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REVIEW PAPER

Structure-activity relationships of oleanane- and ursane-type triterpenoids

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ABSTRACT. The chemistry of oleanane- and ursane-type triterpenoids has been actively explored in recent years, and their biological and pharmacological activities of these compounds have been found to span a variety of properties. These include antitumor, anti-viral, anti-inflammatory, hepatoprotective, gastroprotective, antimicrobial, antidiabetic, and hemolytic properties as well as many others. This review summarizes the isolation and structure modifications of these triterpenoids as well as the biological and pharmacological activities discovered in the past ten years, with an emphasis on their structure-activity relationships.

Keywords: Antidiabets; Anti-inflammatory; Antimicrobial; Antitumor; Antiviral; Gastroprotective; Hepatoprotective; Oleanane; Structure-activity relationship; Ursane.

Abbreviations: **GI_{50}**, concentration required to inhibit tumor cell growth by 50%; **ED_{50}**, concentration caused 50% inhibition of cell proliferation *in vitro*; **CC_{50}**, 50% cytotoxic concentration; **LC_{50}**, 50% lethal concentration; **TI**, *in vitro* therapeutic index; **MIC**, minimum inhibitory concentration; **PKC**, protein kinase C; **HLE**, human leukocyte elastase; **UISO-SQC-1**, squamous cervix carcinoma; **OVCAR-5**, human ovarian cancer; **fMLP**; N-formyl-methionyl-leucyl-phenylalanine; **PMA**, phorbol-12-myristate-13-acetate; **AA**, arachidonic acid; **ALT**, alanine aminotransferase; **ID_{50}**, doses inhibiting the oedematous response by 50%.

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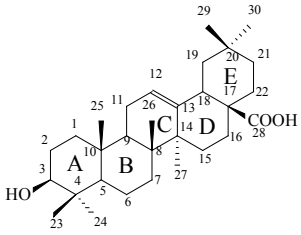
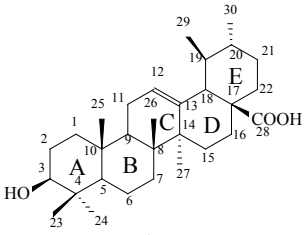
INTRODUCTION

Oleanolic acid (**OA**) (3β-hydroxy-olea-12-en-28-oic acid) and its isomer, ursolic acid (**UA**) (3β-hydroxy-urs-12-en-28-oic acid) are triterpenoid compounds which exist widely in nature in free acid form or as aglycones for oleanane- and ursane-type triterpenoid saponins (Liu, 1995). Oleanane and ursane are also called β-amyrane and α-amyrane, respectively. Saponins glycosylated at either C-3 or C-28 are termed monodesmosides, and those glycosylated at both C-3 and C-28 are termed bisdesmosides. These types of triterpene saponins exhibit diverse activities, which may be attributable to the different substructures in the A-, C-, E-rings or other positions. Many comprehensive reviews of two type triterpenoids have been published covering different areas of interest, such as isolation and structure determination (Joseph, 1999; 2000; 2001a; 2001b; 2002; 2003; 2005a; 2005b), and pharmacological activities (Liu, 1995; Safayhi et al., 1997; Setzer and Setzer, 2003; Rios et al., 2000; Baglin et al., 2003), but reviews of structure-activity relationships are scarce. In this review, our discussion will focus mainly on the chemistry and pharmacology of oleanane- and ursane-type triterpenoids discovered in the past ten years, with an emphasis on the relationships between their structures and activities. These triterpenoids are often mentioned simultaneously because they share similar structural features and pharmacological activities. In addition, other pentacyclic triterpenoids such as those of the lupane type are often cited in order to compare their structures and activities with those of oleanane and ursane type triterpenoids.



OA



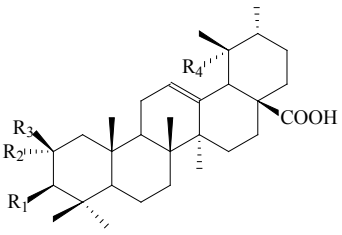
UA

ANTITUMOR ACTIVITIES

UA has been reported to be effective at different stages for tumor prevention and inhibition, e.g. inhibiting tumorigenesis (Huang et al., 1994), differentiation (Lee et al., 1994), and promotion (Tokuda et al., 1986), Moreover, **UA** and **OA** have exhibited potent activity against human leukemia and lymphoma cells. For example, **UA** was effective against P3HR1 cells (IC_{50}=2.5 μg/mL) and chronic myelogenous leukemia cells K562 (IC_{50}=17.8 μg/mL), while **OA** inhibited the growth of P3HR1 cells (IC_{50}=26.74 μg/mL) (Chiang et al., 2003). They also showed anti-angiogenic activities, with **UA** (IC_{50}=5 μM) found more active than **OA** (IC_{50}=20 μM) (Sohn et al., 1995). Bioassay-guided fractionation of *Polylepis racemosa* led to the isolation of four cytostatic triterpenoids **UA** and **1-3** (GI_{50}=6.9~>250 μg/mL), in which the 19-OH substituted compound **1** was the most active (GI_{50}=6.9~25 μg/mL) (Neto et al., 2000).

Six triterpenes **UA, OA** and **4-7** were isolated from stem bark of *Physocarpus intermedius*, and their ED_{50} values against five different tumor cells are shown in Table 1 (Kim et al., 2000). While introduction of 2α-OH substituents showed almost no influence on their activity, 9α-OH in the UA series was detrimental to activity. Coffemoylation of 3β-OH enhanced antitumor activity by several times.

Compound **6**, Corosolic acid, has also been isolated from the fruit of *Crataegus pinnatifida* var. *psilosa*. It displayed both cytotoxicity and PKC inhibition. The ED_{50} values of **6** and **UA** are shown in Table 2. Both compounds were selectively more potent against solid cancer cells HeLa S_3 and SNU C_4. Besides, it incompletely inhibited rat brain PKC activity *in vitro* by concentrations higher than 20 μg/mL (Ahn et al., 1998).



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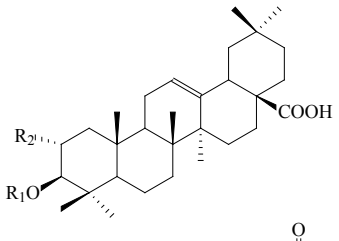
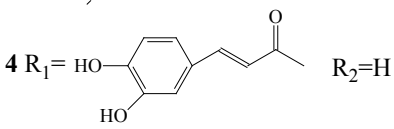
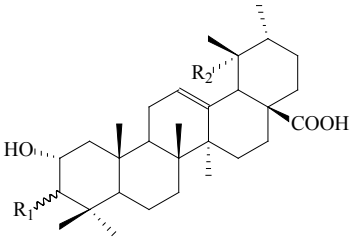
2 R_1=OAc R_2=H R_3=H R_4=OH
3 R_1=OH R_2=R_3=O R_4=OH





7 R_1=H R_2=OH



5 R_1=β-OH R_2=OH
6 R_1=α-OH R_2=H

Table 1. Inhibition ED_{50} (μg/mL) of tumor cell proliferation with **UA**, **OA** and **4-7**.

	A549	SK-OV-3	SK-MEL-3	XF498	HCT15
UA	4.2	3.6	4.6	4.5	4.4
OA	16.4	12.4	18.5	>30	12.1
4	1.6	1.6	1.7	19.8	1.7
5	>30	18.4	>30	30	>30
6	4.4	3.9	5.1	5.5	4.7
7	19.4	18.4	19.8	>30	15.3
Cisplantin	1.4	0.9	0.8	0.9	2.2

A549: non small cell lung; SK-OV-3: ovary; SK-MEL-3: melanoma; XF498: central nerve system; HCT15: colon; Cisplantin was positive control.

Table 3. Cytotoxic activity was determined by the MTT.

	CC_{50} (μg/mL)		
	HSC-2	HSG	HGF
UA	29	48	25
OA	130	230	>500
6	10	12	12
7	21	26	24
13	21	25	24
14	102	148	184
15, **16**	22	30	50

HSC-2: human oral squamous cell carcinoma; HSG: human salivary gland tumor; HGF: human normal gingival fibroblasts.

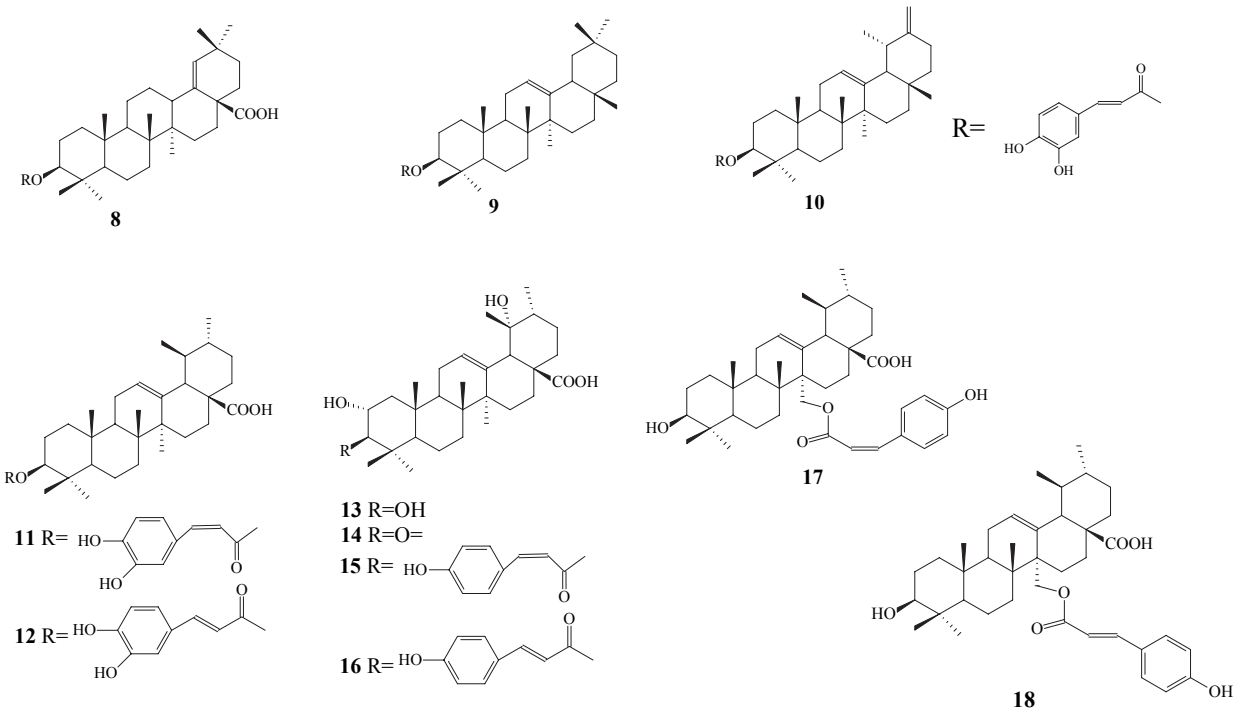
Table 2. ED_{50} (μg/mL) of corosolic acid and **UA** against tumor cells.

	Hep G_2	SNU-C_4	HeLa S_3	K-562
6	4.8	0.4	1.0	4.3
UA	3.0	1.4	1.5	12.5

Hep G_2: human hepatocellular carcinoma; SUN-C_4: human colorectal cancer; HeLa S_3: human cervix carcinoma.

It is interesting to note that the cinnamoyl substituent can be found in oleanane and ursane type triterpenoids that exhibit antitumor activity. Compounds **4**, **8**, **9**, and **10** were reported to inhibit both free radical and cyclooxygenase I activity (IC_{50}=0.9~4.6 μg/mL) (Hamburger et al., 2003). Cis-3-O-*p*-hydroxycinnamoyl ursolic acid (**11**) (GI_{50}=18.8~46.4 μM) was slightly more effective than its trans-isomer (**12**) (GI_{50}=40~25-100 μM) in inhibiting tumor growth against nine different tumor cell lines (Murphy et al., 2003).

However, the presence of the cinnamoyl segment might not always increase antitumor activity. Callus cultures induced from an axenic leaf of *Eriobotrya japonica* (Rosaceae) produced nine triterpenes **OA**, **UA**, **6**, **7**, **13**, **14**, **15** and **16**. All of these triterpenes exhibited significant activity in terms of CC_{50} against HSC-2, HSG and HGF (Table 3), but the activity of the mixture of cinnamoyl esters **15** and **16** was weaker than either non esterified **6** or **13** (Taniguchi et al., 2002). Moreover, when **UA**, 27-*p*-Z-coumaroyloxy UA (**17**) and 27-*p*-E-coumaroyloxy UA (**18**) were isolated through a bioactivity-guided fraction from aerial parts of *Viburnum jucundum* Morton, only **UA** exhibited cytotoxic activity with ED_{50} values of *ca*. 3 μg/mL against HCT-15, UISO-SQC-1 and OVCAR-5 (Rios et al., 2001).



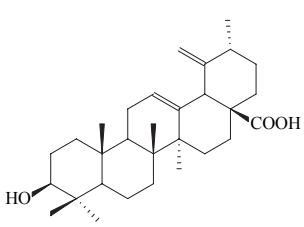
Due to its ability to repair damaged DNA (Narayan and Wilso, 1996), DNA polymerase is a potential target for adjuvant antitumor therapy, i.e., selective inhibition of this enzyme by other noncytotoxic agents could possibly potentiate chemotherapeutic effects of other DNA-damaging agents. **UA** at 100 μM was tested for inhibitions of calf DNA polymerase α, rat DNA polymerase β, plant DNA polymerase I (α-like), and DNA polymerase II (β-like). The percent inhibitions were 92%, 86%, 0%, and 9%, respectively (Mizushina et al., 2000). Four triterpenoids (**OA**, **UA**, **19** and **20**) were isolated from *Baeckea gunniana*, and all showed inhibition of DNA polymerase β (IC_{50}=2.5~4.8 μM). Because **19** and **20** displayed slightly more potent inhibitory activity than that of **UA** and **OA**, it is proposed that the exocyclic double bond on their E-ring might contribute to this improvement (Deng et al., 1999).

