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Review

Phytochemical profile and biological activities of the genus *Ornithogalum* L. (Hyacinthaceae)

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Summary. This review summarizes literature published from 1954-2013 on the characterization and biological activities of isolated compounds or crude extracts from thirteen different plants of the genus *Ornithogalum* L. (Hyacinthaceae, Asparagales). Mechanisms of action and structure activity relationships are briefly discussed.

Keywords: biological activity, cardenolides, cholestane glycosides, *Ornithogalum*, polysaccharides, spirostane glycosides.

INTRODUCTION

The genus *Ornithogalum* L. (Hyacinthaceae, Asparagales) comprises approximately 200 species, distributed among the temperate climate zones of Europe, Africa and southwest Asia (Zahariadi 1966; Obermeyer 1978; Landstrom 1989). A few species from the genus are cultivated for ornamental purposes: *Ornithogalum umbellatum*, *O. pyramidale*, and *O. nutans* are grown as garden plants, while *O. saundersiae* and *O. thyrsoides* are used as cut flowers (Kubitzki and Huber 1998). Many plants from this genus are used by traditional healers for various medicinal purposes, while several species have been implicated in livestock poisoning (Watt and Breyer-Brandwijk 1932; Botha et al. 2000). Such observations served as impetus for scientific investigations into the chemical composition and possible biological activities of compounds isolated from these plants.

Early work on the genus began in the 1950s, on the *O. umbellatum* European species introduced in North America (Waud 1954; Vogelsang 1955), while later work included species from Africa and Asia (Kubo et al. 1992a, 1992c; Shi et al. 2003). The classes of isolated chemical compounds are strongly linked to the geographic origins of the source plant species (Littlejohn 2007). For example, European taxa contain primarily cardenolides, while African taxa contain cholestane and spirostane glycosides. In addition, some flavonoids, sterols and homoisoflavanones have been isolated from plants originating from all of the regions studied.

Studies conducted on isolated compounds and/or crude extracts of *Ornithogalum* species revealed a wide range of biological activities. Recent studies focused on isolated compounds which display significant cytotoxic activities against cultured tumor cells and have anticancer potential. In addition to medicinal significance, phytochemical studies also provided data which helped clarify systematic classifications of the genus *Ornithogalum* (Pfosser and Speta 1999; Goldblatt and Manning 2011; Martinez-Azorin et al. 2011).

In this review, we analyze the phytochemical profiles of 13 species of the genus *Ornithogalum* (Table 1): biological activities associated with crude extracts and isolated compounds from these plants will also be discussed.

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Table 1. Origin of *Ornithogalum* spp. and their main secondary metabolites.

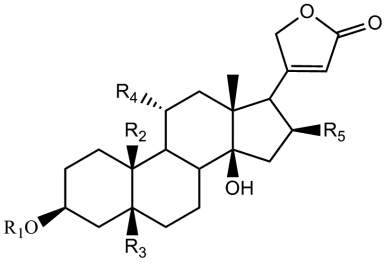
Species	Origin	Secondary metabolites	References
O. umbellatum L.	Canada	Cardenolides (compounds **1**-**15**)	Mrozik et al. 1959; Smith and Paterson 1967; Ferth and Kopp 1992
O. magnum Krasch et Schischk	Caucasia and eastern Trans-Caucasia	Cardenolides (compounds **3**, **4**, **21**-**23**)	Komissarenko 1965, 1969, 1971, 1972
O. gussonei Ten.	Mount Kinzhal (Russia)	Cardenolides (compounds **3**, **21**, **24**)	Komissarenko and Krivenchuk 1974
O. boucheanum Aschers.	Central Europe (Austria)	Cardenolides (compounds **27**-**34**)	Ghannamy et al. 1987
O. nutans L. (2n = 28)	Central Europe (Austria)	Cardenolides (compounds **29**, **32**, **33**, **35**-**48**)	Ferth et al. 1992b
O. nutans L. (2n = 30)	Central Europe (Austria)	Cardenolides (**49**-**59**)	Ferth et al. 1992a
O. procerum Stapf.	Iran	Oxygenated hydrocarbons (aerial parts), polysterol-type compounds (bulbs)	Delazar et al. 2009
O. cuspidatum Bertol.	Iran	Saturated hydrocarbons (flowers and bulbs), oxygenated hydrocarbons (leaves)	Nafizi et al. 2010
O. sintenisii Freyn	Iran	Phenols and flavonoids	Ebrahimzadeh et al. 2010
O. alpigenum Stapf.	Turkey	-	Makasci et al. 2010
O. thyrsoides Jack.	Japan	Cholestane bisdesmosides (compaunds **60**-**63**)	Kubo et al. 1992a
		Cholestane glycosides (compounds **64**-**75, 80**-**86**)	Kuroda et al. 2002b; Kuroda et al. 2004
		Spirostanol saponins (compounds **76**-**79**)	Kuroda et al. 2004
		Polyoxygenated steroidal glycosides (compounds **88**-**91**)	Kuroda et al. 2006
O. saundersiae Baker	Japan	Acylated cholestane glycosides (**92**-**94**, **111**-**119**)	Kubo et al. 1992c, 1999b
		Polyhydroxylated cholestane glycosides (**95**-**99**)	Kubo et al. 1992b
		Bisdesmoside (**102**)	Mimaki et al. 1996b
		Rearranged cholestane glycosides (**100**-**101**, **103**-**110**)	Mimaki et al. 1996c
O. caudatum Aiton.	China	Stigmastane derivates	Tang et al. 2001
		Water-soluble polysaccharide	Shi et al. 2003

DISCUSSION

Investigations of the European species of *Ornithogalum* were initially focused on *O. umbellatum* (common Star of Bethlehem, snowdrop), a native Mediterranean plant. The bulbs of this plant are toxic due to the presence of cardenolides (Quattrocchi 2012). An extensive investigation into the effects of local plant extracts on the heart revealed digitalis-like activity in alcohol extracts of *O. umbellatum* bulbs. Positive inotropic action, decreased conduction, and eventually systolic standstill were demonstrated using isolated and intact frog heart, as well as intact cat heart (Waud 1954). However, in a clinical trial substituting *O. umbellatum* extract tablets for digitalis, digitalization was lost, while heart rate, fluid retention and dyspnoea were increased. It was concluded that there are differences in absorption efficiency between oral and direct drug administration; in an attempt to circumvent this problem, the tablets were coated with salol (phenyl salicilate) to protect them from gastric acid. Consequently, digitalis-like activity was retained but at only half of the expected strength, which led to the conclusion that only half of the active components were being properly absorbed. However, in comparison with digitoxin, the drug displayed less slowing effects on heart rate, increased diuretic effects, increased cardiac contraction strength and less gastrointestinal nausea (Vogelsang 1955). The main active components, convallatoxin **1** and convalloside **2**, were isolated from the bulbs of *O. umbellatum* (Mrozik et al. 1959). *In vitro* cytotoxicity studies on convallatoxin found an IC_{50} of 0.002 μg ml^{-1}, when assayed against Eagle's KB strain of human epidermoid carcinoma cells (Kelly et al. 1965). In addition, two cardenolides containing sarmentogenin as the aglycone moiety were isolated. One was a rhamnoside, while the other was the corresponding rhamnoside-glucoside. Further identifica-

tion of the monoglycoside as rhodexin A **3**, was confirmed by comparison with an authentic sample. The diglycoside, an apparently new compound composed of sarmentogenin-rhamnose-glucose, was designated rhodexoside **4** (Smith and Paterson 1967). Further investigation of the bulbs and leaves of *O. umbellatum* afforded strophalloside **5**, convallatoxol **6**, lokundjoside **7**, tholloside **8** and seven new cardenolide glycosides **9**-**15**. In addition, β-D-Ribose and 3-acetyldigitoxose were for the first time found as sugar moieties in the genus *Ornithogalum* (Ferth and Kopp 1992). The structures of cardenolide compounds **1**-**15** are presented in Fig. 1.

