REVIEW

School of Chinese Pharmacy, Beijing University of Chinese Medicine, Beijing, China

Oleanolic acid synthetic oligoglycosides: a review on recent progress in biological activities

KUO XU, FUHAO CHU, GUOLIANG LI, XIN XU, PENGLONG WANG, JIXIANG SONG, SEN ZHOU, HAIMIN LEI

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Prof. Haimin Lei, School of Chinese Pharmacy, Beijing University of Chinese Medicine, 6 Wangjing Middle Ring South Road, Beijing 100102, China
hm_lei@126.com

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The natural product oleanolic acid has been widely used for treating hepatopathy in China, whereas its clinical application was confined by poor solubility in water. Inspired by remarkable bioactivities and physical properties of triterpenoid saponins, synthesis and biological evaluation of oleanolic acid oligoglycosides drew considerable attention. In the past several years, chemical efforts were made toward glycosylated modifications of oleanolic acid at C_3-OH and C_{17}-COOH, of the carbons at ring A/C, and of the functional groups of oleanolic acid lactone. To provide useful information for further study and applications of oleanolic acid derivatives, a total of 177 oleanolic acid synthetic oligoglycosides and their bioactivities (e.g., antiosteoporosis, antidiabetes, antibacterial, anticancer and hemolytic effects) were reviewed; structure-activity relationships and promising agents are indicated.

1. Introduction

As a natural pentacyclic triterpenoid, oleanolic acid (Fig. 1) is a bioactive component that is widely spread in various plants including 146 families, 698 genera and 1620 species up to Sep. 2007 (Fai and Tao 2009); it's especially prevalent in plants belonging to Oleaceae, among which *Olea europaea* still serves as the main source of commercial oleanolic acid (Pollier and Goossens 2012). Oleanolic acid not only occurs as a free molecule in plants, but also serves as an aglycone precursor for triterpenoid saponins, which were a structurally and biologically diverse class of glycoconjugates of triterpenoids and widely distributed in terrestrial plants and some marine organisms (Yu and Sun 2009). A variety of oleanolic acid oligoglycosides might function as defense compounds on herbivores or pathogens, or as allelopathic agents (Szakiel et al. 2003, 2005).

Oleanolic acid has been proved to possess a wide range of biological activities (Liu 1995). A number of oleanolic acid-containing Traditional Chinese Medicine prescriptions have been approved by SFDA as hepatoprotective, antiinflammatory, analgesic, and cardiotonic drugs. Oleanolic acid appeared on the market in 2010 and had been widely used for adjuvant treatment of hepatic injury and hepatitis; it was proved to possess other promising pharmacological activities, such as anticancer, antidiabetic, and antiinflammatory effects (Khathi et al. 2013; Li et al. 2002; Liu 2005; Ngubane et al. 2011; Sultana and Ata 2008; Wang et al. 2013). However, oleanolic acid's poor solubility limited its clinical application; so many structural modifications were done to search effective and water-soluble lead compounds. In view of the remarkable pharmacological and physical properties of triterpenoid saponins, studies on oleanolic acid oligoglycosides draw considerable attention; the lack of a comprehensive and lately review on this subject prompted us to gather much new information. Unlike the review on novel synthetic methods toward triterpenoid saponins (Yu and Sun 2009), the present paper aimed to provide a summary of the glycosylation efforts and activity overview of oleanolic acid oligoglycosides.

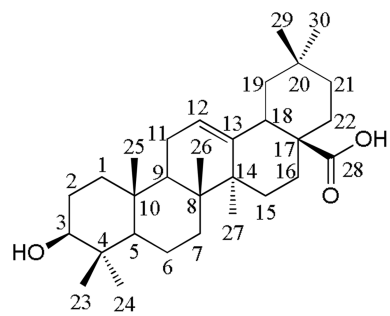


Fig. 1: The structure of oleanolic acid.

2. Design and synthesis of the oleanolic acid oligoglycosides

Over the past few years, a lot of research has been committed to the synthesis of oleanolic acid oligoglycosides. The reported triterpenoid oligoglycosides mainly originated from two methods, one is the total synthesis of natural saponins; the other is synthesis of natural saponins' analogues. As far as we know, oleanolic acid oligoglycosides could be classified in three groups, C_3-OH or/and C_{17}-COOH derivatives of oleanolic acid, carbon rings derivatives of oleanolic acid, and functional group derivatives of oleanolic acid lactone; although they possessed enormous structural diversity, all of them were synthesized from oleanolic acid.

