationale for the putative antiphogistic activity of this saikosaponin (Bermejo Benito et al., 1998).

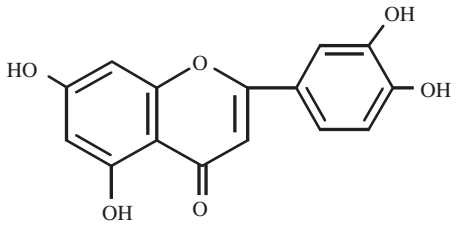
Seven iridoid glycosides isolated from different extracts of *S. scorodonia* L., namely bartsioside (**25**), aucuboside (**3**), harpagide (**1**), harpagoside (**2**), 8-*O*-acetylharpagide (**26**), scorodioside (**27**) and scropolioside B (**28**), have been evaluated for their *in vitro* antiinflammatory activity in cellular systems generating cyclooxygenase (COX) and lipoxygenase (LOX) metabolites (Bermejo Benito et al., 2000). Iridoids did not show a cytotoxic effect even at the higher concentration of 100 µM. Most compounds assayed did not exhibit any significant effect on prostaglandin E_2 (PGE_2) and leukotriene C_4 (LTC_4) released from calcium ionophore-stimulated mouse peritoneal macrophages. In the PGE_2-release assay, only harpagoside (**2**) and 8-*O*-acetyl-harpagide (**26**) showed an inhibition rate of 30–40%. In the LTC_4 assay, only aucuboside (**3**) showed a significant effect, with a IC_{50} value of 72 µM. Harpagoside (**2**) and harpagide (**1**) also inhibited release of LTC_4, but it was not a very significant effect. However, most iridoids assayed showed a significant effect on thromboxane B_2 (TXB_2) release from calcium ionophore-stimulated human platelets, with inhibition percentages slightly lower than the reference drug ibuprofen. Only harpagide (**1**), scorodioside (**27**) and scropolioside B (**28**) had no significant effect on TXB_2-release. These results indicated that selective inhibition of thromboxane synthase enzyme may be the primary target of action of most of these iridoids, and one of the mechanisms through which they exert their antiinflammatory effects. This result does not contradiction information in the literature, where some authors found negative results with *in vivo* models after oral administration (Lanhers et al., 1992) and other authors obtained positive results in topical processes (Recio et al., 1994). Further conclusions about iridoid structure-activity relationships are that substitutions with an additional moiety at C-8



COMPOUND	R	SPECIES	REFERENCE
(13) Verbascosaponin A	R_1 = Rha (1→4) Glc(1→3)[Glc(1→2)] Fuc	*S. auriculata*	(Giner et al., 2000)



COMPOUND	R	SPECIES	REFERENCES
(14) Verbascosaponin	R = H	*S. auriculata*	(Giner et al., 2000)
(24) Buddlejasaponin I	R = OH	*S. scorodonia*	(Emam et al., 1997) (Bermejo Benito et al., 1998)

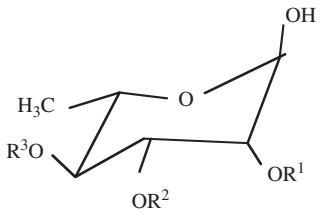


COMPOUND	SPECIES	REFERENCE
(36) 5,7,3′– trihydroxy-4′-flavone (tetrahydroxy-*m*-hydroxyflavone)	*S. grossheimi*	(Akhmedov et al., 1969)

Figure 6. Structures and sources of compounds from *Scrophulania* ssp.

is a positive chemical feature for thromboxane-synthase activity [8-*O*-acetylharpagide (**26**) and harpagoside (**2**) versus harpagide (**1**)]. The presence of a foreign moiety at C-6 is unfavourable, as is apparent when the activity of bartsioside (**25**) (iridoid with no hydroxyl substituents in the body of the molecule, and only active on thromboxane synthase) is compared with scorodioside (**27**) and scropolioside B (**28**), which are inactive.

S. nodosa has also been considered to possess antiinflammatory properties. From this species have been isolated aucuboside (**3**), catalpol (**29**), catalposide (**30**), ferulic acid (**19**) and ester derivatives of harpagide. These compounds could be responsible of the activity, together with other substances (Paris & Moyse, 1976; Schaunbenger & Paris, 1977; Vigneau, 1985). *S. oldhamii* has been used traditionally in medicine for the treatment of inflammation (Won Sick Woo, 1963).