Further investigations of plant bulb extracts resulted



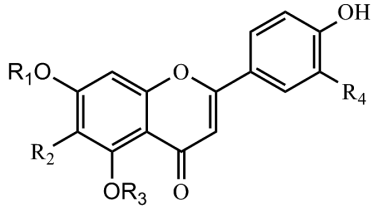
	R_1	R_2	R_3	R_4	R_5
1	α-L-rhamnopyranoside	CHO	OH	H	H
2	α-L-rhamnopyranosyl-β-D-glucopyranoside	CHO	OH	H	H
3	α-L-rhamnopyranoside	CH_3	H	OH	H
4	α-L-rhamnopyranosyl-β-D-glucopyranoside	CH_3	H	OH	H
5	6-deoxy-β-D-allopyranoside	CHO	OH	H	H
6	α-L-rhamnopyranoside	CH_2OH	H	H	H
7	α-L-rhamnopyranoside	CH_3	OH	OH	H
8	α-L-rhamnopyranoside	CHO	OH	OH	H
9	3-acetyl-β-D-digitoxopyranosyl-β-D-glucopyranosyl-α-L-rhamnopyranoside	CHO	OH	H	H
10	β-D-quinovopiranosyl-β-D-glucopyranoside	CH_3	H	OH	H
11	β-D-quinovopiranoside	CH_3	H	OH	H
12	6-deoxy-β-D-allopyranoside	CH_3	H	OH	H
13	β-D-allopyranoside	CH_3	H	OH	H
14	β-D-ribopyranoside	CH_3	OH	OH	H
15	β-D-allopyranoside	CHO	OH	H	H
21	α-L-rhamnopyranoside	CH_3	H	H	OH
22	α-L-arabinopyranoside	CH_3	H	OH	H
24	H	CH_3	H	OH	H
27	6'-deoxy-β-D-allopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside	CH_3	H	OH	H
28	6'-deoxy-β-D-allopyranosyl-4'-β-D-xylopyranosyl-α-L-rhamnopyranoside	CH_3	H	OH	H
30	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside	CH_3	H	OH	H
32	α-L-rhamnopyranosyl-4'-β-D-apiofuranoside	CH_3	H	OH	H
34	6-deoxy-β-D-allopyranosyl-4'-β-D-xylopyranoside	CH_3	H	H	H
44	6'-deoxy-β-D-allopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside	CHO	OH	H	H
45	α-L-rhamnopyranosyl-4'-β-D-apiofuranoside	CH_3	H	OH	OH
46	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-3''-β-D-apiofuranoside	CH_3	H	H	OAc
47	2'-deoxy-β-d-allopyranosyl-4'-β-xylopyranosyl-3''-β-apiofuranoside	CH_3	H	H	OAc
49	β-D-quinovopiranoside	CHO	OH	H	H
50	α-L-rhamnopyranosyl-4'-α-L-rhamnopyranoside	CH_3	H	OH	H
51	β-D-digitoxopyranosyl-4'-β-D-glucopyranoside	CHO	OH	H	H
52	β-D-quinovopyranoside	CHO	OH	OH	H
53	α-L-rhamnopyranosyl-4'-α-L-rhamnopyranoside	CH_3	H	OH	H
54	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	CH_3	H	OH	H
55	β-D-glucopyranoside	CH_3	OH	OH	H

Fig. 1. Cardenolide glycosides from the genus *Ornithogalum*. –A.

in the isolation and identifcation of two flavonoids, **16** and **17** (Gasic et al. 1989), while four flavonoids **16-19** (Fig. 2) were isolated from the leaves (Azzioui et al. 1989; Gasic et al. 1989). Later phytochemical examination of *O. umbellatum* bulbs led to the isolation of a new steroidal stigmastane glycoside compound, whose structure was determined to be 3-O-[2'-methoxy-4'-(2-pentenal)] phenylsitosterol **20** (Fig. 3), by spectroscopic and chemical evidence (Sabudak and Oyman 2002). Colonization of the roots of *O. umbellatum* by the arbuscular mycorrhizal fungus *Glomus intraradices* N.C. Schenck & G.S. Sm. induced the accumulation of different types of apocarotenoids (Schliemann et al. 2006).

Rhodexin A **3**, rhodexin B **21** (Fig. 1) and rhodexoside **4,** as well as two new cardenolides designated as ornithogaloside **22** (Fig. 1) and ornithogalin **23** (Fig. 4), were isolated from seedpods and seeds of *O. magnum*, (Komissarenko 1965, 1969, 1971, 1972). In addition, the aglycone sarmentogenin **24**, the monosides rohodexin A **3**, and rohodexin B **21** were found in the flowers and bulbs of *O. gussonei* (Kommisarenko and Krivenchuk 1974). The aerial part of *O. gussonei* yielded two flavonoids (Fig 2), saponaretin **25** and saponarin **26** (Bandyukova 1979). However, these results for *O. gussonei* should be considered with caution, since this species has a strictly Mediterranean areal, and plant material was likely misidentified: several species of *Ornithogalum s. str.* could be hidden under this name.

In further investigations of cardenolide complexes in *Ornithogalum* spp., three species from Central Europe were studied: *O. boucheanum, O. nutans* (2n = 28) and *O. nutans* (2n = 30). Eight new cardenolides **27**-**34** (Fig. 1, 4) were isolated and identified from the leaves and bulbs of *O. boucheanum*. For the first time, the occurrence of 15β,16α-



	R_1	R_2	R_3	R_4
16	H	H	H	H
17	H	H	H	OH
18	H	β-D-glucopiranoside	H	H
19	β-D-glucopiranoside	β-D-glucopiranosyl-β-D-glucopiranoside	H	H
25	H	β-D-glucopiranoside	H	H
26	H	OH	β-D-glucopiranoside	H

Fig. 2. Flavonoids from the genus *Ornithogalum*.