Table 1: Inhibitory rate on osteoclast-like multinucleated cells (OCLs) formation (%) (Li et al. 2009)

NO.	Mp/°C	Yield (%)	20 μM (%)	2 μM (%)
5	239–241	87.6	1.3± 0.2	98.7 ± 5.2
6	260–262	78.2	5.7 ± 0.5	99.3 ± 5.2
17	210	69	0	78.1 ± 9.3
18	192	71	0	64.4 ± 12.8
19	252	73	0	30.2 ± 10.7
20	240	70	9.5 ± 5.0	98.4 ± 7.4
21	229	67	0	54.4 ± 15.6
22	212	68	0	98.5 ± 6.9
23	196	69	0	61.3 ± 13.7
24	193	68	0	96.7 ± 10.9
25	215	71	0	99.0 ± 6.7
26	210	70	0	91.3 ± 12.2
27	171	71	0	88.3 ± 8.2
28	178	72	0	59.4 ± 18.3
160	243–245	91	0	98.2 ± 5.2
161	239–241	87.60	1.3 ± 0.2	98.7 ± 5.2
162	> 280	95.00	54.7 ± 2.9	95.5 ± 5.0
163	260–262	78.20	5.7 ± 0.5	99.3 ± 5.2
164	194–196	66.80	19.3 ± 1.1	16.0 ± 0.8

Notice: [a]) Mp refers to Melting point; [b]) Yield refers to comparative productivity for the last reaction.

2.1. Glycosylation modifications at C_3-OH and C_{17}-COOH of oleanolic acid

Oleanolic acid has two potential glycosylation sites at C_3-OH and C_{17}-COOH, which could be modified to form 3-O-monoglycosides, 28-O-monoglycosides and 3, 28-di-O-glycosides. With no processing on C_3-OH, C_{17}-COOH linking to monoglycosides is the common way; these monoglycosides are often composed of different carbon chains or comprise a triazole moiety (Cheng 2009; Li et al. 2009; Sha et al. 2008; Yan 2008). Oleanolic acid oxidized to be a 3-keto derivative, then a mixture of the 3-keto derivative and phenylhydrazine under special condition could provide [3,2-b] indole oleanolic acid, while the 3-keto derivative mixed with 2,4-dinitrophenylhydrazine could afford 3-phenylhydrazone oleanolic acid. Using oleanolic acid's 3-keto derivative and 3-phenylhydrazone oleanolic acid as the parent structures, Li et al. (2005, 2009) designed and synthesized a series of compounds under phase-transfer-catalyzed conditions. Just like the above mentioned reaction route, catalyzed by pyridine, the 3-keto derivative of oleanolic acid and hydroxylamine hydrochloride could form another mother structure; then evolving into corresponding glycosides (Meng et al. 2011). In order to improve the aqueous solubility and cell penetration of a bioactive furoxan-based NO releasing derivative of oleanolic acid, eleven monosaccharide and three disaccharide derivatives have been synthesized by coupling those related O-acetylated glycosyl bromides to C_{17}-COOH with subsequent deacetylation (Huang et al. 2010, 2011).

C_3-OH was commonly modified to form 3-glycosides of oleanolic acid bearing different natural monosaccharides and disaccharides (Li et al. 2009; Qian et al. 2010; Sha et al. 2008; Yan 2008). The Schmidt method was used for glycosylation of oleanolic acid, and benzyl was chosen as the protective group for C_{17}-COOH group to avoid difficulties in the final deprotection (Zhao et al. 2011). To simplify the previous structure and investigate the role of L-rhamnopyranosyl residues in oleanane-type saponins, especially in the *Di Wu* saponins, Huang et al. (2009) reported some structural analogues of the natural saponins. Except for those esterifications on C_{17}-COOH, Qu et al. (2003) introduced ω-aminocarboxylicacid into the same location, and connected C_3-OH with oligosaccharides.