COMPOUND	R	SPECIES	REFERENCES
(41) **Buergeriside A_1**	R^1 = CH_3-CO- R^2 = (E) *p*-CH_3O-C_6H_4-CH = CH-CO- R^3 = (E) *p*-CH_3O-C_6H_4-CH = CH-CO-	*S. buergeriana*	(Kim & Kim, 2000)
(42) **Buergeriside B_1**	R^1 = CH_3-CO- R^2 = (E) *p*-CH_3O-C_6H_4-CH = CH-CO- R^3 = OH-	*S. buergeriana*	(Kim & Kim, 2000)
(43) **Buergeriside B_3**	R^1 = CH_3-CO- R^2 = (Z) *p*-CH_3O-C_6H_4-CH = CH-CO- R^3 = OH-	*S. buergeriana*	(Kim & Kim, 2000)
(44) **Buergeriside C_1**	R^1 = OH- R^2 = OH- R^3 = (E) *p*-CH_3O-C_6H_4-CH = CH-CO-	*S. buergeriana*	(Kim & Kim, 2000)

Figure 7. Structures and sources of compounds from *Scrophulania* ssp.

Antibacterial

S. nodosa, *S. auriculata* and *S. canina* have been used since the Middle Ages as a remedy for scrophulas and several dermatoses (scabies, tumours) (Paris & Moyse, 1976). Also, different reports have suggested that the antiseptic properties of these species could be attributed to the presence of phenolic acids (Swiatek, 1970, 1973; Van Hellemont, 1986). At present, *S. nodosa* is considered by several authors to possess basteriostatic properties (Schaunbenger & Paris, 1977; Swiatek, 1970). The following glycosides have been isolated from this species: aucuboside (**3**), catalpol (**29**), catalposide (**30**), ferulic acid (**19**) and ester derivates of harpagide (**1**). The therapeutic properties of the Figwort, *S. nodosa*, probably depend of these constituents. For example, aucuboside (**3**) and ferulic acid (**19**) possess antibacterial properties (Rombouts & Links, 1956; Davini et al., 1986; Fernández et al., 1998).

The phenolic fractions of the aerial parts of *S. frutescens* and *S. sambucifolia* showed potent antibacterial activity (Fernández et al., 1996). However, *S. frutescens*, the species most rich in phenolic acids, demonstrated a more pronunced activity than *S. sambucifolia*. The phenolic fractions of both species showed more activity against Gram-positive bacteria, specifically against *Bacillus* sp. The higher concentration of the phenolic compounds detected in *S. frutescens* could explain the more potent activity of this species. These preliminary results suggest that the antibacterial activity of these species can be attributed to the presence of phenolic acids [ferulic (**19**), isovanillic (**23**), *p*-hydroxybenzoic (**31**), syringic (**22**), caffeic (**18**), gentisic (**20**), protocatechuic (**21**), *p*-coumaric (**17**) and vanillic (**32**) acids]. Therefore, these species could be considered as potentially antiseptic agents on bacteriologic infections, especially in processes where Gram-positive bacteria are involved (Fernández et al., 1996). Methoxycinnamic acid (**33**), isolated by EtOH extract from roots of *S. oldhamii*, showed good antipyretic action. Both *p*-methoxycinnamic (**33**) and the EtOH extract from *S. oldhamii* exhibited good antipyretic activity when tested on typhoid-vaccinated rabbits (Won Sick Woo, 1963).

Hepatoprotective

The alcoholic extract of the aerial parts of *S. koelzii* significantly protected against thioacetamide-induced hepatic damage (Garg et al., 1994). This extract was fractionated with different solvents (hexane, chloroform, butanol and water). Hepatoprotective activity was localized in the chloroform fraction from which four iridoid glycosides, namely, scropolioside A (**15**), koelzioside (**34**), harpagoside (**2**) and 6-*O*-α-L-(3″-*O*-*p*-methoxycinnamoyl)-rhamnopyranosyl-catalpol (**35**), were isolated. Among these, scropolioside A (**15**) showed the greatest hepatoprotective activity. The activity of this compound was comparable to that of silymarin, a clinically used hepatoprotective drug. The important observation, however, is that the greatest protection was achieved with the alcoholic extract only. Hence, it is likely that the hepatoprotective activity of *S. koelzii* may not be due to any single constituent. Rather, there may be

certain other constituents acting synergistically for a better activity profile.