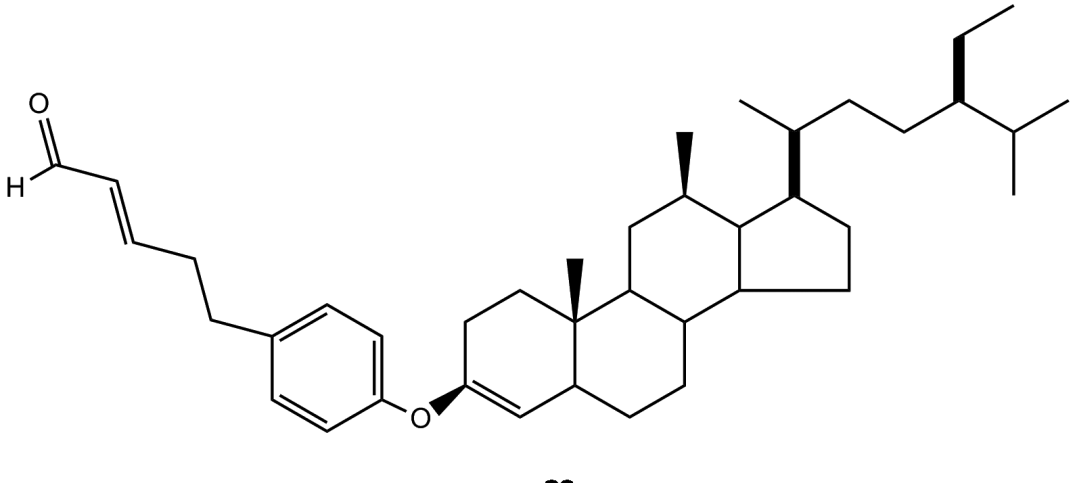
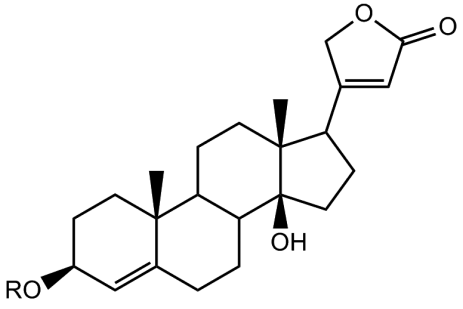
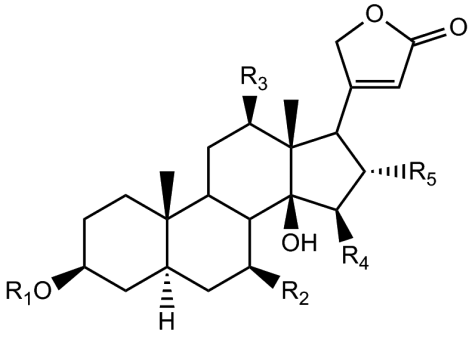


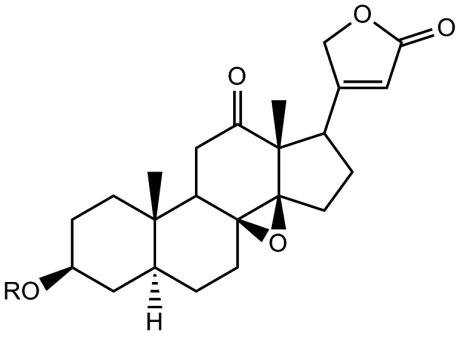
Fig. 3. Phenylsitosterol from the bulbs of *Ornithogalum umbellatum*.



23 **R** = β-D-glucopyranoside

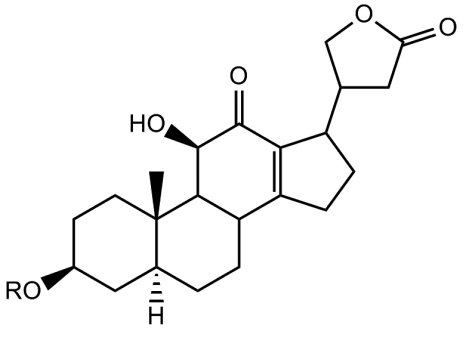


	R_1	R_2	R_3	R_4	R_5
29	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	H	H	OH	OH
31	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	H	OH	H	H
33	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	H	H	H	H
35	β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	OH	H	OH	OH
59	3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside	H	OH	H	H



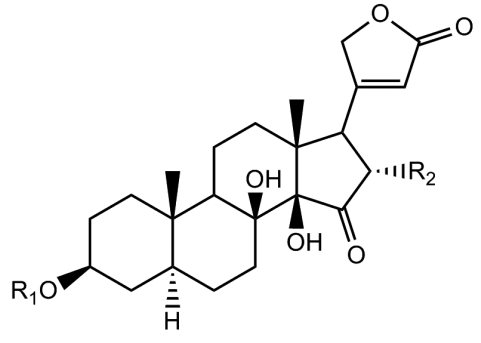
36 **R** = 3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside

58 **R** = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside



42 **R** = 3'-O-acetyl-β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside

43 **R** = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside



	R_1	R_2
37	β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside	OH
38	3'-O-β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside	OH
39	β-D-digitoxopyranosyl-β-D-xylopyranosyl-β-D-apiofuranoside	H
40	3'-O-β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside	H
41	β-D-digitoxopyranosyl-β-D-xylopyranosyl-α-L-rhamnopyranoside	H

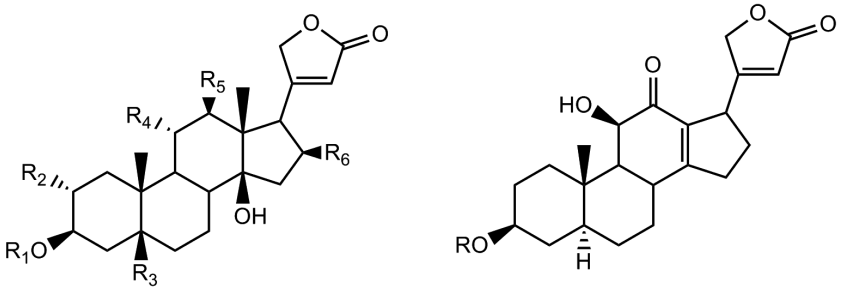
Fig. 4. Cardenolide glycosides from the genus *Ornithogalum*. –B.

dihydroxyuzarigenin was reported. Additionally, the presence of three genins–syriogenin, uzarigenin, and digitoxigenin–in the genus *Ornithogalum* was described for the first time. Interestingly, three different monosaccharides in one glycoside were found among the identified cardiac glycosides (unusual at the time), as well as an apiose monosaccharide (Ghannamy et al. 1987).

From the leaves and bulbs of *O. nutans* (2n = 28) seventeen cardenolides were isolated. Three isolated cardenolides (**29**, **32**, **33**) were identified by comparison with authentic samples of cardenolides previously isolated from *O. boucheanum*, while structure elucidation for the other fourteen **35**-**48** (Fig. 1, 4, 5) was performed by spectroscopy. Glycosides 7β,15β,16α-trihydroxy-uzarigenin, 8β,16α-dihydroxy,15-oxo-uzarigenin, 3β,11β-dihydroxy,12-oxo,18-nor-5α-card-13-enolid, 11α-hydroxygitoxigenin, 12-oxo,8β,14β-epoxy-uzarigenin, 8β-hydroxy,l5-oxo-uzarigenin and 12β-hydroxy-oleandrigenin were described for the first time, as well as the presence of oleandrigenin-glycosides in the genus *Ornithogalum*. The natural occurrence of two aglycones with a saturated lactone ring was surprising, since previously such substances were only obtained by catalytic hydrogenation of cardenolides (Ferth et al. 1992a).