A new polyacylated oleanane triterpene **21** and **OA** were isolated from *Couepia polyandra*. They inhibited the lyase activity of DNA polymerase β, with IC_{50} values of 13.0 and 8.8 μM, respectively (Chaturvedula et al., 2003a).

Three acetyl-boswellic acid analogues **22**, **23** and **24** were investigated for their topoisomerase inhibitory activity, and the relative activity **22>23>24** was observed. The IC_{50} values for the inhibition of topoisomerase I and IIα catalytic activities by **22** were 3 μM and 1 μM, respectively. Other structurally related pentacyclic triterpenes, —including **OA**, **UA**, α-amyrin (**25**), β-amyrin (**26**), betulinic acid (**27**), and 18-β-glycyrrhetinic acid (**28**), —were tested for both types of topoisomerase inhibition. However, neither the amyrin isoforms nor **28** had significant effects at the concentration range observed for **22**. Of all the compounds, **27** was the most effective with IC_{50} values of 43 μM and 5 μM for topoisomerase I and IIα, respectively. An analysis of their structural features concluded that the shared pentacyclic ring architecture was important but not sufficient for the inhibition of topoisomerases. Moreover, the combination of carboxyl group at C-4 and two methyl groups at C-20 were important for enhancing the inhibitory activity of the molecule toward both topoisomerases (Syrovets et al., 2000).

A/B–ring partial analogues (**29-33**) of **OA** were enantioselectively synthesized. These compounds showed cytotoxicity against human malignant melanoma cell SK-MEL (IC_{50}=112~ 484 μM), except for **31,** which was not active (Assefa et al., 2001). Some partial analogous e.g. **32** and **33** had activity almost comparable to **OA**.

Tritepene saponins have been extensively explored as antitumor agents. Pentacyclic triterpene glycosides have been reported to be active against various tumors. Considering the diverse structures of both aglycones and attached sugars among various species, one can expect that they will play important roles in anticancer drug discovery.



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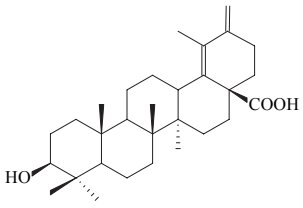

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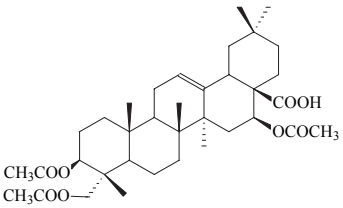

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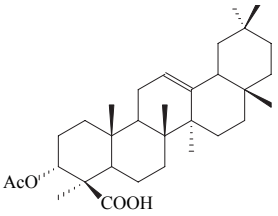

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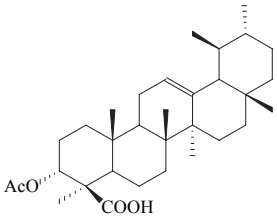

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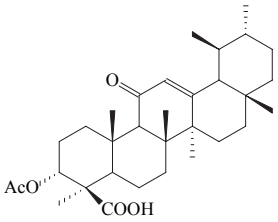

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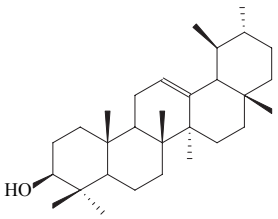

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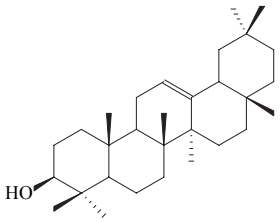

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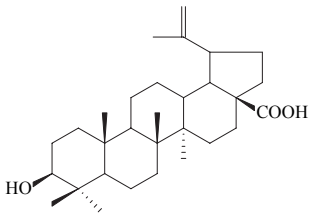

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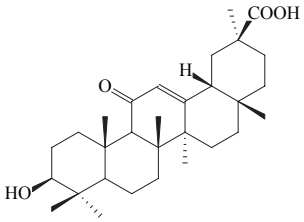

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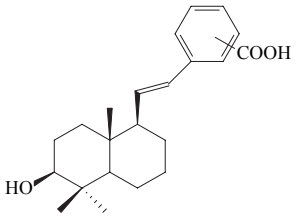
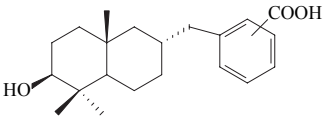


29a *p*-COOH
29b *m*-COOH
29c *o*-COOH



30a *p*-COOH
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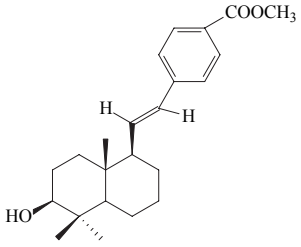
30c *o*-COOH



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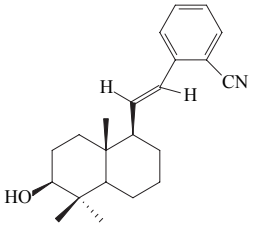

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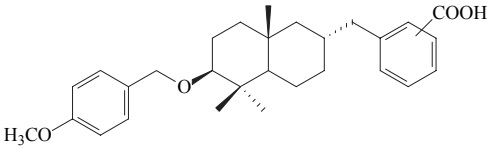


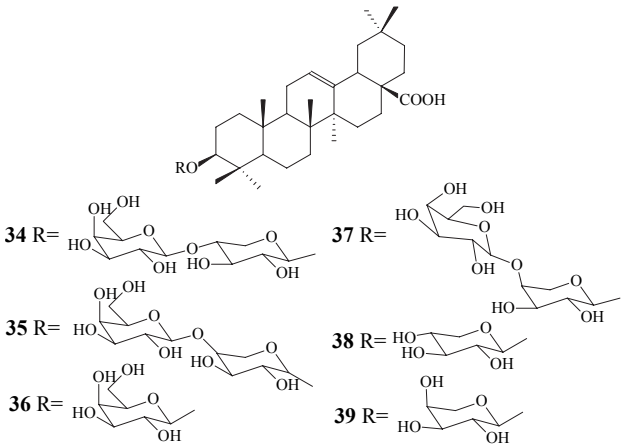
33a *p*-COOH
33b *m*-COOH
33c *o*-COOH

Triterpene saponins **34-37** from *Polyscias amplifolia,* together with two monoglycosides **38** and **39** formed by the partial hydrolysis of **34** and **35**, exhibited cytotoxicity against A2780 ovarian cancer cells (Table 4) (Chaturvedula et al., 2003b). The isolated cinnamoylated compounds **40** (IC_{50}=13.5 μg/mL) and **41** (IC_{50}=13.0 μg/mL) from *Acacia tenuifolia* also showed weak activity against A2780 ovarian cancer. Moreover, saponins **42** and **43**, which possess unique aminosugar moieties, were isolated along with **40** and **41**. These exhibited significant activity against the M109 lung cancer cell line, with IC_{50} values of 1 μM (Seo et al., 2002). Compound **43** was synthesized and tested for cytotoxic activity against the A2780 and M109 lung cancer cell lines with the IC_{50} 0.8 and 1.0 μg/mL, respectively (Sun et al., 2003). The above results clearly indicated the importance of 3-O-aminosugar, and the activity was compromised by the presence of C-16 and C-21 substituents in **40** and **41**, as compared to **43**.

Nine triterpenes (**44-52**) containing **OA** or hederagenin aglycones were isolated from the roots of *Pulsatilla chinensis* and tested for their cytotoxic activity against HL-60 human leukemia cells (IC_{50}=2.3~>10 μg/mL). Compound **46** was the only one that differed in C-3 sugar substituents in these saponins and no activity was detected. The results suggested that the glycoside

Table 4. Cytotoxicity against A2780 of compounds **35-43**.

	IC_{50} (μg/mL)
OA	20.4
35	6.7
36	9.2
37	10.8
38	9.6
39	8.9
40	8.6
41	13.5
42	13.0
43	0.8



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37 R=
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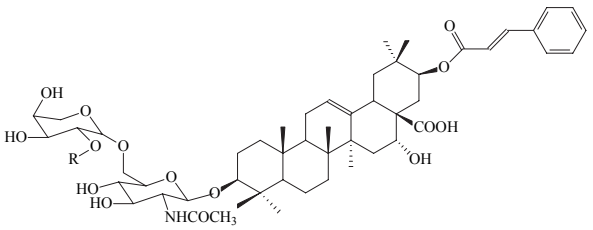

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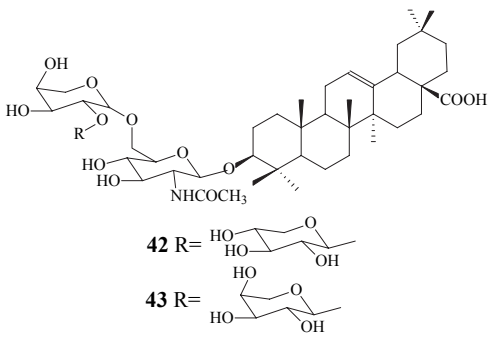
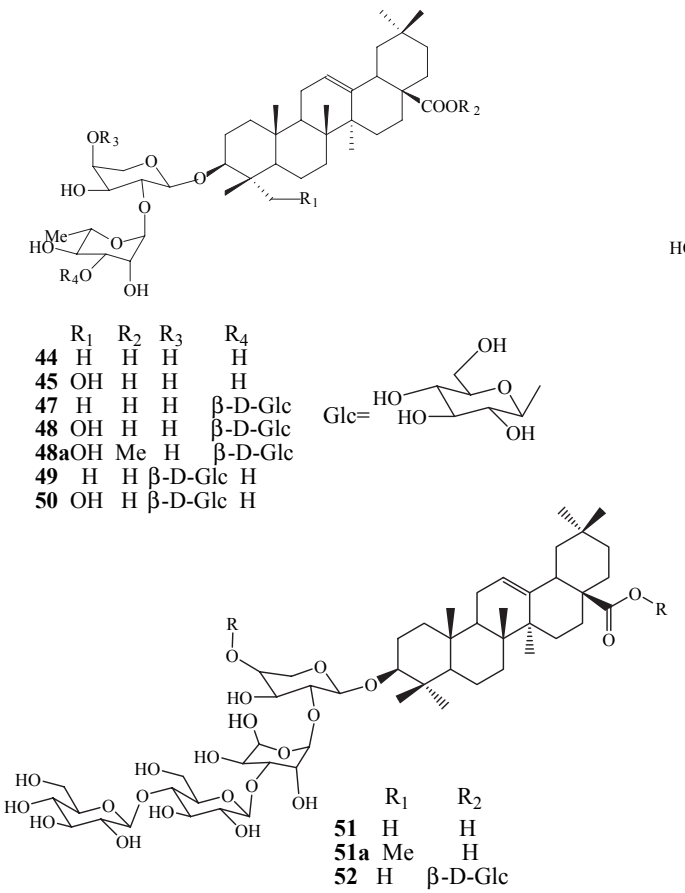
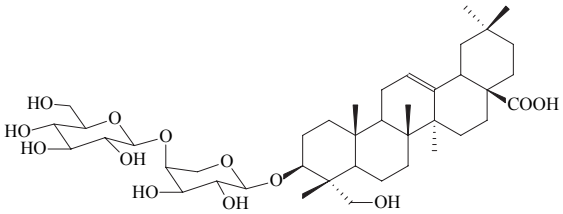
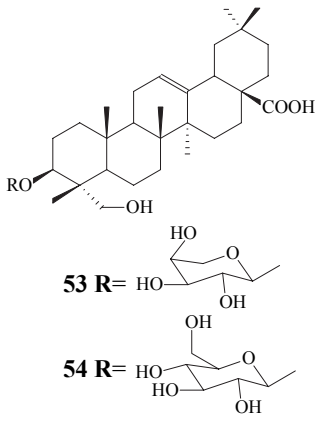


42 R=
43 R=







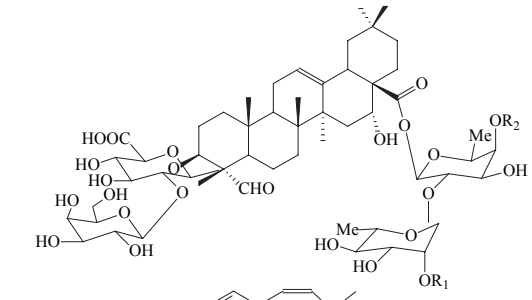
moiety attached to C-3 of the aglycone was essential for cytotoxicity (Mimaki et al., 1999). In addition, there was no significant difference in activity between the OA-based and hederagenin-based saponins. The presence of a C-28 methyl ester imposed no influence on the activity.

Compound **49** (Hederacolchisid A_1) was also isolated from *Hedera colchica* K. Koch, and exhibited moderate *in vitro* antiproliferative activities against six human cell lines as well as normal human fibroblasts. Comparison of the cytotoxicity of **49** (IC_{50} 4.5~12 μM) with **44** (IC_{50} 9~15 μM), **45** (IC_{50} 24~36 μM), **50** (IC_{50} 24~32 μM), **53** (IC_{50} 18~41 μM), and **54** (IC_{50} 26~47 μM) from the same plant offers some new information about structure-activity relationships. The sugar sequence OA-3-O-α-L-rhamnopyranosyl (1→2)-α-L-arabinopyranoside at C-3 appears essential for antitumor activity of OA monodesmosides. Unlike the previous results (Mimaki et al., 1999), monodesmesides with **OA** as aglycone were more active in this study than those with hederagenin (Barthomeuf et al., 2002).