Ferulic acid (**19**), isolated from *S. nodosa*, has been shown to possess cholagogue properties (Swiatek, 1970) and the flavonoid fractions of *S. grossheimi* showed weak but positive cholagogue activity (Akhmedov et al., 1969).

Immunomodulating

Scropolioside A (**15**), koelzioside (**34**), harpagoside (**2**) and 6-*O*-α-L-(3″-*O*-*p*-methoxycinnamoyl)-rhamnopyranosylcatalpol (**35**), were isolated from the chloroform soluble fraction of an alcoholic extract of the aerial parts of *S. koelzii*. This fraction was shown to have immunomodulating activity (Garg et al., 1994). Therefore, an immunostimulant response was observed with all the four iridoids. Maximum induction of immune response with respect to all the parameters studied (macrophage migration index, haemagglutinating antibody titre and plaque forming cell) was observed with harpagoside (**2**) and 6-*O*-α-L-(3″-*O*-*p*-methoxy-cinnamoyl)-rhamnopyranosylcatalpol (**34**) when administered intraperitoneally. The immunostimulant activity observed with pure glycosides was of nearly equal intensity and suggests that the catalpol nucleus of the iridoid is responsible for this activity. The hepatoprotective activity and immunostimulant activity of these four iridoids seem to be complimentary.

Some of the catalpol glycosides are reported to show immunostimulant activity (Pandey & Das, 1988) and these compounds are present in a number of species from the *Scrophularia* genus (Bhandari et al., 1992, 1997; Calis et al., 1993; De Santos et al., 1998; Giner et al., 1998; Zhang et al., 1992).

Cardiovascular

In sedated rabbits, cats and dogs, an infusion of *S. nodosa* considerably reduced arterial pressure, stimulated respiration, caused bradycardia, lengthened the PQ segment (interval between auricle and ventricle contraction) and changed the configuration of the T wave (representing repolarization of the ventricles) of the electrocardiogram. *S. nodosa* increased the amplitude and slowed down the frequency of contractions of an isolated frog heart. This activity of *S. nodosa* apparently could be due to the saponins present in the plant extract (Karimova et al., 1966). However, the dependence of the cardiovascular activity on these compounds is still obscure.

Small doses of an extract from *S. grossheimi* showed hypotensive activity and increased capillary tonicity. Different flavonoid aglycones, mainly 5,7,3′-trihydroxy-4′-flavone (**36**) and its derivates (tetrahydroxy-*m*-hydroxyflavones), have been isolated from this species (Akhmedov et al., 1969).

Some authors (Kajimoto et al., 1989; Ody, 1993) have attributed hypotensive activity to the aqueous extract of *S. ningpoensis*. However, pharmacological investigations are necessary for assessing the potential as a hypotensive agent.

Diuretic

S. nodosa and *S. grossheimi* have been used in traditional medicine as diuretic agents (Akhmedov et al., 1969; Schaunbenger & Paris, 1977). The aqueous extract and the ash from the aerial parts of *S. frutescens* and *S. sambucifolia* subsp. *sambucifolia* have also shown pronounced diuretic activity. The increase in urine volume was more significant with *S. frutescens* than with *S. sambucifolia*. Flavonoids and saponins, which are present in the extract tested, were suggested as being responsibles for the activity (Fernández Arche et al., 1993).

Protozoocidal, fungicidal and molluscicidal

The methanol extract from flowers of *S. scorodonia* revealed protozoocidal activity against *Trichomonas vaginalis* (LC_{100} = 100 µg/ml) and *Leishmania infantum* (LC_{100} = 250 µg/ml) (Martín et al., 1998). From this extract, a saikosaponin, buddlejasaponin I (**24**), has been isolated. The biological activity of this saikosaponin was evaluated *in vitro* as a protozoocidal agent against *Trichomonas vaginalis* and *Leishmania infantum*, as a molluscicidal agent against *Biomphalaria alexandrina* snails, and as a fungicidal agent against nine yeast strains. The results showed that the saponin killed 100% of the snails at 10 µg/ml within 24 h, whereas the LC_{100} values against *Trichomonas*, *Leishmania* and the nine yeast strains were 20, 40, and 100 µg/ml, respectively (Emam et al., 1997).