Another study on the bulbs of *O. nutans* (2n = 30) isolated nineteen cardenolides in total (Ferth et al. 1992b). Thirteen substances were structurally elucidated by ^{1}H, ^{13}C NMR spectroscopy and FAB-MS, coupled with sugar moiety identification by GLC following cardenolide acid hydrolysis. Six of these glycosides were identified by co-chromatography (HPLC and TLC) with authentic samples. Investigation of the bulbs of *O. nutans* L. (2n = 30) resulted in the isolation of 11 additional new cardenolide glycosides **49**-**59** (Fig. 1, 4, 5). The authors of this study concluded that although these three species are only slightly different morphologically, differences in cardenolide patterns are substantial, and could thus be used for systematic classification of the genus *Ornithogalum*.

Some Iranian *Ornithogalum* species were also investigated. The aerial parts of *O. procerum* (common Persian name: 'Shir-morghe dayhimi') and *O. cuspidatum* are used in Iran as food additives and in traditional medicine to sooth throat and bronchial irritation associated with dry coughs. The composition of essential oil extracts from the aerial parts, n-hexane bulb extracts and hydrolysed methanolic bulb extracts of *O. procerum* were investigated by GS-MS analyses. A total of 20 compounds were identified from essential oil extracts of aerial plant parts, consisting of mainly oxygenated hydrocarbons. Seven hydrocarbons were obtained from n-hexane bulb extracts, where hexatriacontane and dioctadecyloxypropane were the most abundant components. Analysis of hydrolyzed methanolic extracts of *O. procerum* bulbs revealed the presence of four polysterol-type compounds (Delazar et al. 2009). The essential oil composition of the leaves, flowers and bulbs of *O. cuspidatum* was also determined by GC-MS: the flowers and bulbs contained primarily saturated hydrocarbons, while the leaves contained oxygenated hydrocarbon compounds. In addition, essential oils from flower parts contained oxygenated terpenoid compounds (Nafizi et al. 2010). Methanolic extracts of *O. cuspidatum* bulbs revealed a moderate level of free radical scavenging activity, mainly attributed to phenolics compounds. In the same study it was established that *O. cuspidatum* bulbs are a rich source of phytosterols, where the most abundant steroids are β-sitosterol, campesterol and stigmaterol (Delazar et al. 2010). Interestingly, phytosterols possess cholesterol-lowering properties (Ostlund et al. 2002) and products enriched with phytosterols have been shown to have protective effects against the development of atherosclerosis (Brufau et al. 2008). Thus, Delazar et al. (2010) sug-



48 R_1 = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-β-D-apiofuranoside
$R_2 = R_3 = R_4$ = H, R_5 = OH, R_6 = OAc

56 R_1 = 2-deosoxy-β-D-allopyranoside
$R_2 = R_3 = R_4$ = OH, $R_5 = R_6$ = H

57 R = β-D-digitoxopyranosyl-4'-β-D-xylopyranosyl-4''-α-L-rhamnopyranoside

Fig. 5. Cardenolide glycosides from the genus *Ornithogalum.* –C.

gested that *O. cuspidatum* bulbs might be used as additives in the formulation of food supplements.

Antioxidant properties were also revealed in the bulbs and aerial parts of another Iranian species, *O. sintenisii*, using a set of *in vitro* antioxidant assays. Extracts of the aerial parts of this plant showed higher DPPH-scavenging activity than bulb extracts, probably due to higher total phenol and flavonoid content (IC_{50} for DPPH radical scavenging activity was 368 and 669 μg $ml^{-1}$for leaves and bulbs, respectively). Extracts from aerial parts also showed moderate nitric oxide-scavenging activity (Ebrahimzadeh et al. 2010).

Ornithogalum alpigenum is a species endemic to Turkey, whose extracts are traditionally used for treatment of alopecia associated with microbial infections. Extracts from the leaves and bulbs of *O. alpigenum* were tested for antimicrobial, antioxidant and free radical scavenging activity. Bulb extracts (methanol, ethanol, acetone and benzene) displayed better activity vs. *Candida albicans* (C.P Robin) Berkhout, *Bacillus subtilis* (Ehrenberg) Cohn *nom. approb.* and *B. cereus* Frankland & Frankland *nom. approb.*, than leaf extracts. Total antioxidant activity was determined using β–carotene–linoleic acid as a model system and the highest antioxidant activity (88.12% ± 0.9%) was found in methanol bulb extracts. Leaf extracts were found to be good free radical scavengers (90.9%) (Makasci et al. 2010).

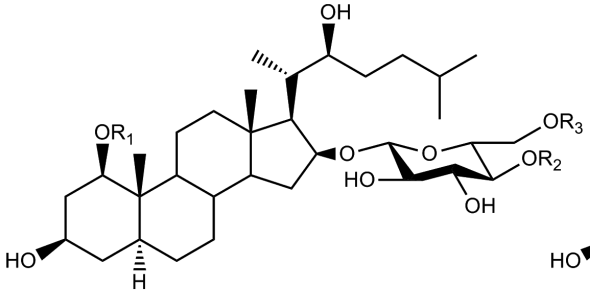
Several investigated species of *Ornithogalum* are indigenous to South Africa, and are cultivated for the cut-flower market. Some of these are highly toxic (*O. thyrsoides, O. saundersiae, O. prasinum, O. toxicarium*) and frequently associated with poisoning small live stock (Botha et al. 2000). Although most *Ornithogalum* plants are not traditionally used in folk medicine, *O. caudatum* is known in Chinese medicine to exhibit anticancer, antimicrobial, and anti-inflammatory activities, and has been used for the treatment of hepatitis, parotitis, and some tumor types in northern China. It should be noted that, South African species have a different phytochemical composition than European species: they are devoid of cardenolide glycosides and contain cholestane, stigmastane and spirostane glycoside types.