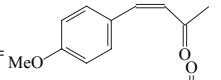
A study of the synergistic effect of saponins on an additional anticancer drug cisplatin showed that the triterpene saponins jenisseensosides A, B, C, and D (**55-58**) increased the accumulation and cytotoxicity of the anticancer agent cisplatin in human colon tumor cells. In contrast, the saponin **59** without the acyl moiety (trans- or cis-*p*-methoxycinnamoyl acid) attached to sugar did not exert such an effect (Gaidi et al., 2002). This agrees with recent findings that acylating groups might be crucial substructures due to their assumed pore-forming capacity. Saponins **60-67** were tested for any observed difference in the cytotoxic activity between acylated and non-acylated states. It was concluded that the number and structure of sugar chains did not play an important role in their cytotoxic properties, and that acylated saponins were more toxic than non-acylated ones (Barbato et al., 1997).

Superoxide generation can cause DNA damage and thereby initiate tumor-genesis (Gerhäuser et al., 2003). Five compounds (**UA**, **1**, **25**, **68**, **69**) isolated from *Diospyros kaki* were tested for stimulus-induced superoxide generation. Compound **1** inhibited fMLP, PMA and AA-induced superoxide generation more effectively than its 24-hydroxy derivative **69**. The hydroxyl group at R_3 and carboxyl group at R_2 appear to decrease superoxide generating activity by the three stimuli (Chen et al., 2002).

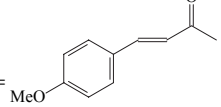
Moreover, the effects of six compounds (**OA**, OA 3-acetate, **44**, **49**, **70**, **71**) isolated from *Anemone raddeana* on fMLP, PMA, and AA-induced superoxide generations were investigated. A methyl group at C-14 caused stronger suppression of the fMLP-induced superoxide generation than a hydroxylmethyl at this position. Diglycoside **70** more strongly suppressed PMA and AA-induced superoxide generation than triglycoside **71** (Lu et al., 2001).



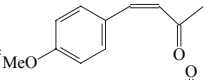
55 R_1=Glc R_2=



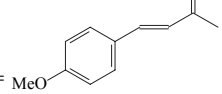
56 R_1=Glc R_2=

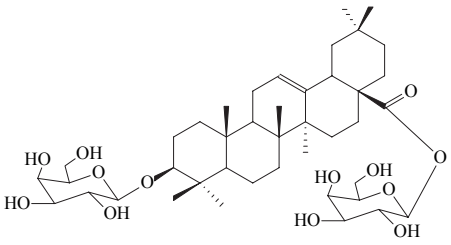


57 R_1=H R_2=



58 R_1=H R_2=





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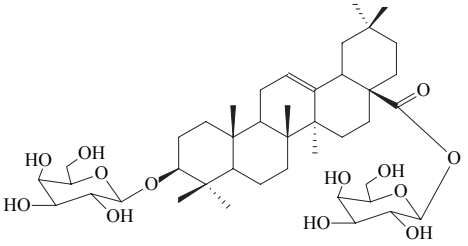

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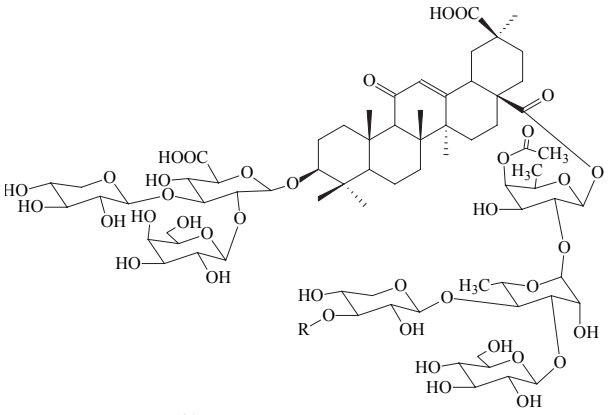
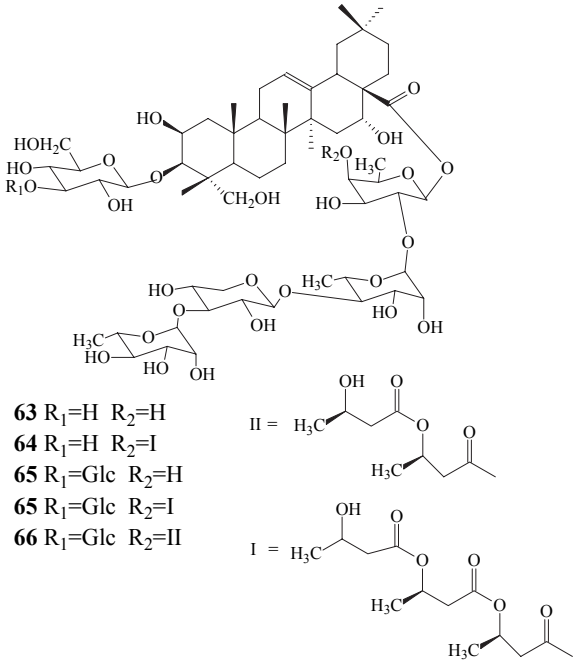


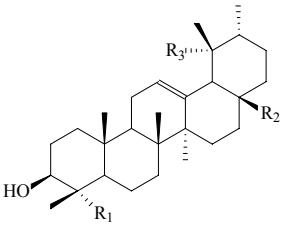
61 R=H
62 R=Xyl Xyl=



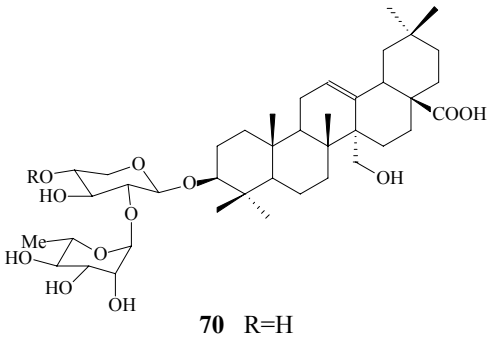
63 R_1=H R_2=H
64 R_1=H R_2=I
65 R_1=Glc R_2=H
65 R_1=Glc R_2=I
66 R_1=Glc R_2=II

II =

I =



	R_1	R_2	R_3
68	CH_3	CH_2OH	H
69	CH_2OH	COOH	OH



70 R=H
71 R=Glc

Inhibitors of nitric oxide (NO) production in macrophages are potential cancer chemopreventive and anti-inflammatory drugs (Ohshima and Bartsch, 1994). Gribble et al. synthesized a series of **OA** and **UA** derivatives as inhibitors of NO production induced by interferon-γ in mouse macrophages (Honda et al., 1997; 1999; 2000a, b and 2002). Some structures and activities were summarized as shown below in Figure 1 and Tables 5-7.

Generally, (1) oleanane and ursane triterpenoids with various enone functionalities in A-ring showed stronger activity. More specifically, a 1-en-3-one functionality in A-ring was important for significant activity (Table 5). (2) Carboxyl, methoxycarbonyl, and nitrile groups at

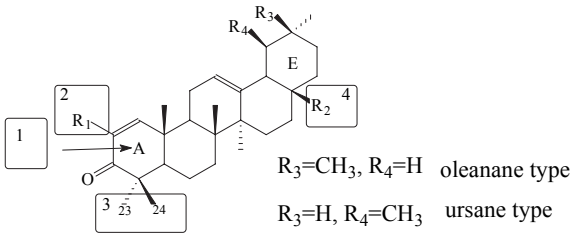
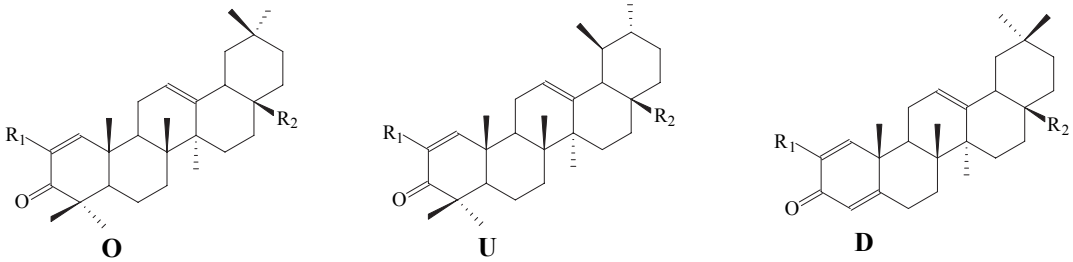


Figure 1. Structure-activity relationships of 1-en-3-one derivatives of oleanane triterpenoids.

Table 5. NO inhibitory activities of olean- and urs-12-ene triterpenoids with various 1-en-3-one functionalities.



	Type	R_1	R_2	IC_{50} (μM)
72	O	H	CO_2Me	31
73	O	H	CO_2H	5.6
74	D	H	CO_2Me	>40
75	D	H	CO_2H	13
76	U	H	CO_2H	13
77	O	OH	CO_2H	27
78	O	$CONH_2$	CO_2Me	14
79	O	OMe	CO_2H	30
80	O	CO_2Me	CO_2Me	0.9
81	O	CO_2Me	CO_2H	2.2
82	O	CO_2H	CO_2Me	0.8
83	O	CO_2H	CO_2H	0.07
84	O	CHO	CO_2Me	Toxic
85	O	CHO	CO_2H	Toxic
86	O	Br	CO_2Me	>40
87	O	Br	CO_2H	7.3
88	O	Cl	CO_2Me	>40
89	O	Cl	CO_2H	>40
90	O	CN	CO_2Me	0.7
91	O	CN	CO_2H	0.6
92	U	CN	CO_2Me	5.1
93	U	CN	CO_2H	6.2
OA				>40
UA				Toxic

C-2 enhanced activity, while hydroxyl, aminocarbonyl, methoxy, chloride, and bromide groups decreased it. A formyl group did not confer activity but only toxicity. (3) 23, 24-Dimethyl groups were also important for significant activity, as **73** was more potent than 23, 24-dinorolean-1-en-3-one derivative **75**. (4) The effect of a free acid or ester form at C-28 was ambiguous. For some analogues, triterpenoids bearing C-28 the carboxyl group were more potent than C-28 methyl; esters, but for others similar activity or even less potent activities were observed when C-28 was carboxylic acid. (5) The oleanane skeleton was usually more potent than the ursane skeleton.

The SARs of modified ring-C oleanane and ursane triterpenoids with Δ^{12} functionality (Table 6) were also summarized as follows:

(1) A 9(11)-en-12-one functionality in ring C could enhance activitiy about 10-100 times; (2) 12-en-11-one, 13(18)-en-11-one, and 12-one functionalities also enhanced potency, and a 9(11)-ene functionality showed similar potency to the original 12-ene; (3) The saturated ring C, 11, 13(18)-diene, and 9, 11-epoxide were less potent than the original 12-ene; as indicated in compounds **110-112**. (4) The combination of a 9(11)-en-12-one functionality with nitrile and carboxyl groups at C-2 enhanced the potency in a synergistic way; Triterpenoids such as **115**, **116** and **119** (IC_{50}=0.1 nM level) were about 10,000 times more potent than **73**. (5) The combination of a 9(11)-en-12-one functionality with amide and formyl groups at C-2 did not enhance potency as strongly as a nitrile or carboxyl group; (6) The combination of a 12-en-11-one and 13(18)-en-11-one functionalities with nitrile group at C-2 also strongly enhanced the potency as 9(11)-en-12-one series by two orders of magnitude.

CDDO (**116**) showed almost the strongest NO inhibitory activity (Table 6) among those synthetic derivatives of **OA**. Moreover, it could also inhibit proliferation of many tumor lines at sub M level and induced cell differentiation of human myeloid leukemia (Suh et al., 2000).

Based on structures of highly active triterpenoids **CDDO**, **115** and **119** (Table 6), a series of oleanane triterpenoids (**123-148**) with various substituents at the C-28 were synthesized (Table 7). Some important SARs regarding substituents at C-17 were also provided: (1) Nitrile group enhanced potency and ester moieties decreased potency. The less polar the ester, the less was its potency. (2) The carbonyl pyrazole was much less potent than that of 28-COOH, while carbonyl imidazole had higher potency, which might have arisen from high reactivity of imidazole with nucleophiles.

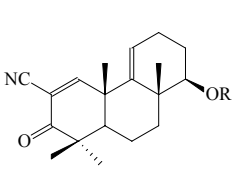
Moreover, many tricyclic compounds (**149-157**), as simplified **CDDO** with same A, B, and C ring architecture, were synthesized and tested for NOS inhibitory activity, the IC_{50} values were between 0.002 and 1.6 μM, in which **(±)-80** showed the most potential (IC_{50}=0.002 μM). It was found that the most active compound **157** was only about one-fourth as potent as **CDDO**, so a nitrile group at this position enhanced potency among the typical electron-withdrawing groups such as in compounds **154** and **156** at C-13. Since **151** and **152** were more potent than **149** and **150,** the bis-enone structure for high potency in relatively small molecules is important (Favaloro et al., 2002).

ANTI-VIRAL ACTIVITIES

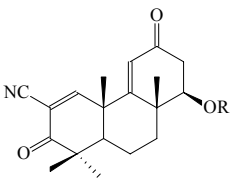
Saponins **158** and **159** were isolated from *Gymnoladus chinensis* (Nakashima et al., 1989) and *Gleditsia japonica*, respectively. Both compounds exhibited potent anti-HIV effects against HIV replication in H-9 cells. Their derivatives (**160-173**) were prepared and evaluated for anti-HIV activity (Table 8). The monoterpenyl moieties in **158** and **159** were found to play an important role in modulating the anti-HIV activity of these compounds. In addition, methylation of 28-COOH increased activity while introduction of *n*-butyryl or valeryl groups to the C-3 and/or C-16 hydroxy group decreased it compared to that of **167** (Konoshima et al., 1995).

A series of natural and semi-synthetic **OA**, **UA** and betulinic acid (**27**) derivatives have been isolated (Ma et al., 2002; Kashiwada et al., 1998) or synthesized. Some relationships of anti-HIV activities and structures were summarized in Table 9.