Table 2: IC_{50} values for rabbit muscle glycogen phosphorylase-α inhibition (μM) (Cheng et al. 2009)

NO.	Mp/°C	$[\alpha]_D$	$[\alpha]_D$ Yield (%)	IC_{50} (μM)
7	138–139	+ 95.2	93	—
8	142–143	+ 56.8	43	1.14
9	73–74	+ 23.1	88	11.6
10	98–100	−9.3	76	—
11	59–61	—	88	50.4
12	84–86	+ 73.1	85	—
13	53–55	—	94	41.6
14	89–91	+ 72.8	86	—
15	72–74	+ 59.2	88	136.5
16	—	—	38	—
87	107–108	+ 102.5	83	466.9
88	116–118	+ 85.5	78	—

Notice: [a]) Mp refers to Melting point; [b]) [α] refers to the Specific Rotation of these compounds; due to different test conditions, the data may be various; [c]) Yield refers to comparative productivity for the last reaction.

Wang (2004) applied triphenylmethyl as the protection group and succeeded in glycosylating C_3-OH into amino oligosaccharide under low temperature. Glycosyl derivatives of NO donor could be recognized by glucose transporter proteins and asialoglycoprotein receptors, thus enhancing glycosylated NO donor's selectivity and cytotoxicity; therefore, O^2-glycosylated diazeniumdiolate-based derivatives of oleanolic acid were synthesized (Huang et al. 2012). Inspired by the structural features of Scabiosaponins E-G (**132**, **141**, **152**), a series of oleanolic acid derivatives were also designed (Liu 2010). Using the association principle of drug design, an oleanolic acid disaccharide with a nitrile at C-17 was reported to be a unique sugar sequence with strong antitumor activity (Pei et al. 2012). Saito et al. (1993) obtained two bisdesmosides of oleanoic acid and examined their cytoprotective effects; Seebacher et al. (1999) reported the first partial synthesis of oleanolic acid trisaccharides with different points of linkage of the terminal glucose units. So far, although a variety of saponins have been disclosed, saponins containing *N*-acetylglucosamine are rare. Referring to the structure of a

Table 3: α-Glucosidase inhibitory activity of synthetic oleanolic acid oligoglycosides (%) (Qian et al. 2010)

NO.	Mp/°C	$[\alpha]_D^{20}$	Yield (%)	Inhibition (%)
45	240–241	+ 21.3	90	11.35
46	235–236	+ 19.0	—	15.49
47	238–239	+ 18.6	—	14.71
54	152	+ 17.1	72	13.33
55	—	—	—	8.97
56	—	—	—	10.48
57	—	—	—	15.11
58	236–238	+ 18.7	—	9.04
114	—	—	—	15.77
115	220–221	+ 16.0	74	12.32
120	—	—	—	15.18
121	220–221	+ 14.9	—	14.38
168	141–143	+ 13.4	57	13.92
169	182–184	+ 27.9	85	16.8
170	—	+ 11.9	—	15.83
171	—	+ 12.3	41	17.17
172	—	+ 21.6	67	15.79

Notice: [a]) Mp refers to Melting point; [b]) [α] means to the Specific Rotation of these compounds; due to different test conditions, the data may be various; [c]) Yield refers to comparative productivity for the last reaction.

natural compound isolated from *Acacia tenuifolia* and *Albizia subdimidiata*, Sun et al. (2003) designed and synthesized a series of *N*-acetylglucosamine derivatives of oleanolic acid. Randianin (**116**) is a haemolytic active saponin from *Catunaregam spinosa*. Its isomers with different carbohydrate side chains and the influence of the linkage within the disaccharide residue on haemolytic activity were investigated (Seebacher et al. 1999).
The other important source is complete synthesis of natural bioactive saponins. As is well known, separation of homogeneous saponins from natural sources is dull and formidable, while chemical synthesis would provide a realistic way to obtain homogeneous saponins. Li et al. (2006) described the preparation processes of two triterpenoid saponins (**113**, **133**) isolated from *Fagonia indica*. Scabiosaponins E-G (**132**, **141**, **152**) exist in *Scabiosa tschiliensis* and possess strong inhibitory activity on pancreatic lipase. They have efficiently be achieved in an one-pot strategy under combined use of glycosyl trichloroacetimidates and *p*-toluene 1-thioglycosides as donors (Guo et al. 2009; Liu 2010). The development of various glycosylation methods and sophisticated approaches, especially the development of a 'one-pot sequential glycosylation' strategy greatly facilitated the synthesis of oligosaccharides and glycoconjugates bearing complicated sugar moieties. Liu et al. (2009) adopted the strategy and completed the synthesis of two natural triterpenoid saponins (**155**, **157**) from *Pulsatilla chinensis*, which exhibited excellent *in vitro* cytotoxic activity on HL-60 cells. All of these C_3-OH or/and C_{17}-COOH oligoglycosides of oleanolic acid are shown in Fig. 2 (-R referrs to substituent groups; OA referrs to C_3-OH of oleanolic acid).