From fresh *O. thyrsoides* bulbs (common name African wonder flower, Cape lily) four new cholestane bisdesmosides **60**-**63** (Fig. 6) were isolated and structurally characterized by spectroscopic and chemical analysis. An advanced Mosher's method was applied to determine the C-22 absolute configuration. Compound **60** showed inhibitory activity on cyclic AMP phosphodiesterase (IC_{50} = 15.3 x 10^{-5} M) (Kubo et al. 1992a). In further studies methanolic bulb extracts of *O. thyrsoides* exhibited potent cytotoxic activity against HL-60 cells (IC_{50} = 0.79 mg ml^{-1}). This result led to the isolation of 12 cholestane glycosides **64**-**75** (Fig. 7), including nine novel compounds **64**-**72**. The 3-*O*-monoglucosides with an aromatic acyl group at the C-16 diglycoside moiety (**64**, **75**) were found to be extremely cytotoxic, with IC_{50} values of 0.00016 and 0.00013 μg ml^{-1} respectively. The other compounds (except **65**, **68**, and **71**) also showed cytotoxic activity. Compound **74**, a deacyl derivative of **64** and **75**, was less cytotoxic vs. **64** and **75**. Compounds **65** and **68**, which are the corresponding deacyl cholestanes of **66** and **67**, and **69** and **70**, respectively, did not show any apparent cytotoxic activity. These facts are consistent with the aromatic acid ester group at the C-16 glycoside playing an important role in conferring strong cytotoxic activity (Kuroda et al. 2002b). Further phytochemical analysis of bulb extracts focusing on steroidal glycoside constituents led to the isolation of four new spirostanol saponins **76**-**79** (Fig. 8) and seven new cholestane glycosides **80**-**86** (Fig. 6), along with three known steroidal compounds **60, 61** and **87** (Fig. 8). Compounds **61**, **76**-**78**, **82** and **86**-**87** showed moderate cytotoxic activity against HL-60 cells with IC_{50} values ranging from 1.6 to 5.3 μg ml^{-1} (Kuroda et al. 2004). Ornithosaponins A–D **88**-**91** (Fig. 8), four new polyoxygenated steroidal glycosides, were also isolated from *O. thyrsoides* bulb extracts (Kuroda et al. 2006).

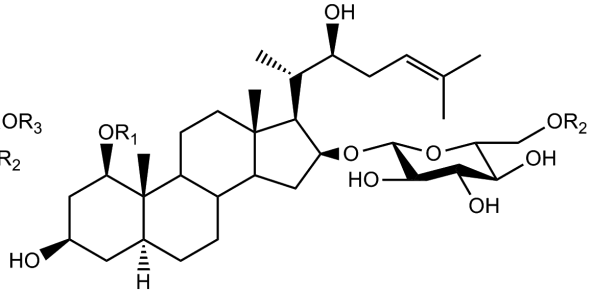
Phytochemical screening of bulbs of *O. saundersiae*, a native of the East coast of South Africa, resulted in the isolation of three acylated cholestane glycosides **92**-**94** (Fig. 7), of which **93** and **94** showed considerable inhibitory activity against cyclic AMP phosphodiesterase (IC_{50} = 0.055 mM and 0.005 mM, respectively). The presence of a benzoyl group attached to the sugar moiety seems to enhance this activity (Kubo et al. 1992c). In addition five new polyhydroxylated cholestane glycosides **95**-**99** (Fig. 6) were isolated and structurally characterized by spectroscopy and chemical correlations. All five were tested for their inhibitory activity on cyclic AMP phosphodiesterase. Compounds **96** and **99** showed potent activity (IC_{50} = 9.9 x 10^{-5} M and IC_{50} = 10.9 x 10^{-5} M, respectively), while the other compounds were inactive. Apparently, the acyl moiety at the C-3 hydroxyl position of the rhamnose group enhances cAMP inhibitory activity (Kubo et al. 1992b). Further studies of *O. saundersiae* bulb extracts revealed the structure of a new 22-homo-23-norcholestane trisaccharide **100** (Fig. 9) which was determined by extensive 2D NMR analysis and hydrolysis. Compound **100** also showed an inhibitory effect on cyclic AMP phosphodiesterase (Kuroda et al. 1993).

In addition, *O. saundersiae* bulbs were found to contain a new 16,23-epoxy-5β-cholestane triglycoside **101** (Fig. 9). Compound **101** showed significant inhibition (IC50 = 3.1 **μ**M) of the proliferation of peripheral blood lymphocytes, provided from a patient with chronic renal failure, without any cytotoxic effects on other lymphocytes or HL-60 human leukemia cells, thus indicating its potential as an immunosuppressive agents (Kuroda et al. 1995). Further studies revealed a new bisdesmoside **102** (Fig. 7) (Mimaki et al. 1996b) with potent cytotoxic activities toward leukemia HL-60 and MOLT-4 cells (LC_{50} = 0.02 μM and 0.0042 μM, respectively). Additionally ten rearranged cholestane glycosides **100**, **101**, **103**-**110** (Fig. 9) were isolated: seven, with a six-membered hemiacetal ring (between C-16 and C-23) were classified as

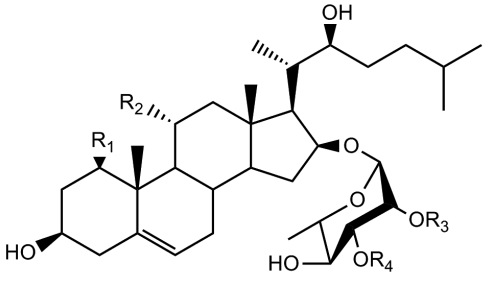
saundersiosides C- I (**104**-**110**); two, with a six-membered hemiacetal ring and five-membered acetal ring (between C-18 and C-20), were classified as saundersiosides A-B (**100**, **103**); and one contained a 16,23-epoxy moiety **101**. Their structures were elucidated by spectroscopy and hydrolysis (Mimaki et al. 1996c; Kuroda et al. 1999a; 2002a), and the conformation of hemiacetal ring was modeled using molecular mechanics and molecular dynamics calculations (Mimaki et al. 1996c; Kuroda et al. 1997). Compounds with an aromatic acid ester group at the glycoside moiety were found to be highly cytostatic to human leukemia HL-60 cells (saundersiosides B, E, F, G and H (**103**, **106**-**109**) IC_{50} = 0.0092, 0.021, 0.019, 0.063 and 0.052 mM, respectively) and MOLT-4 cells (saundersiosides B and E (**103**, **106**) IC_{50} =



	R_1	R_2	R_3
60	α-L-rhamnopyranoside	H	H
61	α-L-rhamnopyranoside	H	Ac
80	α-L-rhamnopyranoside	β-D-apiofuranoside	Ac
81	β-D-glucopyranoside	H	H
82	6-O-3,4,5-trimethoxybenzoyl-β-D-glucopyranoside	H	H

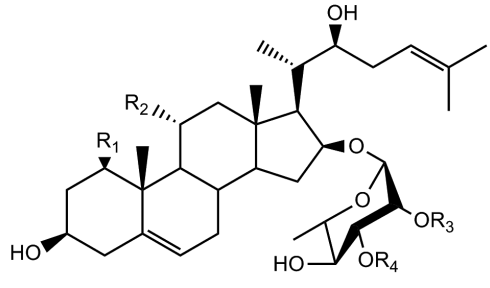


	R_1	R_2
62	α-L-rhamnopyranoside	H
63	α-L-rhamnopyranoside	Ac
83	6-O-3,4,5-trimethoxybenzoyl-β-D-glucopyranoside	H