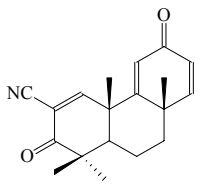
(1) Esters especially dicarboxylic acid hemiesters of 3-OH in OA, tended to increase inhibitory activity (Ma et al., 1999). For the 3-acyl chains within five carbons, the HIV-1 PR inhibitory activity of the compounds increased as the lengths of the 3-acyl chains increased (Ma et al., 2000). (2) Methylation of the 28-COOH or the carboxyl



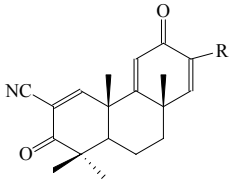
149 R=H
150 R=Ac



151 R=Ac
152 R=H

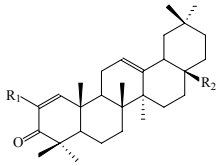


153

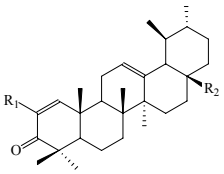


154 R=CO_2CH_3
155 R=COOH
156 R=$CONH_2$
157 R=CN

Table 6. NO inhibitory activity of olean-1-en-3-one and urs-1-en-3-one triterpenoids with various C-ring functionalities.



O



U

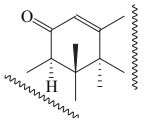
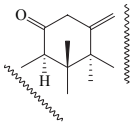
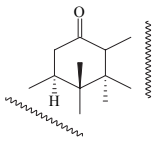
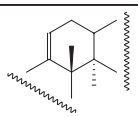
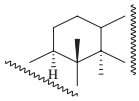
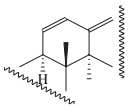
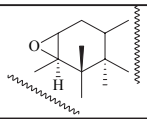
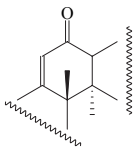
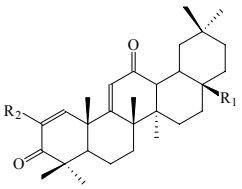
	Type	Structure of ring C	R_1 at C-2	R_2 at C-17	IC_{50} (μM)
94	O		H	CO_2Me	2.8
95	O		H	CO_2H	1.1
96	U		H	CO_2Me	8.9
97	U		H	CO_2H	5.1
98	O		H	CH_2OAc	>40
99	O		H	CH_2OH	3.0
100	O		H	CHO	3.8
101	O		CN	CO_2Me	0.02
102	O		CN	CO_2H	0.04
103	U		CN	CO_2Me	0.1
104	U		CN	CO_2H	0.8
105	O		H	CO_2H	2.6
106	O		CN	CO_2H	0.07
107	O		H	CO_2Me	14
108	O		H	CO_2H	3.3
109	O		H	CO_2H	5.2
110	O		H	CO_2H	8.5
111	O		H	CO_2H	9.7
112	O		H	CO_2H	36
113	O		H	CO_2Me	0.7
114	O		H	CO_2H	0.2
115	O		CN	CO_2Me	0.0001
116	O		CN	CO_2H	0.0002
117	O		CO_2Me	CO_2Me	Toxic
118	O		CO_2Me	CO_2H	0.1
119	O		CO_2H	CO_2Me	0.0008
120	O		CO_2H	CO_2H	0.2
121	O		$CONH_2$	CO_2Me	0.1
122	O		CHO	CO_2Me	0.1

Table 7. NO inhibitory activities of compounds **123-148**.



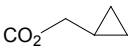
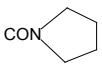
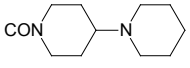
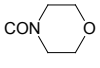
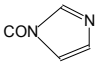
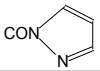
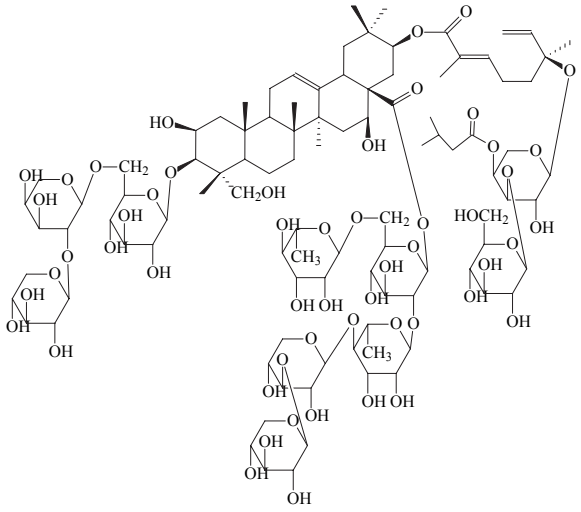
	R_1	R_2	IC_{50} (μM)
123	CN	CN	0.0035
124	CN	CO_2H	1.68
125	CO_2Et	CN	0.80
126	CO_2Et	CO_2H	7.93
127	$CO_2CH_2CH{=}CH_2$	CN	1.33
128	$CO_2(CH_2)_3CH_3$	CN	6.65
129		CN	4.45
130	CO_2CH_2Ph	CN	4.35
131	$CO_2(CH_2)_7CH_3$	CN	60.4
132	CO-D-Glc$(OAc)_4$	CN	0.07
133	CO-D-Glc	CN	10.1
134	$CONH_2$	CN	0.098
135	$CONHNH_2$	CN	0.26
136	CONHMe	CN	0.58
137	$CONH(CH_2)_2CH_3$	CN	1.50
138	$CONH(CH_2)_5CH_3$	CN	14.9
139	CONHPh	CN	28.6
140	$CONHCH_2Ph$	CN	9.2
141	$CONMe_2$	CN	1.55
142	CON(n-Pr)$_2$	CN	32.9
143		CN	0.80
144		CN	0.95
145		CN	1.00
146		CN	2.4
147		CN	0.014
148		CN	12.0

Table 8. HIV inhibitory effects for **158-173**.

Compd	ED_{50} (μM)	IC_{50} (μM)
158	1.1	9.8
159	2.7	14
160	>100	43
161	>100	37
161a	9.9	22
162	13	50
163	95	63
164	100	>100
165	42	74
166	8	40
167	3.1	4.9
168	5.1	7.6
169	2.3	13
170	27	27
171	15	>160
172	30	180
173	31	54

group in the C-3 hemiester chain decreased the inhibitory activity against HIV-1 PR significantly (Kashiwada et al., 1998). Methylation at both sites led to complete loss of activity, e.g. **210** (Ma et al., 1999). (3) Replacement of the 28-COOH with a methyl group resulted in a significant loss of activity (**25** *vs* **UA; 26** *vs* **OA)** (Kashiwada et al., 1998). (4) The structure of E-ring might play an important role in anti-HIV potency. Derivatives of betulinic acid, **27**, were more potent than those of **UA** and **OA** (Kashiwada et al., 2000). (5) Saturation of the C_{12}-C_{13} double bond could be a major cause of anti-HIV activity enhancement (**238-240**), while a C-3 acyl side chain was essential for optimal activity. In addition, changing the C_{28}-carboxyl to aminomethyl could significantly enhance anti-HIV activity **(241**, **242)** (Zhu et al., 2001). (6) Replacement of C-3 hemiester in the OA series with hemi-amide retained activity (**219-223** *vs* **204-205**) (Ma et al., 1999).

Oleanane-type triterpenoid saponins (**243-258**) were examined for the anti-herpes virus (anti-HSV-1) activity (Table 10). It has been found that (1) the trisaccharide glycosides were more potent than the disaccharide glycosides. The order of activity was **247**>**250**>>**253**. (2) The saponins having a glucosyl unit in the central sugar moiety seemed to show greater action. Among the trisaccharide group, the order of activity was **245>244>246>>243**. (3) The carbonyl group at C-22 would be more effective than the hydroxyl group in anti-HSV-1 activity, while the hydroxyl group at C-24 could reduce the activity. Comparing the activities of a group having the same trisaccharide, the order of potency was **254>247>243** (Kinjo et al., 2001).



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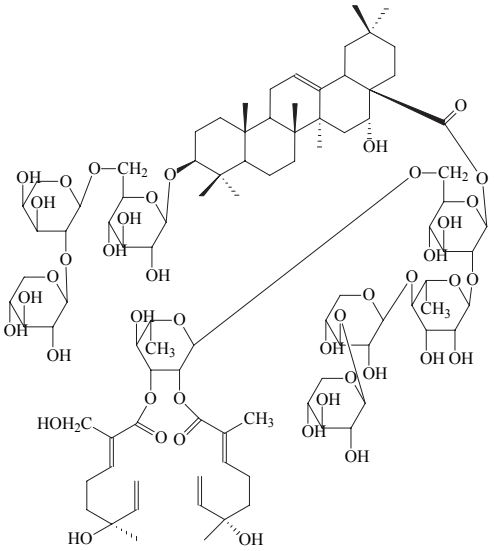

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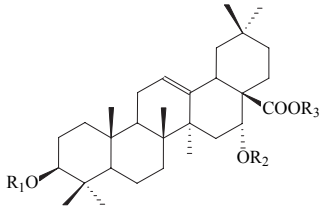
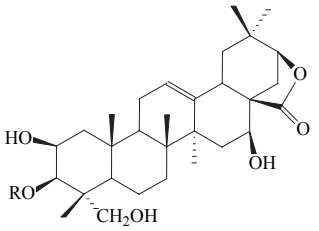
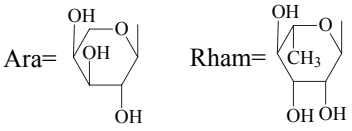


160	Glc^6-Ara^2-Xyl	H	Glc^2-Rham
161	Glc^6-Ara^2-Xyl	H	H
161a	Glc^6-Ara^2-Xyl	H	Me
162	Glc^6-Gra	H	H
163	Glc	H	H
165	H	H	H
167	H	H	Me
168	Ac	H	Me
169	Ac	Ac	H
170	Butyryl	H	Me
171	Butyryl	Butyryl	Me
172	Valeryl	H	Me
173	Valeryl	Valeryl	Me



164 R=Glc^6-Ara^2-Xyl
165 R=H



ANTI-INFLAMMATORY ACTIVITIES

In *vivo* studies

OA and **UA** inhibited the Croton oil-induced ear oedema in mice in a dose-dependent manner, and **UA** (ID_{50}=0.14 μMoles/cm^2) was twofold more potent than **OA** (ID_{50}=0.36 μMoles/cm^2) and indomethacin (ID_{50}=0.26 μMoles/cm^2), which was used as a reference non-steroidal anti-inflammatory drug (NSAID) (Ismaili et al., 2001 and 2002; Baricevic et al., 2001).

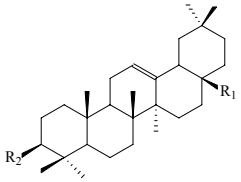
The anti-inflammatory activities of ten triterpenoids [**25**, **26**, **68**, **259**, **260**, **OA**, Hederagenin (**261**), **28**, α-glycyrrhetinic acid (**262**), and lupeol (**263**)] were evaluated. It was found that the basic carbon skeletons had no influence on the activity; the presence of a C-28 or C-30 carboxylic group and an alcoholic group at C-28 increased the activity in carrageenan and TPA-induced edemas in mice (Recio et al., 1995).

The following mechanistic aspects of anti-inflammatory activities of **OA** and **UA** derivatives have been investigated.

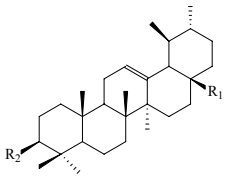
Inhibition of cyclooxygenase (COX) activity

UA was a selective inhibitor of COX-2 catalyzed prostaglandin biosynthesis, with IC_{50} value of 130 μM and a COX-2/COX-1 selectivity ratio of 0.6. **OA** (IC_{50} 295 μM) was found to be less active than **UA**, but showed a similar selectivity ratio (0.8). Furthermore, no significant inhibition on COX-2 or COX-1 was observed by **28** (Ringbom et al., 1998). 1 μM or less of **CDDO** (**116)** blocked expression of both iNOS and COX-2 protein (Syrovets et al., 2000). Compounds **247**, **260** and 3-epi-UA **(264)** (assayed at 10 μM) blocked the inductive effect of lipopolysaccharide on the production of PGE_2, while **OA** and **UA** did not substantially suppress the production of PGE_2 (Suh et al., 1998). Compounds **5** and **9** strongly

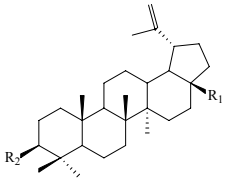
Table 9. HIV inhibitory effects for derivatives of **OA**, **UA** and **28**.