2.2. Glycosylation modifications of the carbons at ring A/C of oleanolic acid

There are also other oleanane-style mother structures derived from oleanolic acid, where free functional groups are glycosylated to obtain the corresponding saponins. Taking advantage of dihydrooleanolic acid produced by Wolff–Kishner reduction of 3-acetoxy-12-oxo-oleanolic acid in diethylene glycol solution, a series of sugar-based derivatives had been designed and obtained at phase-transfer-catalyzed conditions (Li et al. 2009). Similarly, Meng et al. (2011) linked C_{17}-COOH of 3-hydroxy-11-oxo-12-alkenyl-oleanolic acid to glucose and gained related saponins. The other common chemical modifications of carbons at ring A/C were designing and synthetizing CDDO analogues. CDDO was a potent, multifunctional agent in various *in vitro* assays and its methyl ester showed high inhibitory activity against production of nitric oxide in mouse macrophages; to better expound structure-activity relationships of CDDO, Honda et al. (2002) modified it at C-2 and C-17. All oligoglycosides of oleanolic acid carbons at ring A/C are shown in the Fig. 3.

2.3. Glycosylation modifications of oleanolic acid lactone

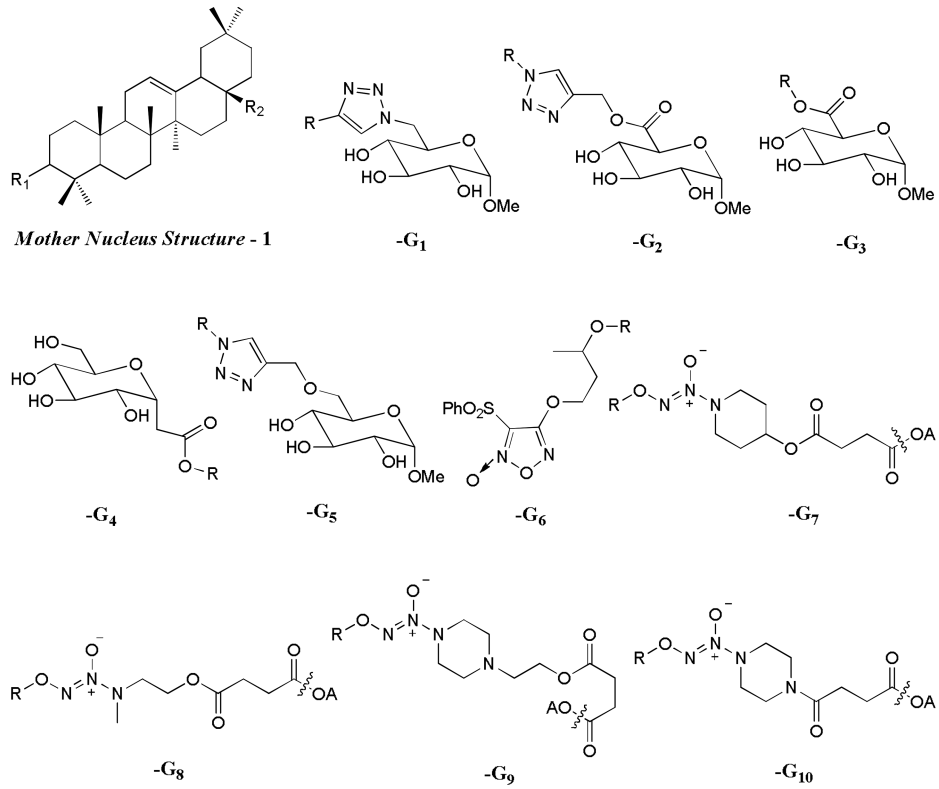
To our knowledge, oleanolic acid lactone was first synthesized by Han et al. (1984); and then, the associated synthetic oligoglycosides of lactone were designed (Cheriti et al. 1994). Ali et al. (2002) reported the synthesis of several oleanolic acid derivatives, among which, dihydroxy-olide derivatives were found to be the most active inhibitors of α-glucosidase. Based on that, and in order to further investigate whether the influence of the carbohydrate residue was comparable, Qian et al. (2010) obtained a series of oleanolic acid lactone derivatives by introducing different sugar moieties. They designed several related glycosides and reported that oleanolic acid lactones exhibited better water-solubility and bioavailability than oleanolic acid; moreover, the preliminary structure-activity relationship analysis indicated that lactone and glyco-groups were active groups with antiosteoporosis effect (Qian et al. 2012). All the functional oligoglycosides of oleanolic acid lactone are shown in Fig. 4.