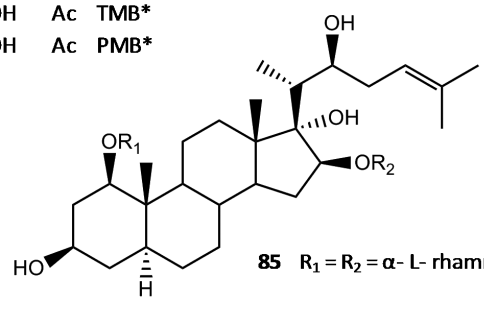


	R_1	R_2	R_3	R_4
84	O-α-L-rhamnopyranoside	H	H	H
95	H	OH	H	H
96	H	OH	H	Ac
97	H	OH	Ac	H
114	H	OH	Ac	Ac
115	H	OH	Ac	TMB*
116	H	OH	Ac	PMB*

*TMB = 3.4.5-trimethoxybenxoyl;
PMB = p- methoxybenzoyl

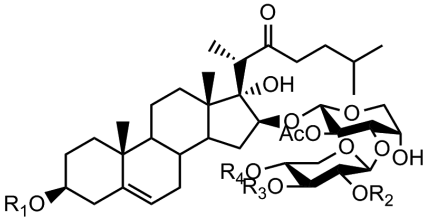


	R_1	R_2	R_3	R_4
86	O-α-L-rhamnopyranoside	H	H	H
98	H	OH	H	H
99	H	OH	H	Ac
117	H	OH	Ac	Ac



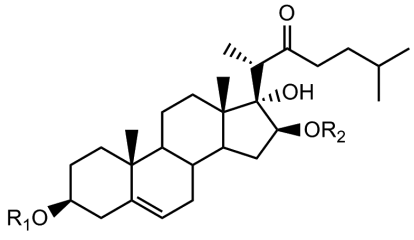
85 $R_1 = R_2$ = α- L- rhamnopyranoside

Fig. 6. Cholestane glycosides from the genus *Ornithogalum*. –A.

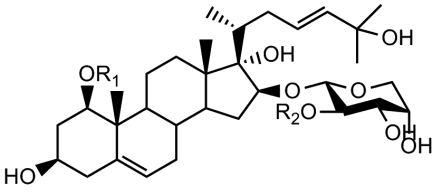


	R_1	R_2	R_3	R_4
64	β-D-glucopyranoside	TMB*	H	H
65	β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	H	H	H
66	β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	DMB*	H	H
67	β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	TMB	H	H
68	β-D-glucopyranosyl-(1? 4)β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	H	H	H
69	β-D-glucopyranosyl-(1? 4)β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	DMB	H	H
70	β-D-glucopyranosyl-(1? 4)β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	TMB	H	H
71	β-D-glucopyranosyl-(1? 4)β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	HMB*	H	H
72	β-D-glucopyranosyl-(1? 4)β-D-glucopyranosyl-(1? 6)-β-D-glucopyranoside	H	DMB	H
74	β-D-glucopyranoside	H	H	H
75	β-D-glucopyranoside	DMB	H	H
92	H	H	H	H
93	H	PMB*	H	H
94	H	DMB	H	H
111	H	CNM*	H	H
112	β-D-glucopyranoside	PMB	H	H
113	β-D-glucopyranoside	CNM	H	H
118	H	DMB	H	β-D-glucopyranoside
119	H	TMB	H	β-D-glucopyranoside

*PMB = p-methoxybenzoyl; HMB = 4-hydroxy-3-methoxybenzoyl DMB = 3,4,dimethoxybenxoyl; TMB = 3,4,5-trimethoxybenzoyl; CNM = (E)-cinnamoyl



73 R_1 = β-D-glucopyranoside
R_2 = α-L-arabinopyranoside



102 R_1 = β-D-glucopyranoside
R_2 = 3,4,5-trimethoxybenzoyl

Fig. 7. Cholestane glycosides from the genus *Ornithogalum.* –B.

0.0032 and 0.0018 mM, respectively). The activity of B (**103**) and E **106** on HL-60 cells appears to be partially mediated through induction of apoptosis according to cell morphology and DNA fragmentation results (Mimaki et al. 1996c, 1996a; Hirano et al. 1996; 1999a). In further studies, nine new acylated cholestane glycosides were found **111**-**119** (Fig. 6, 7), and together with four previously isolated cholestane glycosides **93**-**95**, **98** were tested for their inhibitory activity against leukemia HL-60 cells (Mimaki et al. 1997; Kuroda et al. 1999b; 2001). Compounds **95** and **114**-**117** exhibited potent cytostatic activity with GI_{50} values of 0.19, 6.9, 1.8, 0.022 and 0.80 mM, respectively. The cytotoxicity of cholestane glycoside **95** was evaluated at the National Cancer Institute using a 60 cell line assay. Results showed a specific activity towards leukemia cell lines (mean GI_{50} 0.052 mM; mean TGI 0.23 mM; mean LC_{50} 27 mM). The maximum tolerated dose of cholestane glycoside **95** in mice was determined to be 400 mg/kg (Kuroda et al. 1999b).