O



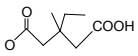
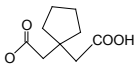
U

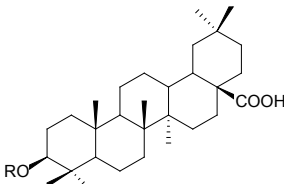


L

	Type	R_1	R_2	IC_{50} (μM)
25	U	CH_3	OH	80
UA	U	COOH	OH	8
174	U	$COOCH_3$	OH	14
175	U	COOH	$OCOCH_3$	13
176	U	COOH	OCOCOOH	7
177	U	COOH	$OCOCH_2COOH$	6
178	U	COOH	$OCO(CH_2)_2COOH$	6
179	U	COOH	$OCO(CH_2)_3COOH$	4
180	U	$COOCH_3$	$OCO(CH_2)_3COOCH_3$	>50
181	U	COOH	$OCOC(CH_3)_2CH_2COOH$	30.7
182	U	COOH	$OCOCH_2C(CH_3)_2COOH$	49.5
183	U	COOH	$OCOCH_2C(CH_3)_2CH_2COOH$	7
184	U	COOH	$OCOCH_2OCH_2COOH$	48.2
185	U	COOH	$OCOCH_2CH(CH_3)_2$	>18.5
186	U	COOH	$OCOCH_2C(CH_3)_3$	>18
187	U	COO^-K^+	OH	1.8
27	L	COOH	OH	9
188	L	$COOCH_3$	OH	>25
189	L	COOH	COCOOH	7
190	L	COOH	$OCOCH_2COOH$	6
191	L	COOH	$OCO(CH_2)_2COOH$	6
192	L	COOH	$OCO(CH_2)_3COOH$	4
193	L	COOH	$OCOCH_2C(CH_3)_2CH_2COOH$	4
194	L	$COOCH_3$	$OCO(CH_2)_2COOCH_3$	40
195	L	COOH	$OCOCH_2C(CH_3)_2COOH$	7.0
26	O	CH_3	OH	>100
OA	O	COOH	OH	8
196	O	$COOCH_3$	OH	20
197	O	COOH	$OCOCH_3$	9
198	O	COOH	OCOCOOH	20
199	O	COOH	$OCOCH_2COOH$	8
200	O	COOH	$OCO(CH_2)_2COOH$	4
201	O	COOH	$OCO(CH_2)_3COOH$	4
202	O	$COOCH_3$	$OCO(CH_2)_3COOCH_3$	>50
203	O	COOH	$OCOCH_2C(CH_3)_2COOH$	19.2
204	O	COOH	$OCO(CH_2)_4COOH$	3.0
205	O	$COOCH_3$	$OCO(CH_2)_4COOH$	7.5
206	O	COOH	$OCO(CH_2)_6COOH$	3.0

Table 9. (Continued)

	Type	R_1	R_2	IC_{50} (μM)
207	O	COOH	$OCO(CH_2)_8COOH$	4.0
208	O	COOH	$OCOCH_2C(CH_3)_2CH_2COOH$	3.8
209	O	COOH	$OCO(CH_2)_4COOCH_3$	5.6
210	O	$COOCH_3$	$OCO(CH_2)_4COOCH_3$	>20
211	O	COOH	$OCO(CH_2)_4CH_3$	>20
212	O	COOH	=O	5.5
213	O	$COOCH_3$	=O	20
214	O	COOH	=NOH	5.5
215	O	$COOCH_3$	=NOH	9.5
216	O	$COOCH_3$	α-NH	>20
217	O	$COOCH_3$	β-NH	>20
218	O	COOH	$=NOCO(CH_2)_4COOH$	5.5
219	O	$COOCH_3$	$=NOCO(CH_2)_4COOH$	4.0
220	O	COOH	β-$NHCO(CH_2)_4COOH$	3.0
221	O	$COOCH_3$	β-$NHCO(CH_2)_4COOH$	3.0
222	O	COOH	α-$NHCO(CH_2)_4COOH$	2.1
223	O	$COOCH_3$	α-$NHCO(CH_2)_4COOH$	3.5
224	O	$COOCH_3$	β-$NHCO(CH_2)_4CONH(CH_2)_3COOH$	6.0
225	O	$COOCH_3$	β-$NHCO(CH_2)_4CONH(CH_2)_3COOCH_3$	>20
226	O	COOH	β-$NHCO(CH_2)_4CONH$-β-OA-28-OH	3.3
227	O	$COOCH_3$	β-$NHCO(CH_2)_4CONH$-β-OA-28-OCH_3	>20
228	O	$CONH(CH_2)_5COOH$	COOH	1.7
229	O	$CONH(CH_2)_5COOH$	$OCO(CH_2)_4COOH$	1.7
	Type	R_1	R_2	IC_{50} (μg/mL)
230	O	COOH	$OCOC(CH_3)_2CH_2COOH$	9.7
231	O	COOH	$OCOCH_2OCH_2COOH$	22.1
232	O	COOH	$OCOCH_2CH(CH_3)CH_2COOH$	27.5
233	O	COOH		4.4
234	O	COOH		4.7
235	O	COO^-K^+	OH	34.3



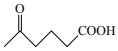
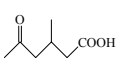
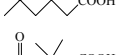
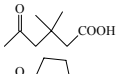
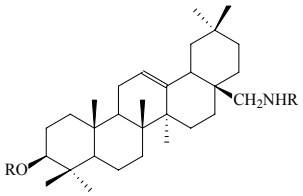
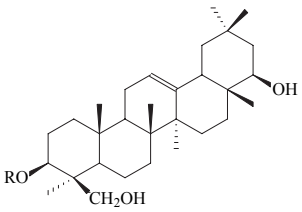
	R	EC_{50} (μg/mL)		EC_{50} (μg/mL)
236	H	0.5	**OA**	1.7
237		2.6	**201**	7.1
238		0.1	**232**	8.3
239		0.1	**208**	1.5
240		0.1	**234**	1.2

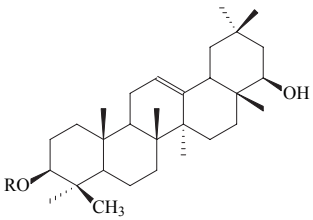
Table 9. (Continued)



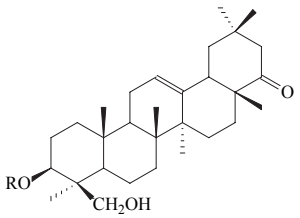
	R	EC_{50} (μg/mL)
241		0.1
242		0.1



243 R=S_1 **244** R=S_3
245 R=S_2 **246** R=S_4
249 R=S_5 **251** R=S_6
252 R=S_7 **256** R=H

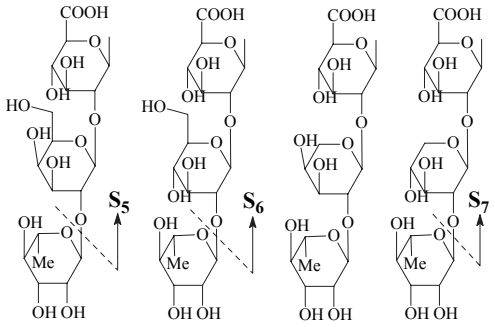


247 R=S_1 **248** R=S_3
250 R=S_5 **253** R=S_7
257 R=H



254 R=S_1
255 R=S_4
258 R=H

S_1 = **S_2 =** **S_3 =** **S_4 =**



inhibited the formation of 6-keto-$PGF_{1\alpha}$ with an IC_{50} value of approximately 0.12 μM, and synthesis of TXB_2 catalyzed by COX-2 with an IC_{50} value in the range of 0.4~2.5 μM (Hamburger et al., 2002). Platycodin D (**265**), isolated from the root of *Platycodon grandiflorum* A. DC. (Campanulaceae), suppressed PGE_2 production at 10 μM in rat peritoneal macrophages stimulated by TPA (Kim et al., 2001).

Inhibition of complement activity

Complement plays a role in various functions of the adaptive immune response. Yet overactivation of complement is implicated in various inflammatory diseases. A/B–ring partial analogues (**29a-c, 30a-c** and **33b**) of **OA** also showed complement inhibitory activity (IC_{50}=72.3~633 μM). The lack of complement inhibitory activity with compounds **31** and **32** showed the importance of the free carboxylic group for complement inhibition. The lack of complement inhibitory activity with compounds **33a** and **33c** while the compound **33b** retained the activity may indicate that the *meta* position of the carboxylic group was more favorable for complement inhibitory activity (Assefa et al., 2001).

Some semisynthetic analogues of **OA** (Table 11) were evaluated for their complement inhibitory and cytotoxic activities. The amide derivatives (**268** and **269**), OA-11-oxo **273**, and the 3-acyl derivatives (**203, 208** and **231**) have retained the complement inhibitory activity. Among these, compounds **269** and **231** showed potency superior to **OA**. Both showed a moderate improvement *in vitro* TI in comparison with **OA** (Assefa et al., 1999).

Table 10. Anti-HSV-1 activity, cytotoxicity and selectivity index of **243-258**.

	Anti-HSV-1 activity (IC_{50}, μM)	Cytotoxicity (CC_{50}, μM)	Selectivity index (CC_{50}/IC_{50})
243	>75.0	–	–
244	27.4	115	4.2
245	21.0	>332	>15.8
246	43.0	>343	>13.7
247	43.2	119	2.8
248	22.3	698	31.3
249	>75.0	–	–
250	64.1	641	10.0
251	54.0	>393	>7.3
252	>75.0	–	–
253	>75.0	–	–
254	19.1	>332	>17.4
255	25.1	>343	>13.7
256	5.6	116	20.7
257	37.8	>141	>3.7
258	61.4	504	8.2

Table 11. Classical complement inhibition and cytotoxicity of **OA**, **196**, **197**, **203**, **208**, **212**, **231**, and **266-273**.

	Complement inhibition IC_{50} (μM)	Cytotoxicity IC_{50} (μM)	TI
OA	72.3	112	1.55
197	NA	NA	0.06
266	NA	70	
267	NA	NA	
268	146.6	115	0.78
269	31.8	127	3.99
270	NA	NA	
271	NA	105	
196	NA	103	
272	NA	NA	
273	233.7	131	0.56
203	108.3	77	0.71
231	31.4	93	2.96
208	103.0	86	0.83
212	NA	31	

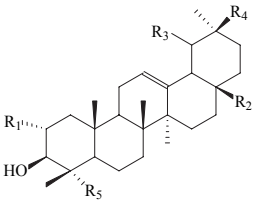
Inhibition of elastase

The hydrolysis of blood vessel elastin by HLE promotes the transendothelial migration of stimulated proinflammatory cells. The IC_{50} values for elastase inhibition by **UA** and **OA** were 4.4 and 6.4 μM, respectively (Ying et al., 1991). The α-boswellic acid (**274**), acetyl-11-keto-β-boswellic acid (AKBA) (**275**), **25, 26, UA,** and **28** were tested for the inhibitory activity of HLE. Dual inhibition of 5-lipoxygenase and HLE was unique to boswellic acid series. **UA** and amyrins, which possessed no 5-LO inhibitory properties, blocked the activity of HLE, but **28** had no inhibitory effects at concentrations up to 20 μM (Safayhi and Sailer, 1997). The presence of an 11-keto group and hydrophilicity on the A-ring of the pentacyclic ring system was crucial for AKBA's potent 5-LO inhibitory activity (Sailer et al., 1996).

In another report, **UA, 27, 263**, and **276** were evaluated as potential inhibitors of HLE. Among these triterpenes, **UA** and **263** showed marked HLE inhibitory activity with IC_{50} values of 4.4 and 1.9 μM, respectively. The appearance of HLE inhibition may depend on the presence and the orientation of two reactive groups in the tested molecules (Mitaine-Offer et al., 2002).

Inhibition of intercellular adhesion molecule (ICAM-1) expression induced by TNF-α

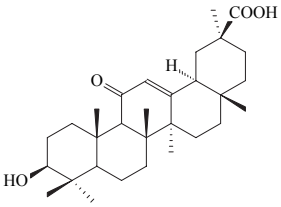
ICAM-1 is a member of the immunoglobulin superfamily of adhesion molecules, and appears to lead to acute and chronic inflammation. The inhibitory effects of oleanane-type triterpenoids from fabaceous plants on the TNF-α-induced expression of ICAM-1 on THP-1 human monocytic leukemia cells were reported. The activity



259 R_1=OH, R_2=COOH, R_3=CH_3, R_4=OH, R_5=CH_3

260 R_1=H, R_2=CH_2OH, R_3=H, R_4=CH_3, R_5=CH_3

261 R_1=H, R_2=COOH, R_3=H, R_4=CH_3, R_5=CH_2OH



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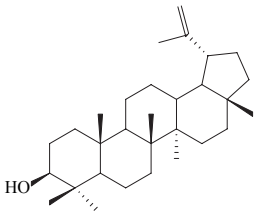

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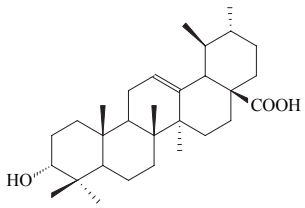

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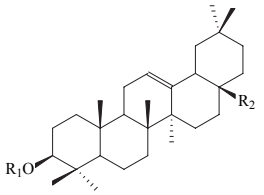
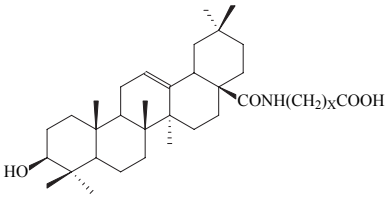


266 R_1=$COCH_3$, R_2=$CONH_2$

267 R_1=H, R_2=$CONH_2$

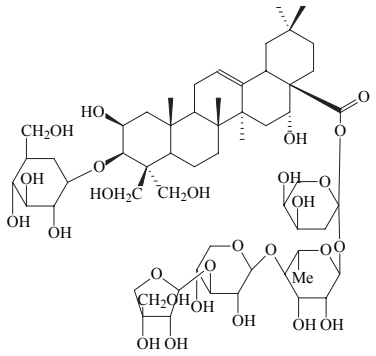
271 R_1=H, R_2=CH_2OH



268 X=1

269 X=4

270 X=10



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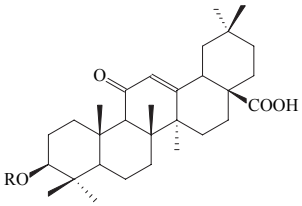


272 R=$COCH_3$

273 R=H

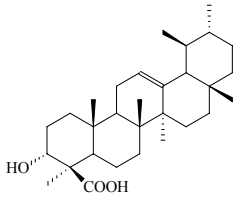
of oleanane saponins and sapogenins against ICAM-1 expression appears to be dependent upon the position of the hydroxyl group, in particular upon the status of the C-21 and C-24 positions, and of the glycosyl group at C-3 position (Ahn et al., 2002).

HEPATOPROTECTIVE ACTIVITIES

OA has been successfully used as an oral drug to treat human acute and chronic liver diseases in China (Qu, 1981). **UA** has been observed to be more potent than **OA** in decreasing chemically induced liver injury in mice (Liu et al., 1994).