3. Biological evaluations of synthetic oleanolic acid oligoglycosides

Oleanolic acid exhibits numerous bioactivities and is widely used to treat liver diseases in China. Recent research verified that oleanolic acid is also a potent anticancer agent to cause apoptosis in HepG2, Hep3B, Huh7 and HA22T cell lines (Kuttan et al. 2011; Pratheeshkumar 2011; Shyu et al. 2010; Yan et al. 2010). It possesses significant antitumor activities against hepatocellular carcinoma *in vivo* and *in vitro* models besides it's potential for treatment of osteosarcoma (Wang et al. 2013; Zhou et al. 2011). Combined use of oleanolic acid and 5-FU synergistically potentiated cell death effects on Panc-28 cells, and pro-apoptotic effects were increased (Wei et al. 2012). Oleanolic acid might advance therapeutic approaches to diseases that were associated with inflammatory reaction and oxidative stress (Dharmappa et al. 2009; Wang et al. 2010); for example, attenuating ischemic stroke, treating vascular inflammatory diseases, or acting as neuro-protective agent (Lee et al. 2013; Rong et al. 2011; Tsai and Yin 2008, 2012). Furthermore, it was proved to improve therapeutic approaches to diabetes mellitus (Wang et al. 2011). Supplementation of oleanolic acid might be helpful for the prevention or alleviation of glycation associated renal diseases (Wang et al. 2010); it ameliorated visceral adiposity and improved glucose tolerance in mice, thus had an antidiabetic potential through modulation of carbohydrate and fat metabolism (Melo et al. 2010). Orally administered oleanolic acid exerted a nephroprotective effect even in the presence of a nephrotoxicant, such as gentamicin, which directly deteriorates the kidney function without prior metabolism (Patil et al. 2010). Except for those above-mentioned bioactivities, oleanolic acid and its glycosides could also be considered as potential antibacterial and antiparasitic agents (Horiuchi et al. 2007; Szakiel et al. 2008). Different from oleanolic acids, biological evaluation of oleanolic acid oligoglycosides mainly concentrated on antiosteoporosis, antidiabetes, antibacterial, anticancer, and hemolytic effects.

3.1. Antiosteoporosis effect

Osteoporosis was widely recognized as a major public health problem, particularly among the postmenopausal women. Extracts from *Achyranthes bidentata* possess antiosteoporosis effects *in vitro* and *in vivo*; further studies verified that oleanolic acid and its glycosides were the active components responsible for antiosteoporosis activity (Li et al. 2005; Zhang et al. 2005). Li et al. (2009) continued to evaluate the inhibitory activity of several synthetic saponins on the formation of osteoclast-like multinucleated cells induced by 1α, 25-dihydroxy vitamin D_3; compounds **19** and **164** displayed quite a strong inhibitory activity even at 2 μM. Any changes in the double bond at the C-ring of oleanolic acid might have a negative impact on activity, while glycosidations improve activity, especially, xylose and glycuronic acid glycosides; a phenylhydrazone moiety at A-ring of oleanolic acid could greatly improve activity, but related glycosides did not show enhanced effects. Preliminary biological *in vitro* screening of lactone derivatives **174–177** for 12 responding protein targets and cells of frequent diseases was processed; compound **177** had significant activity (IC_{50} = 3.58 μg/mL) against cathepsin K, and might be a potent agent for treating osteoporosis (Qian et al. 2012). The