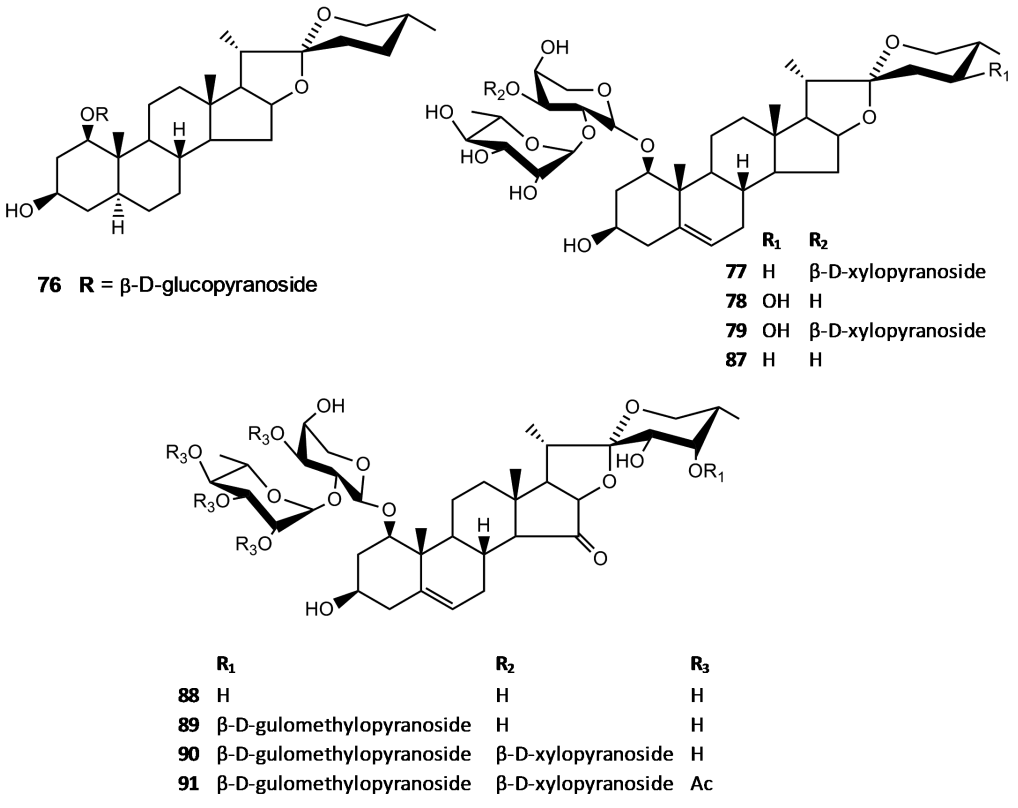


Fig. 8. Spirostane glycosides from the genus *Ornithogalum.*

Significant attention was given to compound **93**, called OSW-1; which showed high cytotoxic activity against various malignant tumor cell lines *in vitro* (primarily against leukemia cells from patients with chronic lymphocytic leukemia) and prolonged the life span of mice bearing P388 leukemia cells (Mimaki et al. 1997). A combination of an acylated diglycoside moiety and C-22 carbonyl group were proposed to be responsible for the significant cytotoxic activity of OSW-1(Kuroda et al. 2001). Further studies suggest that OSW-1's mechanism of action is due to structural and functional mitochondrial damage which triggers calcium-dependent apoptosis. Moreover, OSW-1 appeared to be less toxic to normal or non-malignant cells than tumor cells *in vitro* (Zhou et al. 2005). The cytotoxic properties of OSW-1 led to increased research resulting in the isolation and evaluation of the bioactivity of several steroidal glycosides and the synthesis of OSW-1 and its analogues (Guo and Fuchs 1998; Gryszkiewicz-Wojtkielewicz et al. 2003; Fernández-Herrera et al. 2009). The total synthesis of the OSW-1 was accomplished in 1999 (Deng et al. 1999), and a large number of analogues have since been produced for structure–activity relationship studies. *O. saundersiae* is a valuable Chinese traditional herb and is commonly used as an anti-inflammatory and anticancer agent to treat liver disease, hepatoma and cholecystitis etc. Because of this, ethanol extracts of whole dried plants were tested for protective effects against induced acute hepatic failure in mice. Some protective effects were demonstrated primarily through suppression of oxidative stress, lipid peroxidation and apoptosis of hepatocytes, as well as a reduction of inflammation (Ying et al. 2010, Wan et al. 2012).

Another South African species, *O. caudatum*, is used by both Zulu and Chinese traditional healers to treat diabetes, some tumor types, hepatitis and parotitis. Phytocemical investigations of the bulbs of *O. caudatum* resulted in the isolation and identification of stigmastane derivates, β-sitosterol **120**, daucosterol **121**, stigmasterol **122**, and stigmasterol 3-O-β-D-glucopyranoside **123** (Fig. 10). Additionally, 22 known flavonoids and acids were isolated, as well as a new natural product, n-butyl pyroglumate **124** (Fig. 11) (Tang et al. 2001). Furthermore, three new homoisoflavanone glycosides **125**-**127** (Fig. 12) (Tang et al. 2002) and one previously known homoisoflavanone **128** (Fig. 12) (Mulholland et al. 2004) were isolated from ethanol extracts of the bulbs. Compounds **125**-**127** were tested for *in vitro* antitumor activities against P388 (mouse leukemia) and A-549 (human pulmonary adenocarcinoma) cells, but no positive activities were recorded (Tang et al. 2002).

Water-soluble polysaccharide fractions from *O. cauda-*

tum was isolated and characterized by gel filtration and column chromatography. Polysaccharide fractions PS_3 showed significant immunoenhancement effects on mice *in vivo*. This PS_3 mediated immunomodulatory effect *in vivo* may be due to proteoglycans which contain a variety of C5-carbohydrates to C6-carbohydrate ratios (Shi et al. 2003). In addition, four isolated polysaccharide fractions exhibited strong antitumor activities against Sarcoma 180 solid tumors implanted in BALB/c mice *in vivo*. The results of this study suggest that antitumor activity of the polysaccharide may be due to activation of the host immune response, via stimulation of T-cell subsets and cytokine (TNF-α and IFN-γ) production (Chen et al. 2010). In a study on genotoxicity, dichloromethane extracts from bulbs and leaves of this species were not genotoxic, whereas extracts from the leaves were found to significantly increase the effect of treatment with mutagen mitomycin C (Verschaeve et al. 2004). Ethanol and aqueous extracts of *O. caudatum* (as *Ornithogalum longibracteatum* Jacq.) bulbs were tested for *in vitro* glucose utilization activity in C2C12 muscle and Chang liver cells and cytotoxic activity in Chang liver cells.