OA 3β-phthalic monoester disodium salt (**277**) was synthesized in order to increase the solubility of **OA** in water. Compound **277** inhibited the rising of serum ALT caused by D-galactosamine and CCl_4, and dramatically decreased liver fat storage, in addition to alleviating the condition of the degeneration of hepatic cells and necrosis (Wan et al., 1998).

OA sodium salt **(278)** obviously inhibited the rising of ALT and serum phosphatase caused by CCl_4 when hypodermically injected (100, 50, and 30 mg/kg) (Zhang et al., 2000). When cadmium is administered as $CdCl_2$ to animals, most of it accumulates initially in the liver. Accordingly, the acute toxic effects of cadmium are observed mainly in the liver. Several triterpenes were investigated for the effect on cadmium toxicity in Hep G2 cells. Among them, 18α-glycyrrhetinic acid (**262**) and 18β-glycyrrhetinic acid (**28**) had no protective effects, **OA, UA**, and glycyrrhizin (**279**) exhibited weak effects, and betulin (**280**) and uvaol (**281**) were more effective in



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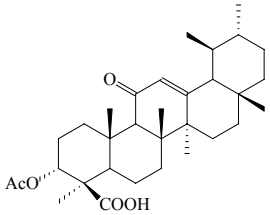

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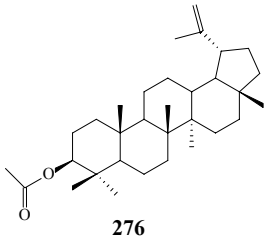

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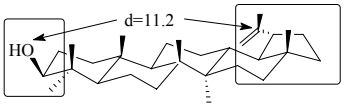

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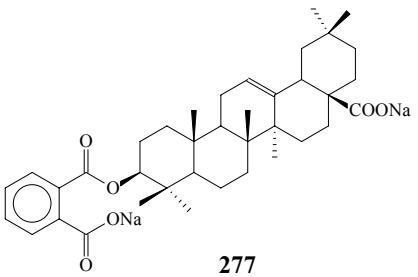

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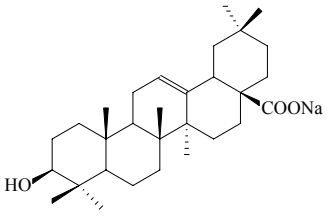

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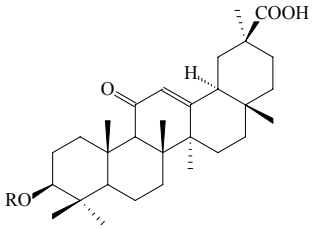
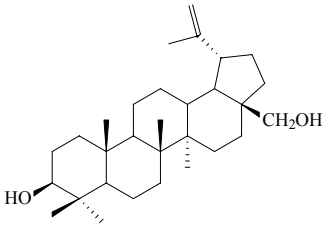


279 R=α-D-Glc(1⟶2) β-D-Glc(1⟶



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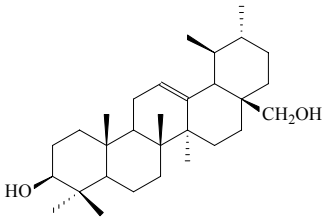


281

reducing the toxicity of $CdCl_2$. Betulin (**280**), in particular, almost completely abolished the cytotoxicity of $CdCl_2$ at concentrations as low as 0.1 μg/mL (Miura et al., 1999).

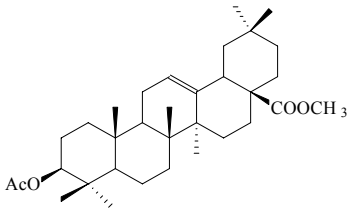
GASTROPROTECTIVE ACTIVITIES

OA displayed gastroprotective effects in three different experimentally induced gastric ulcer models in rats (Astudillo et al., 2001). Five semi-synthetic derivatives of OA (**OA-28-methyl ester**, **282**, **OA-3-acetyl**, **OA-3-oxo**, and **OA-3-oxo-28-methyl ester**) were assessed for gastroprotective effects in the HCl/ethanol ulcer model in mice. The lesion index was 15.7~39.3 mm. Oxidation of the OH at C-3 reduced the activity of **OA** and its derivatives, while methylation of the 28-COOH with or without acetylation at C-3 did not affect the gastroprotective activities of the compounds (Astudillo et al., 2001).

Eight glycosides (**283-290**) of **OA** were examined for the effects on ethanol- or indomethacin-induced gastric mucosal lesions in rats. Saponins **283**, **284** and **287** were effective on ethanol- or indomethacin-induced lesions, but **285**, **286**, **288**, **290** and their aglycone **OA** did not show such effects. Diglycoside **289** did not inhibit the indomethacin-induced lesions, but **288** (50 mg/kg) did have gastroprotective effect. The results demonstrated that the 3-O-glycoside moiety was essential for the activity, and the 28-ester glucoside reduced the activity (Matsuda et al., 1998b).

ANTIMICROBIAL ACTIVITIES

OA was reported to have antimicrobial activity against *B. subtilis* (MIC=8 μg/mL), methicillin-sensitive (MIC=8 μg/mL) and resistant (MIC=64 μg/mL) *S. aureus*. In this study, 3-*O*-(E)-hydroxycinnamoyl OA (**5**) did not show antimicrobial activity (Woldemichael et al., 2003b). In a separate study OA-28-methyl ester showed weak antibacterial activity against *M. luteus* and *E. coli* (Weimann et al., 2002).



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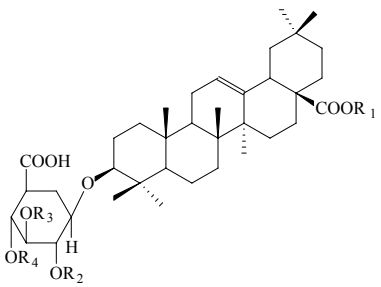
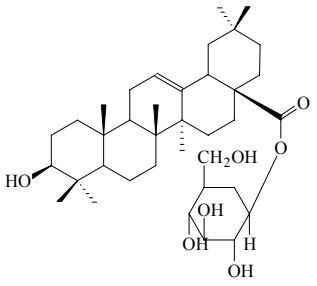


	R_1	R_2	R_3	R_4
283	H	H	H	H
284	H	H	Xyl	H
285	Glc	H	Xyl	H
286	Glc	H	H	Ara(f)
287	H	H	H	Ara(f)
288	Glc	Glc	H	H
289	H	Glc	H	H



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OA, **UA**, **25**, α-amyrin acetate (**291**), **UA-3-acetyl**, and **292-295** were isolated from *Alyxia insularis* Kanehira & Sasaki, and examined for antimicrobial activity. Only two compounds, both of which contained an 11-carbonyl group (**292**, **293**), showed inhibitory activity on the growth of *S. epidermidis, M. luteus, S. aureus, B. subtilis,* and *S. faecium* (at 100 and 50 µg/mL) (Wang et al., 1993). Compounds **296-299** were isolated from *Dillenia papuana* and showed antibacterial activity (Table 12). It was presumed that the carboxylic group and $\Delta^{12, 13}$ double bond played an important role in antibacterial activity (Nick et al., 1994). The MICs of **OA**, **OA-3-oxo**, 3-epi-OA (**300**), **28**, **301**, and **302** against *M. tubercular* were 50, 16, 16, 128, 64 and 64, respectively. It was concluded that the low polarity pentacyclic triterpenes with a hydroxyl or keto group in the A or B ring and an acid group in the E ring possess moderate antitubercular activity (Caldwell et al., 2000).

3-epi-UA (**264**) and **300** showed antimycobacterial activity with MIC values of 8 and 16 µg/mL, respectively (Woldemichael et al., 2003a). Six triterpene saponins **54,** and **303-307**, were isolated from *Hedera helix* L., and tested against *C. albicans, B. cereus, S. epidermidis* and *E. coli.* Only compound **303**, a monodesmosidic saponin with **OA** as aglycone, showed inhibitory activity. The MIC values of **303** were 64 ppm against *C. albicans,* and 128 ppm against *S. epidermidis* and *B. cereus*. The MIC value of reference chloramphenicol was 16 ppm for *S. epidermidis* and *B. cereus*. The other saponins (**54**, **304-307**) showed no inhibitory activity. Thus, it was presumed the antibacterial activity was related to the presence of a monodesmosidic saponin with **OA** as aglycone (Bedir et al., 2000).

Table 12. Antibacterial activity of **296-299**.

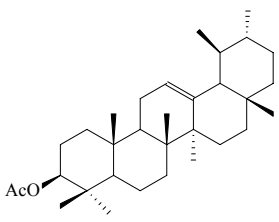
	Minimum growth inhibition (µg)		
	B. subtilis	*E. coli*	*M. luteus*
296	2.4	2.4	1.2
297	2.0	1.0	1.0
298	2.0	5.0	2.0
299	1.0	1.0	1.0

Positive control: Chloramphenicol MGI=0.1, 0.04, and 0.04 µg, respectively.

OA and **UA** also showed trypanocidal activity. **UA** stopped the movement of all *T. cruzi* epimastigotes at the minimum concentration (MC_{100}) of 88 µM after 48 h of incubation. **OA** was less active (MC_{100}=550 µM), and **27** was inactive (Abe et al., 2002). In contrast, the methyl esters (**UA-** and **OA-28-methyl ester**) and acetates (**UA-** and **OA-3-acetyl**) of **UA** and **OA** were not active, but **OA-3-oxo** (IC_{50}=294.9 µM), **308** (IC_{50}=402.3 µM) and **309** (IC_{50}=56.6 µM) retained the activity. These results suggested the importance of the polar groups to trypanocidal activity (Cunha et al., 2003).

Two OA saponins, **290** and **310**, from *Viguiera decurrens* showed insecticidal activity, and their LC_{50} values were 1380 and 80 µg/mL against *Epilachna varivestis* larvae, respectively (Marquina et al., 2001). 3-epi-OA (**300**) possessed antiprotozoal activity (IC_{50}=18.8 µM against *L. donovani* promastigotes; and 28.3 µM against *P. falciparum*) (Camacho et al., 2000).

Four saponins (**49**, **50**, **311** and **312**) were isolated from *Serjania salzmanniana* and were mollusicidal, causing 70-100% mortality at 10 ppm against *Biomphalaria alexandrina*. The saponins also showed antifungal activity against *Cryptococcus neoformans* and *Candida albicans* with MIC at inhibitory concentrations of 8 and 16 µg/mL, respectively (Ekabo and Farnsworth, 1996).



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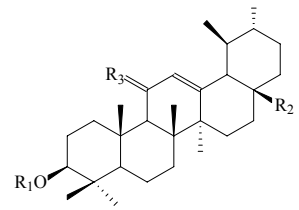
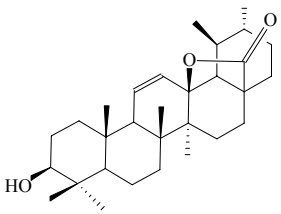


292 R_1=Ac, R_2=COOH, R_3=O
293 R_1=H, R_2=COOH, R_3=O
294 R_1=Ac, R_2=CH_3, R_3=O



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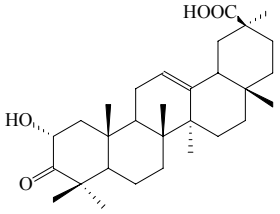

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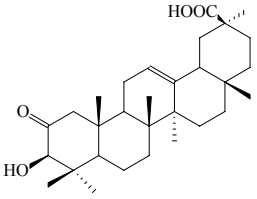

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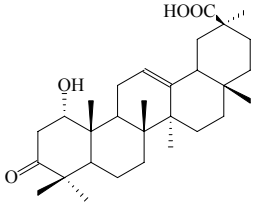

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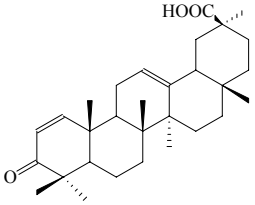

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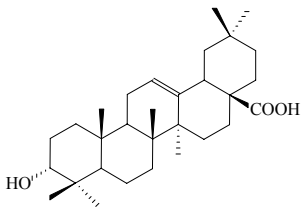

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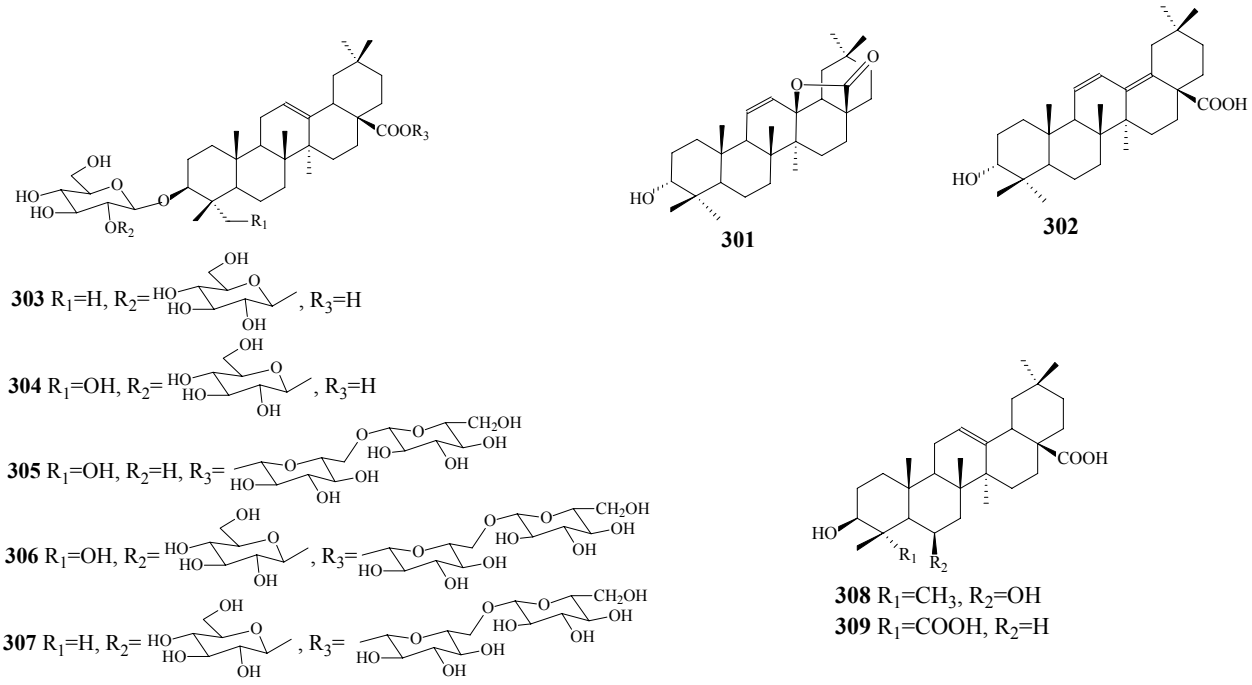