NO.	R_1	R_2	Synthesis Process
1	β-OH	-COO-β-D-Gal	Sha et al., 2008; Yan, 2008; Li et al., 2009
2	β-OH	-COO-β-D-Xyl	Sha et al., 2008; Yan, 2008; Li et al., 2009
3	β-OH	-COO-α-D-Glc-(1→4)-β-D-Glc	Sha et al., 2008; Yan, 2008; Li et al., 2009
4	β-OH	-COO-α-D-Rha	Sha et al., 2008; Yan, 2008; Li et al., 2009
5	β-OH	-COO-β-D-Glc	Li et al., 2009
6	β-OH	-COO-β-D-Ara	Li et al., 2009
7	β-OH	$-COOCH_2(CH_3CO\text{-}G_1)$	Cheng et al., 2009
8	β-OH	$-COOCH_2G_1$	Cheng et al., 2009
9	β-OH	$-COO(CH_2)_6(Bn\text{-}G_2)$	Cheng et al., 2009
10	β-OH	$-COO(CH_2)_6G_2$	Cheng et al., 2009
11	β-OH	$-COO(CH_2)_6(Bn\text{-}G_3)$	Cheng et al., 2009
12	β-OH	$-COO(CH_2)_6G_3$	Cheng et al., 2009
13	β-OH	$-COO(CH_2)_6(Bn\text{-}G_4)$	Cheng et al., 2009
14	β-OH	$-COO(CH_2)_6G_4$	Cheng et al., 2009
15	β-OH	$-COO(CH_2)_6(Bn\text{-}G_5)$	Cheng et al., 2009
16	β-OH	$-COO(CH_2)_6G_5$	Cheng et al., 2009

Fig. 2: *Continued*

antiosteoporosis effects of oleanolic acid oligoglycosides with their melting points and yields are listed in Table 1.

3.2. Antidiabetes effect

Inhibition of glycogen phosphorylases (GP) was regarded as a therapeutic strategy for blood glucose control in diabetes, and various studies proved the efficacy of GP inhibitors in lowering blood glucose in animal models of diabetes and in clinical trials (Somsak et al. 2008). Oleanolic acid and related pentacyclic triterpenoids represent a new class of GP inhibitors; results of X-ray crystallographic studies disclosed the molecular basis of the pentacyclic triterpenoid binding to GP at the allosteric site (Wen et al. 2008). Considering oleanolic acid might bind to GP at the allosteric site and glucose analogue inhibitors bind to GP at the catalytic site, biological evaluation of some synthesized derivatives as GP inhibitors was presented by Cheng et al.

17	=O	-COO-β-D-Gal	Li et al., 2009
18	=O	-COO-β-D-Glc	Li et al., 2009
19	=O	-COO-β-D-Xyl	Li et al., 2009
20	=O	-COO-β-D-Ara	Li et al., 2009
21	[3,2-b]indole	-COO-β-D-Gal	Li et al., 2009
22	[3,2-b]indole	-COO-β-D-Glc	Li et al., 2009
23	[3,2-b]indole	-COO-β-D-Xyl	Li et al., 2009
24	[3,2-b]indole	-COO-β-D-Ara	Li et al., 2009
25	2,4-Dinitrophenylhydrazone	-COO-β-D-Gal	Li et al., 2009
26	2,4-Dinitrophenylhydrazone	-COO-β-D-Glc	Li et al., 2009
27	2,4-Dinitrophenylhydrazone	-COO-β-D-Xyl	Li et al., 2009
28	2,4-Dinitrophenylhydrazone	-COO-β-D-Ara	Li et al., 2009
29	=NOH	-COO-acetyl-β-D-Glc	Meng et al., 2011
30	=NOH	-COO-β-D-Glc	Meng et al., 2011
31	β-OCO$(CH_2)_2$COOH	-COO-β-D-Gal	Huang et al., 2010; Huang et al., 2011
32	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Glc	Huang et al., 2010; Huang et al., 2011
33	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Gal	Huang et al., 2010; Huang et al., 2011
34	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Glucuronyl	Huang et al., 2010; Huang et al., 2011
35	β-OCO$(CH_2)_2$COOG_6	-COO-2-acetylamino-2-deoxy-β-D-Glc	Huang et al., 2010; Huang et al., 2011
36	β-OCO$(CH_2)_2$COOG_6	-COO-2-deoxy-β-D-Glc	Huang et al., 2010; Huang et al., 2011
37	β-OCO$(CH_2)_2$COOG_6	-COO-2-deoxy-β-D-Gal	Huang et al., 2010; Huang et al., 2011
38	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Xyl	Huang et al., 2010; Huang et al., 2011
39	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Ara	Huang et al., 2010; Huang et al., 2011
40	β-OCO$(CH_2)_2$COOG_6	-COO-α-D-Glc-(1→4)-β-D-Glc	Huang et al., 2010; Huang et al., 2011
41	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Glc-(1→4)-β-D-Glc	Huang et al., 2010; Huang et al., 2011
42	β-OCO$(CH_2)_2$COOG_6	-COO-β-D-Gal-(1→4)-β-D-Glc	Huang et al., 2010; Huang et al., 2011
43	β-OCO$(CH_2)_2$COOG_6	-COOCH_2CONH-2-deoxy-β-D-Glc	Huang et al., 2010; Huang et al., 2011
44	β-OCO$(CH_2)_2$COOG_6	-COOCH_2CONH-2-deoxy-β-D-Gal	Huang et al., 2010; Huang et al., 2011
45	β-O-β-D-Glc	-COOH	Sha et al., 2008; Yan, 2008; Qian et al., 2010