Antitumour, cytotoxic and cytostatic

Several phenylpropanoid glycosides were found to show antitumour activity. Angoroside A (**9**) isolated from *S. scopolii* showed cytotoxic and cytostatic activities, but the methylated derivates [angoroside B (**37**) and C (**10**)] isolated from the same species did not show any cytotoxic activity at 1–200 µg/ml concentrations against cancer cell lines.

Angoroside A (**9**) (1–50 µg/ml) exhibited cytostatic activity against HeLa cells (human epithelial carcinoma) and also showed slight cytotoxic activity at higher concentrations (>50 µg/ml) against HeLa cells. Angoroside A (**9**) exhibited cytostatic activity against S-180 cells (sarcoma) at 1–40 µg/ml concentrations. This compound, at a concentration of 12.7 µg/ml, showed cytostatic activity against P-388/D1 cells (mouse lymphoid neoplasma). By contrast, when angoroside A (**9**) was used at 119 µg/ml, it showed cytotoxic activity (biphasic effect). Phenylpropanoid glycosides did not show any cytotoxic effects against primary-cultures of rat hepatocytes. Against dRLh-84 cells (rat hepatoma), angoroside A (**9**) exhibited significant cytotoxic activity. As a result, the cytotoxic and cytostatic activies of phenylpropanoid glycosides were found to be mainly dependent on the *ortho*-dihydroxy aromatic systems in their structures. Methylation of at least one of the phenolic hydroxyl groups abolished the activity which may explain why the methylether derivatives,

angorosides B (**37**) and C (**10**), completely lost their activities (Saracoglu et al., 1997). The mechanism by which phenylpropanoid glycosides exhibit these activities is under investigation.

Seven phenolic acids: *p*-coumaric (**17**), caffeic (**18**), ferulic (**19**), gentisic (**20**), protocatechuic (**21**), syringic (**22**), and isovanillic (**23**) acids, isolated from *S. frutescens*, have been tested on two cell lines: Hep-2 and McCoy (derived from the synovial fluid in the knee joint of a patient suffering from degenerative arthritis) (García et al., 1998). All the compounds tested showed higher activity against Hep-2 and McCoy cells. Since the phenolic acids of the cinnamic group demonstrated an ID_{50} value below those recommended by protocols of the National Cancer Institute of U.S.A. (for natural products, 6 µg/ml for first stage and 4 µg/ml for the second stage), this could be interesting for further investigations.

However, the data obtained with the phenolic acid of the benzoic group showed the ID_{50} for these samples were higher than those recommended by the National Cancer Institute, except for syringic acid (**22**) (ID_{50} = 3.87 ± 0.34) and isovanillic acid (**23**) (ID_{50} = 5.25 ± 0.70) against McCoy cells. The results are in accord with the popular uses of different species of the *Scrophularia* genus, traditionally used in scrophulas, and indicate that some of the phenolic acids assayed may be promising for the therapy malignant skin inflammatory affections. Related to this application, these authors demonstrated previously the antiseptic and antiinflammatory effects of the phenolic acids isolated from *S. frutescens* (García et al., 1996; Fernández et al., 1998).

On the other hand, the methanol extract from *S. ningpoensis* showed antimutagenic activity. *Trans*-cinnamic acid (**38**), *p*-methoxycinnamic acid (**33**), 3,4-dimethoxycinnamic acid (**39**) and 4-hidroxy-3-methoxycinnamic acid (**40**), isolated from this extract, exhibited the same activity, especially *trans*-cinnamic acid (**38**). Methyl esters of these compounds showed greater suppressive potency against all mutagens assayed, especially the methyl ester of *p*-methoxycinnamic acid (**33**) (Miyazawa et al., 1998).