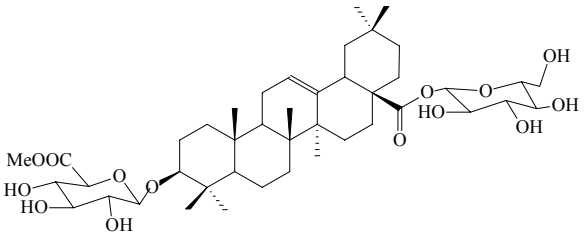
Various dosages (1.9 to 3.0 g/kg) of **OA** could affect the survival, growth, and development of the larvae of *heliothis zea*. This might be one of the plant's defense mechanisms against phytophagous insects (Argandona and Faini, 1993). **OA, UA,** and their synthesized 3-O-fatty acid ester analogues (**313-318**) were examined for antifeedant activity against the agricultural pest tobacco caterpillar *S. litura* larvae. At the dosages of 150, 100, 50 μg/mL, all of the compounds showed antifeedant activity. At 150 μg/mL dose, all the tested compounds showed more than 50% activity, except compounds **OA** and **318**. At 100 μg/mL dose, the compounds showed 40~78% activity, while compound **318** again showed the lowest activity. Even at 50 μg/mL, compounds **314-317** exhibited more than 50% activity. Compounds **316** (74%) and **317** (71%) were found to exhibit exceptionally potent activity at 50 μg/mL (Mallavadhani et al., 2003).

ANTI-DIABETES ACTIVITIES

Many late complications of diabetes are associated with hypoglycemia. OA glycosides (**283**, **286**, **287**, and **319-324**) from the root of *Aralia elata*, which has been used for treating diabetes, were examined for hypoglycemic activity in the oral sucrose tolerance in rats (Table 13). It was concluded the 3-O-glycoside moiety was essential to the activity, while the 28-ester glucosidal moiety significantly reduced the activity. In the 3-O-oligoglycoside structure, the 3'-O-glucopyranosyl moiety tended to decrease the activity, while the 4' -O-arabinofuranosyl moiety increase it (Yoshikawa et al., 1994; 1996a, b; Fujimura et al., 1996). The 6'-methyl ester of the glucuronic acid (**325**) moiety strongly reduced the activity (Matsuda et al., 1998c). The above summaries for SARs were substantiated further by bioassay results of compounds (**326-329**) from *Beta vulgaris* L., among which **327** and **329** showed hypoglycemic activity, **328** showed weaker activity, and **326** was inactive (Yoshikawa et al., 1996c). **OA** sodium salt **(278)** (s.c. 20 mg/kg·d) obviously reduced blood sugar (Zhang et al., 2000).

Table 13. Inhibitory effects of **283**, **286**, **287**, **319-324**, **326-329** (100 mg/kg, p.o.) on the rise in plasma glucose level by oral sucrose tolerance test.

	Plasma glucose concentration (mg/dl)		
	0.5 h	1 h	2 h
319	18.2	18.7	15.5
320	76.6	44.9	18.9
321	27.7	33.4	36.4
323	71.4	45.4	32.4
322	31.9	28.1	29.5
287	18.0	23.0	16.6
283	26.9	24.4	28.6
324	55.2	37.4	20.0
286	36.0	17.7	20.6
OA	82.8	58.1	30.8
326	81.1	48.9	23.4
327	36.1	41.9	31.2
328	66.9	39.3	12.4
329	39.1	30.0	23.4



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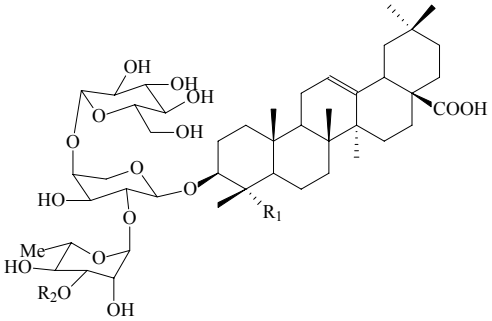
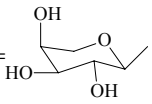
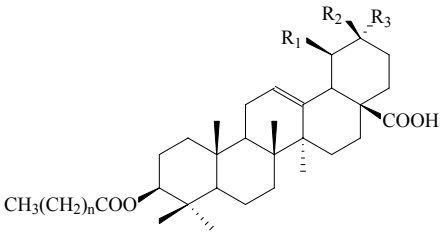


311 R_1=CHO, R_2=H

312 R_1=CH_2OH, R_2= 



313 R_1=CH_3, R_2=H, R_3=CH_3, n=10

314 R_1=CH_3, R_2=H, R_3=CH_3, n=12

315 R_1=CH_3, R_2=H, R_3=CH_3, n=14

316 R_1=CH_3, R_2=H, R_3=CH_3, n=16

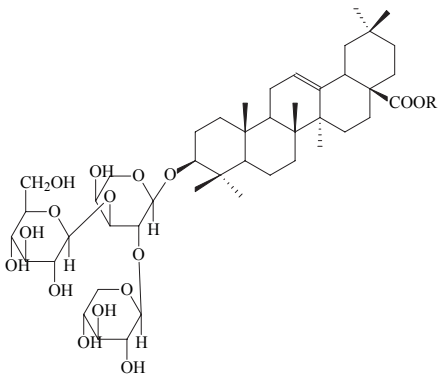
317 R_1=H, R_2=R_3=CH_3, n=14

318 R_1=H, R_2=R_3=CH_3, n=16

Inhibition of α-glucosidase can prevent late complications of diabetes by decreasing the postprandial rise in blood glucose (Bischoff, 1994). **OA** and its five synthetic derivatives (**OA-28-methyl ester**, **OA-3-acetyl**, **330**, **331** and **332**) were found to inhibit α-glucosidase, with IC_{50} values of 11.16, 55.097, 19.012, 7.97, 89.71 and 21.63 μM, respectively. Compound **330** was the most potent among them (Ali et al., 2002).

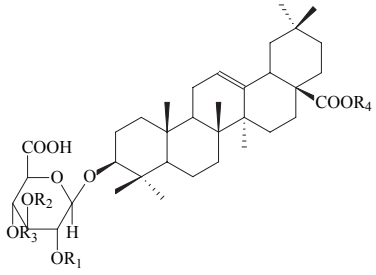
OA and **OA-28-aldehyde** were reported to stimulate insulin production in INS-1 cells. At 12.5 μg/mL, **OA** increased insulin production by 87.97 ng/mg of protein in INS-1 cells. At 25 and 50 mg/ml of **OA**, the secretion of insulin was reduced considerably in a dose-dependent manner, similar to the dose-dependent insulin production by glucose in INS-1 cells. **OA-28-aldehyde** also enhanced insulin secretion by about 4ng/mg in those concentrations (Zhang et al., 2004).

Slowing gastric emptying will prolong the postprandial absorption of food, with a resultant improvement in blood glucose control. **OA** and its oligoglycosides (**283-290**, **333**) were examined for their effects on gastric emptying in mice, and the 3-O-glycosides moiety was found to be essential. The 2'-O-β-D-glucopyranosyl moiety of the glucuronic acid reduced the activity, and the 28-ester glucose moiety markedly reduced it (Matsuda et al., 1999).

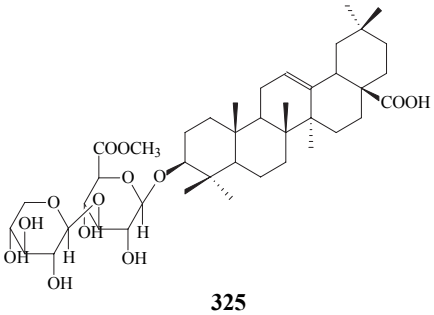


319 R=H

320 R=Glc



	R_1	R_2	R_3	R_4
321	Xyl	Gal	H	H
322	H	Gal	H	H
323	Xyl	Gal	H	Glc
324	H	Gal	Ara	Glc
333	H	Ara(p)	H	H



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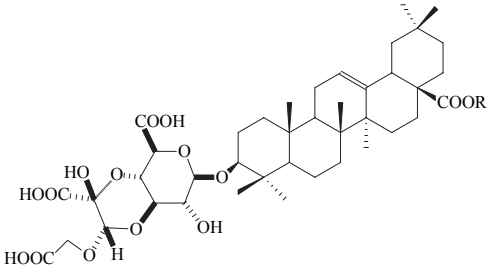
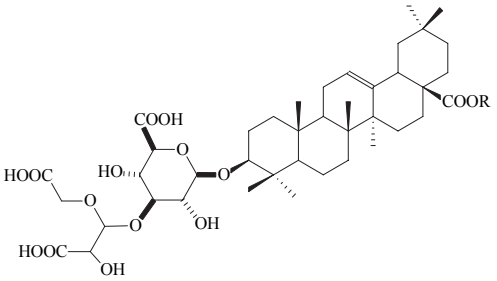


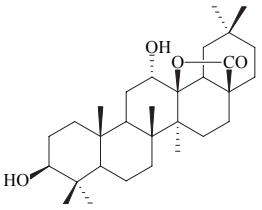
326 R=Glc

327 R=H



328 R=Glc

329 R=H



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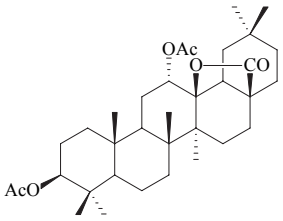

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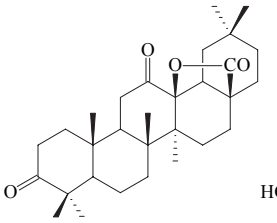

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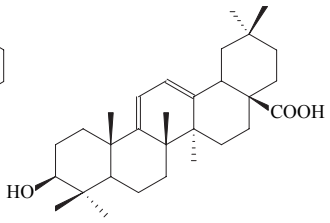


334

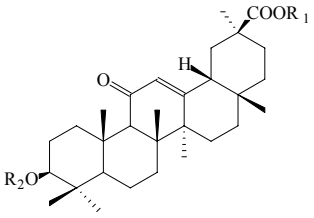
HEMOLYTIC ACTIVITIES

Hemolytic activity is one of the well known characteristics of triterpene saponins. Monodesmosidic OA disaccharides and trisaccharides (**335-355**) were prepared and their hemolytic activity compared (Table 14). The authors concluded that for lactosides of glycyrrhetic acid, its 11-deoxo and 18α-derivatives, and their methyl esters (**335-341**), it was found that 28-COOH might be a basic requirement for strong hemolytic activity of lactosides. Compound **357**, which possessed no detectable hemolytic properties, differed from the highly active **341** only by interchanged positions of a methyl. Esterification increased the hemolytic activity, but esterification of the most OA lactoside **341** led to the almost non-hemolytic compound **340**. The linkage between rings D and E had remarkable influenced on the activity of esters of glycyrrhetic acid lactosides (Ullah et al., 2002). A separate study showed that the connectivity between the sugar units strongly influenced the hemolytic activity of OA disaccharides (**341-346**). The 1→4 linked saponin **341** showed the highest activity. β-configuration of the outer anomeric position showed higher potency in the 1→6 linked saponins, while 1→2 linked glycosides exhibited very low hemolytic properties. Linkage positions 3 or 4 were structural requirements for higher hemolytic activity. The 1→3 linked saponin was more active than the 1→4 linked one, but the hemolytic activities of 1→6 and 1→2 linked analogues were less active (Seebacher et al., 2000). It was also found that OA trisaccharides (**347-350**) usually proved to be less potent than the corresponding disaccharides. A α-configuration of the terminal sugar residue was able to enhance hemolytic activity (Seebacher et al., 1999).

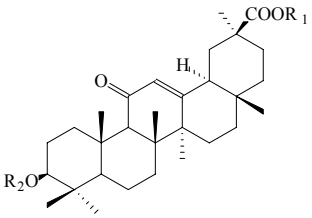
Glycyrrhetic acid disaccharides (**351-355**) were not found to possess detectable hemolytic properties, so the influence of the structure of the aglycon on the hemolytic activity is crucial (Ullah et al., 2000).

Table 14. Hemolytic index (HI) of compounds **335-350**.