Fig. 2: *Continued*

(2009). Molecular docking simulation result of the most active compound **8** and other derivatives indicated a clear preference for hydrophobic groups with a long chain linker and hydrophilic groups with a short chain linker. The antidiabetes activities of oleanolic acid oligoglycosides with their melting points, optical rotation and yields are listed in Table 2.

α-Glucosidase served as a membrane-bound enzyme at small intestine epithelium, which hydrolyses the cleavage of glucose

46	β-O-β-D-Gal	-COOH	Sha et al., 2008; Yan, 2008; Qian et al., 2010
47	β-O-β-D-Xyl	-COOH	Sha et al., 2008; Yan, 2008; Qian et al., 2010
48	β-O-α-L-Ara	-COOH	Sha et al., 2008; Yan, 2008
49	β-O-α-L-Rha	-COOH	Sha et al., 2008; Yan, 2008; Zhao et al., 2011
50	β-O-β-D-Gal	-COO-β-D-Glc	Sha et al., 2008; Yan, 2008
51	β-O-α-L-Ara	-COO-β-D-Glc	Sha et al., 2008; Yan, 2008
52	β-O-β-D-Gal	-COO-β-D-Xyl	Sha et al., 2008
53	β-O-β-D-Xyl	-COO-α-D-Glc-(1→4)-β-D-Glc	Sha et al., 2008; Yan, 2008
54	β-O-β-D-Glc	-COOBn	Qian et al., 2010
55	β-O-β-D-Gal	-COOBn	Qian et al., 2010
56	β-O-β-D-Ara	-COOBn	Qian et al., 2010
57	β-O-β-D-Xyl	-COOBn	Qian et al., 2010
58	β-O-β-D-Ara	-COOH	Qian et al., 2010
59	β-O-α-L-Rha	-COO-α-L-Rha-(1→4)-β-D-Glc-(1→6)-β-D-Glc	Huang et al., 2009
60	β-O-α-L-Rha	-COO-α-L-Rha	Huang et al., 2009
61	β-O-α-L-Rha	-COO$(CH_2)_6$-O-α-L-Rha	Huang et al., 2009
62	β-O-β-D-Glc	-CONH$(CH_2)_5$COOH	Qu et al., 2003
63	β-O-β-D-Gal	-CONH$(CH_2)_5$COOH	Qu et al., 2003
64	β-O-6-deoxy-α-L-Tal	-COOH	Zhao et al., 2011
65	β-O-β-D-Gal	-COOH	Zhao et al., 2011
66	β-O-α-D-Man	-COOH	Zhao et al., 2011
67	β-O-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
68	β-O-2-deoxy-2-amino-β-D-Glc	-COOH	Wang, 2004
69	β-O-β-D-Glucuronyl	-CONH$(CH_2)_5$COOH	Qu et al., 2003
70	β-O-4-O-acetyl-α-L-Ara	-COOH	Yan, 2008
71	β-OG_7-β-D-Glc	-COO-β-D-Glc	Huang et al., 2012
72	β-OG_7-β-D-Glc	-COO-β-D-Gal	Huang et al., 2012
73	β-OG_7-β-D-Gal	-COO-β-D-Glc	Huang et al., 2012
74	β-OG_7-β-D-Gal	-COO-β-D-Gal	Huang et al., 2012
75	β-OG_8-β-D-Glc	-COO-β-D-Glc	Huang et al., 2012
76	β-OG_8-β-D-Glc	-COO-β-D-Gal	Huang et al., 2012
77	β-OG_8-β-D-Gal	-COO-β-D-Glc	Huang et al., 2012
78	β-OG_8-β-D-Gal	-COO-β-D-Gal	Huang et al., 2012
79	β-OG_9-β-D-Glc	-COO-β-D-Glc	Huang et al., 2012
80	β-OG_9-β-D-Glc	-COO-β-D-Gal	Huang et al., 2012
81	β-OG_9-β-D-Gal	-COO-β-D-Glc	Huang et al., 2012
82	β-OG_9-β-D-Gal	-COO-β-D-Gal	Huang et al., 2012
83	β-OG_{10}-β-D-Glc	-COO-β-D-Glc	Huang et al., 2012
84	β-OG_{10}-β-D-Glc	-COO-β-D-Gal	Huang et al., 2012
85	β-OG_{10}-β-D-Gal	-COO-β-D-Glc	Huang et al., 2012