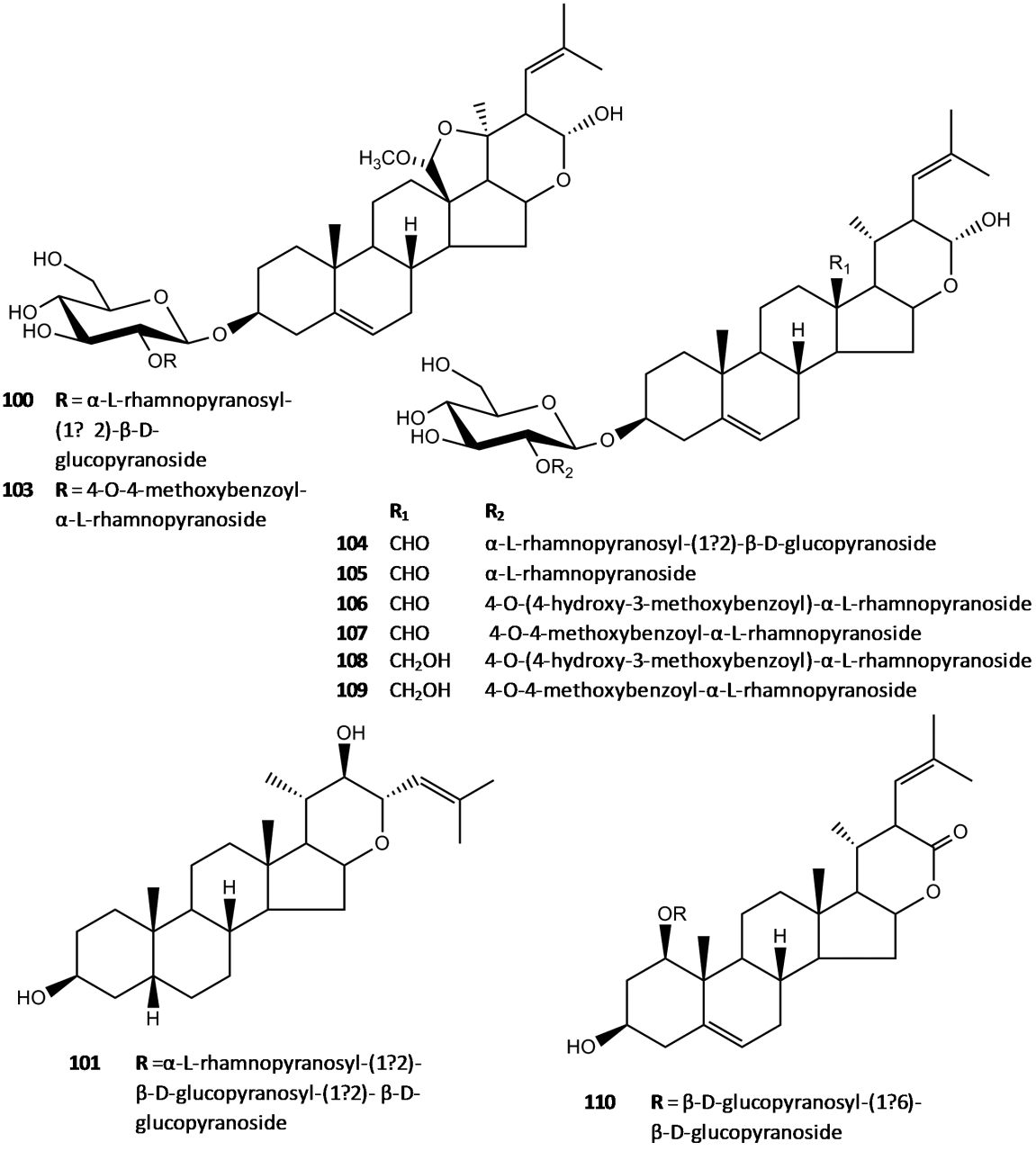
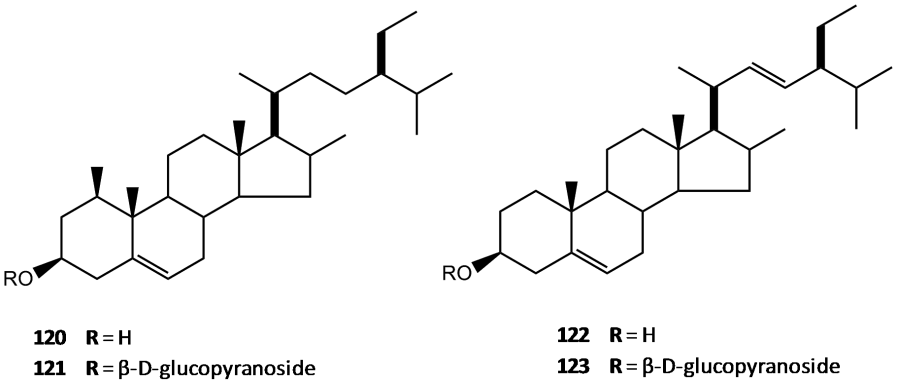


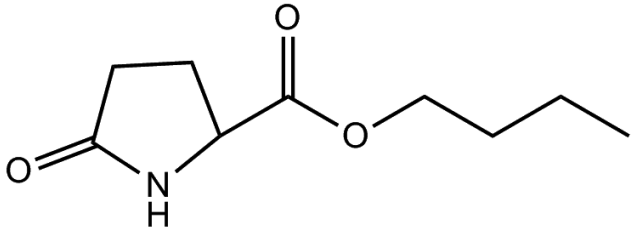
Fig. 9. Rearranged cholestane glycosides from the genus *Ornithogalum*.



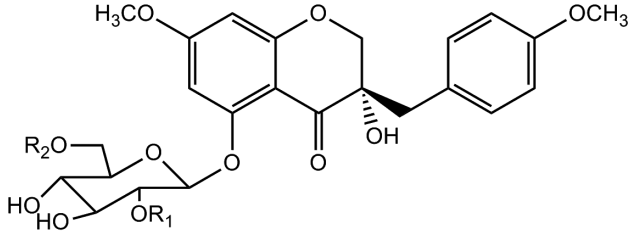
120 **R** = H
121 **R** = β-D-glucopyranoside

122 **R** = H
123 **R** = β-D-glucopyranoside

Fig. 10. Stigmastane glycosides from the genus *Ornithogalum*.

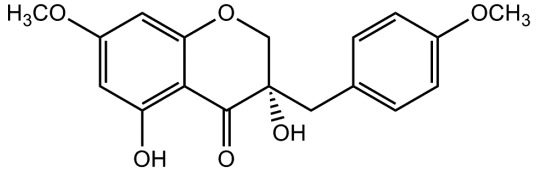


124



	R_1	R_2
125	H	H
126	H	α-Lrhamnopyranoside
127	α-Lrhamnopyranoside	H

Fig. 11. New natural product isolated from *Ornithogalum cuspidatum* - n-butyl pyroglumate.



128

Fig. 12. Homoisoflavanone glycosides from the *Ornithogalum caudatum*.

Both extracts increased glucose utilization, but aqueous extracts produced significant growth inhibition on Chang liver cells (Van Huyssteen et al. 2011).

In 2013. Mulholland et al. published a review on the Hyacinthaceae family on a global level, considering the phytochemical composition of 38 genera of four Hyacinthaceae subfamilies, including Ornithogaloideae (Mulholland et al. 2013). The isolated compounds were mostly subfamily-restricted to the subfamily Ornithogaloideae cardenolides, and steroidal glycosides were the main secondary metabolites. The authors noted the importance of further studies on these plant species, taking into account the large number of isolated biologically active compounds and their potential medical applications, as well as their application in the systematization of the family Hyacinthaceae.

CONCLUSIONS

In this review, the phytochemical profiles of 13 *Ornithogalum* plants are discussed, including biological activities of both crude extracts and isolated compounds. *Ornithogalum* species are highly toxic due to the presence of cardenolide or cholestane glycosides, and have been implicated in small live stock poisoning. However, traditional healers have used some plants from this genus to treat various medical conditions, including diabetes, hepatitis and even some cancer types.

Standardized tablets of *O. umbelatum*, in clinical trials, exhibit digitalis-like effects on the heart. Further studies conducted on the European species of *Ornithogalum* revealed the presence of numerous cardenolide glycosides in the whole plant, which could explain these digitalis-like effects. In spite of this, cardenolides from *Ornithogalum* have not been fully investigated for possible clinical use. Scientists showed more interest in African species. Methanol extracts,

as well as, cholestane, rearranged cholestane and spirostane glycosides isolated from the bulbs of *O. thyrsoides* and *O. saundersiae* displayed cytotoxic activity. OSW-1 is one isolated compound from the bulbs of *O. saundersiae* with potent anticancer activities. Its proposed unique mechanism of action makes OSW-1 worthy of further investigation for its potential to overcome drug resistance. Furthermore, *O. caudatum* polysaccharides exhibited immunoenhancement and antidiabetic activities. Thus, it is necessary to continue research into to their biological activities, as well as their mechanisms of action.

Phytochemical studies of these plants are also significant for taxonomy clarification of the genus *Ornithogalum*, which has been a matter of controversy in recent decades.

ACKNOWLEDGMENTS

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Abbreviations

IC_{50} – the half maximal inhibitory concentration

GI_{50} – the concentration required to achieve 50% growth inhibition

LC_{50} – the concentration lethal to 50% of the cells

TGI – the concentration required to achieve total growth inhibition

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