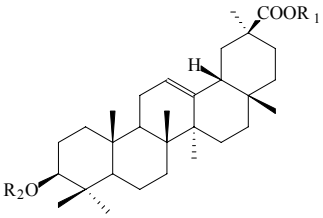
Saponin	Class	HI
335	Monosacchride	<1000
336	Monosacchride	<1000
337	Monosacchride	<1000
338	Monosacchride	135000
339	Monosacchride	19500
340	Monosacchride	10000
341	Monosacchride	150700
342	Disacchride	100100
343	Disacchride	3400
344	Disacchride	3400
345	Disacchride	22000
346	Disacchride	35000
347	Trisacchride	22000
348	Trisacchride	11000
349	Trisacchride	19500
350	Trisacchride	<2000



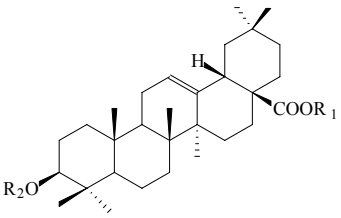
335 R_1=H, R_2=β-D-galp-(1→4)-β-D-glc-(1→
338 R_1=CH_3, R_2=β-D-galp-(1→4)-β-D-glc-(1→
351 R_1=H, R_2=β-D-glc-(1→2)-β-D-glc-(1→
352 R_1=H, R_2=β-D-glc-(1→3)-β-D-glc-(1→
353 R_1=H, R_2=α-D-glc-(1→4)-β-D-glc-(1→
354 R_1=H, R_2=β-D-glc-(1→4)-β-D-glc-(1→
355 R_1=H, R_2=β-D-glc-(1→6)-β-D-glc-(1→



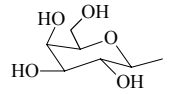
336 R_1=H, R_2=β-D-galp-(1→4)-β-D-glc-(1→
339 R_1=CH_3, R_2=β-D-galp-(1→4)-β-D-glc-(1→

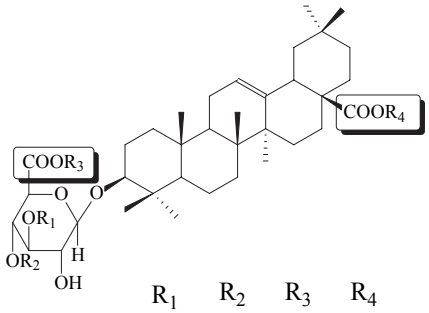


337 R_1=H, R_2=β-D-galp-(1→4)-β-D-glc-(1→



340 R_1=CH_3, R_2=β-D-galp-(1→4)-β-D-glc-(1→
341 R_1=H, R_2=β-D-galp-(1→4)-β-D-glc-(1→
342 R_1=H, R_2=β-D-galp-(1→3)-β-D-glc-(1→
343 R_1=H, R_2=α-D-galp-(1→2)-α-D-glc-(1→
344 R_1=H, R_2=β-D-galp-(1→2)-β-D-glc-(1→
345 R_1=H, R_2=α-D-galp-(1→6)-β-D-glc-(1→
346 R_1=H, R_2=β-D-galp-(1→6)-β-D-glc-(1→
347 R_1=H, R_2=β-D-glc-(1→2)-β-D-glc-(1→6)-β-D-glc-(1→
348 R_1=H, R_2=β-D-glc-(1→3)-β-D-glc-(1→6)-β-D-glc-(1→
349 R_1=H, R_2=α-D-glc-(1→4)-β-D-glc-(1→6)-β-D-glc-(1→
350 R_1=H, R_2=β-D-glc-(1→2)-β-D-glc-(1→6)-β-D-glc-(1→

galp= 



	R_1	R_2	R_3	R_4
356	H	H	Bu	Glu
357	H	H	Me	Glu
358	H	Ara	Me	Glu
359	Gal	H	Me	Glu
360	H	H	Me	H
361	H	Ara	Me	H
362	Gal	H	Bu	H
363	Gal	H	Me	H

Membrane-disrupting activity may cause hemolysis and other various biological activities. Fifteen triterpenoid saponins were classified into four types based on their chemistries and membrane-disrupting activities (Hu et al., 1996).

I: 356-359. Are glycosylated at two sites (C-3 and C-28), and the carboxylic group of the glucuronic acid residue connecting to C-3 was esterified by an alkyl group. Their actions are so strong that they can cause catastrophic rupture when sufficiently accumulated.

II: 360-363. Are glycosylated at a single site (C-3). They bind to the liposomal membrane more strongly than type I, but not enough to cause membrane disruption.

III: 290, **286** and **324**. Are glycosylated at two sites (C-3 and C-28), and the carboxylic group of the glucuronic acid was free. Although these saponins bind to the membrane as efficiently as type I, their disruptive ability was much weaker.

IV: 283, **333** and **322**. Are glycosylated at a single site (C-3) with two carboxylic groups. Their membrane disrupting activity could only be shown in the presence of cholesterol.

MISCELLANEOUS

Oleanane- and ursane-type triterpenoids have many other activities besides the above nine activities, but they have been researched and reported less. The following activities, which have structure-activity relationships, are introduced briefly all together.

Spasmolytic activity

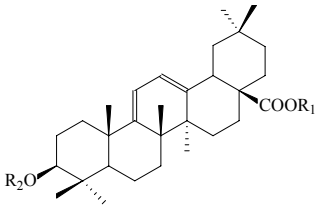
Eucalyptanoic acid (**364**) and its acetyl (**365**) and acetylmethyl (**366**) derivatives, as well as **OA** and **OA** acetyl (**197**) and acetylmethyl (**282**) derivatives, were tested for spasmolytic activity (Table 15). Among them, the presence of the 28-COOMe and C-9(11) double bond enhanced the activity, while the acetoxy group at C-3 decreased it (Begum et al., 2002).

Antipruritic activity

OA 3-O-monodesmosides (**283-285**, **288**, **289**, and **367-370**) were examined for the antipruritic effects using a compound 48/80-induced pruritic model in mice (Table 16). OA 3-O-monodesmosides showed antipruritic effects, while **OA** and its 3, 28-O-bisdesmosides did not. Moreover, the 3-O-glucuronides showed more potent activity than the corresponding 3-O-glucosides (Kubo et al., 1997; Matsuda et al., 1998a).

Anti-thrombotic activity

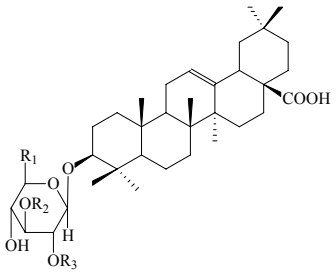
OA showed inhibitory effects on blood platelet aggregation. It not only inhibited blood platelet aggregation induced by adenosine 5'-diphosphate (ADP) and collagen in old mice, but also increased electrophoretic mobility at therapeutical dosage (75-300 mg/kg) (Liu and Wang, 1993). Compounds **371**, **372**, **UA** and **OA** were isolated from *Chaenomeles sinensis*, and tested for the inhibitory activity of tissue factor (TF), which could accelerate the blood clotting. Among these compounds, only **371** and its aglycone **371a** inhibited TF activity, and IC_{50} values were 0.036 and 0.028 mM/unit, respectively. However, **372**, **UA**, **OA** and the dimethyl ester derivative **371b** of **371a** showed no inhibitory activity. These results indicated that the presence of two free carboxyl groups of **371a** played an important role in exerting the inhibitory activity on TF (Lee and Han, 2003).



364 R_1=R_2=H
365 R_1=H, R_2=CH_3CO
366 R_1=CH_3, R_2=CH_3CO

Table 15. Effect on Spontaneous conreactions and K^+-inducedcontractions.

	Effect (% inhibition)	
	Spontaneous conreactions	K^+-induced contractions
364	58.2	31.1
365	No effect	No effect
366	95.3	85.9
OA	No effect	No effect
197	No effect	No effect
282	67.7	35.5

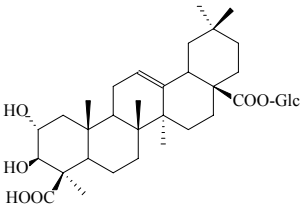


367 R_1=CH_2OH, R_2=R_3=H
368 R_1=CH_2OH, R_2=Xyl, R_3=H
369 R_1=COOH, R_2=Ara, R_3=H
370 R_1=COOH, R_2=Glc, R_3=Glc

Table 16. Effects on compound 48/80-induced scratch behavior in mice.

	Dose (mmol/kg)	Inhibition (%)
OA	0.05	13.7
	0.2	9.9
283	0.05	-0.9
	0.2	52.4
284	0.05	2.2
	0.2	65.8
288	0.05	16.0
	0.2	2.0
367	0.05	-4.5
	0.2	17.0
368	0.05	28.5
	0.2	48.9
289	0.05	-16.8
	0.2	64.0
369	0.065	4.2
	0.13	58.9
370	0.05	43.6
	0.10	43.6
285	0.05	-1.1
	0.11	9.4

Positive control was diphenhydramine hydrochloride, which inhibitions were 26.4 and 84.7 at dosage 0.05 and 0.2 mmol/kg, respectively.



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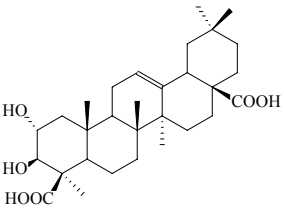
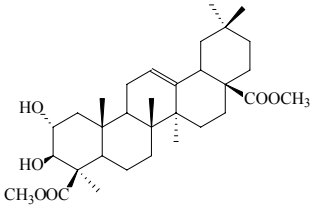


371a



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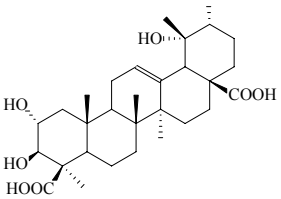

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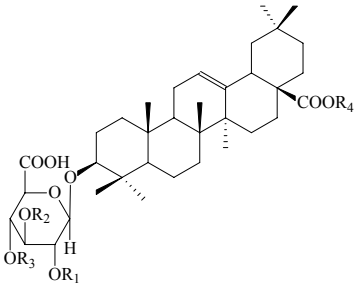


	R_1	R_2	R_3	R_4
373	Gal	Gal	H	H
374	Gal	Gal	H	Glc
375	H	Glc	H	H
376	H	Glc	Ara(f)	H
377	H	Glc	H	Glc
378	H	Glc	Ara(f)	Glc

Table 17. Inhibitory activity of **321**, **323**, **373-378** on ethanol absorption.

	Dose (mg/kg p.o.)	Ethanol absorption in blood (mg/ml)		
		1 h	2 h	3 h
321	25	0.11	0.13	0.02
	50	0.01	0.04	0.01
	100	0	0	0
373	25	0.56	0.19	0.01
	50	0.50	0.19	0.02
	100	0.25	0.18	0.02
341	100	0.57	0.24	0.04
374	100	0.57	0.23	0.04
375	25	0.26	0.20	0.03
	50	0.03	0.04	0.02
	100	0.03	0.02	0.01
376	25	0.42	0.21	0.03
	50	0.34	0.18	0.01
	100	0.08	0.09	0
377	100	0.58	0.21	0
378	100	0.56	0.23	0.04

Inhibitory activity of ethanol absorption

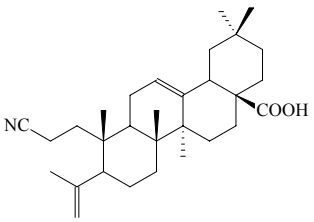
Excessive consumption of ethanol is known to profoundly affect nearly every organ in the body. OA 3-O-monodesmosides (**321**, **373**, **375** and **376**) were found to show potent inhibitory activity on ethanol absorption, while 3, 28-O-bisdesmosides (**323**, **374**, **377** and **378**) lacked the inhibitory activity (Table 17). Some OA 3-O-monodesmosides were found to show potent inhibitory activity on ethanol absorption, while 3, 28-O-bisdesmosides lacked the inhibitory activity (Yoshikawa et al., 1993 and 1996c).

Effects on nonmalignant prostate cell proliferation

Eight synthesized A-ring cleaved oleanane and ursane analogues (**379-386**) were assessed for their ability to inhibit cell proliferation in NRP.152 (nonmalignant) prostate cells (Table 18). It was found that each pair of ursane and oleanane derivatives exhibited similar activities, and A-ring cleaved compounds were more active. In A ring cleaved series, both conversions of nitriles corresponding aldehydes and reduction of the nitriles to the amines resulted in increased activity (Finlay et al., 1997).

Table 18. Inhibitory activity on NRP 152 prostate cell proliferation.

Compound	IC_{50} (μM)	Compound	IC_{50} (μM)
386	0.3	**OA**	>5.0
385	0.7	**UA**	>5.0
383	1.5	**OA-3-oxo**	>5.0
384	2.4	**UA-3-oxo**	>5.0
379	3.8	**381**	>5.0
380	>5.0	**382**	>5.0



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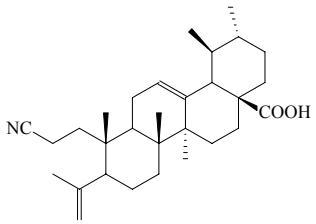

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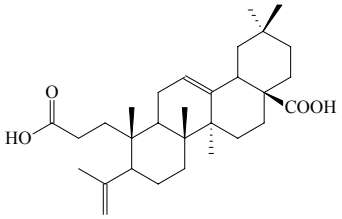

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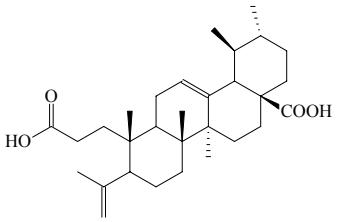

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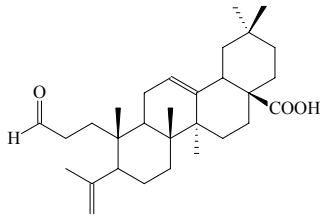

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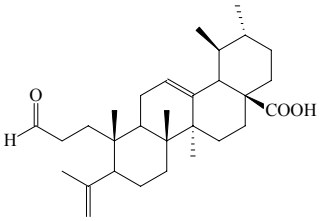

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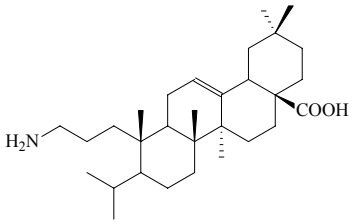

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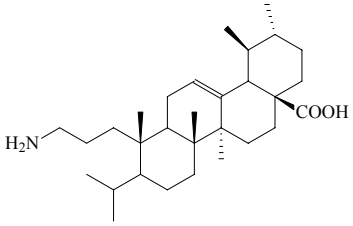

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