S. ningpoensis is present in a formula officially used for bronchopulmonary cancers. No mention for any anticancer activity *in vitro* or *in vivo* has been found until now for this species. According to Chinese medicine, bronchopulmonary cancer could be due to a fluid or mucous concentration in lungs. This could be the reason why *S. ningpoensis* (considered as expectorant) is included in this formula. Clinical research work should be necessary to support the justification of traditional medicine theories, the possible complementary contribution of which could be very useful for modern occidental therapy in this difficult field (Pinkas et al., 1994). *S. ningpoensis* has also been shown to alleviate the adverse effects of high-dose methotrexate plus vincristine which is utilized in chemoterapy of postoperative osteogenic sarcoma (Liu & Wu, 1993). *S. nodosa* has been used as a folk medicine for cancer (Pauli et al., 1995).

Neuroprotective

A chloroform-methanol extract from the roots of *S. buergeriana* Miq. exhibited significant neuroprotective activity against glutamate-induced neurotoxicity (Kim & Kim, 2000). Ten phenylpropanoids [buergerisides A_1 (**41**), B_1 (**42**), B_2 (**43**), C_1 (**44**) and cinnamic (**38**), *p*-methoxycinnamic (**33**), *p*-methoxycinnamic methyl ester (**45**), *p*-coumaric (**17**), caffeic (**18**) and ferulic acids (**19**)] isolated from this species may exert significant protective effects against glutamate-induced neurodegeneration in primary cultures of cortical neurons. At concentrations of 0.1–10.0 µM, compounds **41**–**44** blocked the release of lactate dehydrogenase (LDH) from glutamate-insulted primary cultures of rat corticals cells significantly and also preserved the cell survival rate. At higher concentrations (above 10 µM), these compounds showed no improvement in the cell survival rate due to inherent cytotoxicity. Compounds **17**–**19**, **33**, **38**, **45** also reduced the release of LDH and showed some improvement in the cell survival rate in a dose-dependent manner. On the basis of these results, phenylpropanoids bearing a cinnamoyl moiety exerted significant neuroprotective effects on primary cultures of rat cortical cells injured by glutamate.

Antipruritic

In a search for new antipruritic drugs, some authors (Tohda et al., 2000) screened a methanol extract from the roots of *S. ningpoensis* using substance P (SP) as a pruritogen in mice. This extract inhibited SP-induced scratching response in mice and showed clear dose-dependent inhibition of the scratching. The methanol extract did not inhibit locomotor activity at 200 mg/kg, a dose which was effective against SP-induced scratching. Therefore, the scratch-inhibition action of this extract may be due to inhibition of the itching sensation and/or scratching reflex, rather than to sedation or depression of general functions of the central nervous system.

Miscellaneous

The chloroform fraction of the alcoholic extract of the whole plant of *S. koelzii* showed significant CNS depressant activity. From this active fraction, koelzioside (**34**) (triacylrhamnopyranosyl catalpol derivate) has been isolated (Bhandari et al., 1992). However, investigations are needed for the pharmaceutical potential of this product.

Infusions of *S. nodosa* injected in mice inhibited locomotor activity and prolonged sleep caused by hexenal. This infusion dilated capillary of an isolated rabbit ear and decreased tone of an isolated rabbit or cat intestine (Karimova et al., 1966).

Discussion

Undoubtedly, the plant Kingdom still holds many species of plants containing substances of medicinal value which have

yet to be discovered; large numbers of plants are constantly being screened for their possible pharmacological value. Some of these plants belong to the *Scrophularia* genus. This genus may prove to be a richer source of compounds with possible pharmacological values, but more pharmacological investigations are neccesary.

However, most of the reported biological studies of *Scrophularia* constituents and extracts were carried out *in vitro*, although bioactive iridoids found in *Scrophularia* can often lead to a multiplicity of compounds after *in vivo* administration. For this reason more biological and chemical attention is needed.

Acknowledgements

This work was supported by: Acciones Integradas España-Francia (Rf.HF-211 & 98B) M.E.C. (Ministerio de Educación y Cultura); Ministerio de Sanidad (FISS Rf. 94/1671); C.A.M. (Comunidad Autonoma de Madrid Rf. C101/91); U.A.H. (Ref. EO01/99); A Grant from Consejería de Educación y Cultura de Madrid, Comunidad Autónoma de Madrid (Conv. 98).

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