Fig. 2: *Continued*

from disaccharides and oligosaccharides. Inhibitors of this enzyme could delay carbohydrate digestion, prolong the overall carbohydrate digestion time, thus causing a reduction in the rate of glucose absorption and lower the postprandial rise in blood glucose. Thus, inhibition of α-glucosidase was considered important in managing non-insulin dependent diabetes. Dihydroxy-olide derivatives have been reported to be active inhibitors of α-glucosidase (Qian et al. 2012). Based

86	β-OG_{10}-β-D-Gal	-COO-β-D-Gal	Huang et al., 2012
87	β-$OCH_2(CH_3CO\text{-}G_1)$	-COOBn	Cheng et al., 2009
88	β-OCH_2G_1	-COOBn	Cheng et al., 2009
89	β-$OCH_2(CH_3CO\text{-}G_1)$	-COOH	Cheng et al., 2009
90	β-OCH_2G_1	-COOH	Cheng et al., 2009
91	β-$OCOO(CH_2)_2$(Bn-G_4)	-COOBn	Cheng et al., 2009
92	β-$OCOO(CH_2)_2G_4$	-COOH	Cheng et al., 2009
93	β-O-α-L-Rha-(1→2)-β-D-Xyl	-COOH	Liu, 2010
94	β-O-α-L-Rha-(1→2)-α-L-Xyl	-COOH	Yan, 2008
95	β-O-α-L-Rha-(1→2)-β-D-Glc	-COOH	Liu, 2010
96	β-O-α-L-Rha-(1→2)-β-D-Gal	-COOH	Liu, 2010
97	β-O-α-L-Rha-(1→2)-α-L-Ara	-COOH	Yan, 2008; Liu, 2010
98	β-O-α-L-Rha-(1→2)-β-L-Ara	-COOH	Liu, 2010
99	β-O-α-L-Rha-(1→3)-β-D-Gal	-COOH	Liu, 2010
100	β-O-α-L-Rha-(1→2)-α-L-Ara	-CN	Pei et al., 2012
101	β-O-α-L-Rha-(1→2)-α-L-Ara	-CO(*N*-cyclohexyl)	Yan, 2008
102	β-O-α-L-Rha-(1→2)-α-L-Ara	-CONHBu	Yan, 2008
103	β-O-α-L-Rha-(1→2)-α-L-Ara	$-CONH(CH_2)_3CH_3$	Yan, 2008
104	β-O-α-L-Rha-(1→2)-α-L-Ara	$-CONH(C_6H_4\text{-}o\text{-}Cl)$	Yan, 2008
105	β-O-α-L-Rha-(1→2)-α-L-Ara	-CO(*N*-morpholinyl)	Yan, 2008
106	β-O-α-L-Rha-(1→2)-α-L-Ara	$-CONH(C_6H_4\text{-}o\text{-}OH)$	Yan, 2008
107	β-O-α-L-Rha-(1→2)-α-L-Ara	-COO-β-D-Gal	Yan, 2008
108	β-O-α-L-Rha-(1→2)-α-L-Ara	-COO-β-D-Glc	Saito et al., 1993; Yan, 2008;
109	β-O-α-L-Rha-(1→2)-α-L-Ara	-COO-β-D-Rha	Yan, 2008
110	β-O-α-L-Rha-(1→2)-α-L-Ara	-COO-α-L-Ara	Yan, 2008
111	β-O-α-L-Rha-(1→2)-α-L-Ara	-COO-β-D-Glc-(1→4)-β-D-Glc	Yan, 2008
112	β-O-α-D-Glc-(1→4)-β-D-Glc	-COOH	Sha et al., 2008
113	β-O-β-D-Glc-(1→3)-α-L-Ara	-COO-β-D-Glc	Li et al., 2006
114	β-O-β-D-Glc-(1→2)-α-L-Ara	-COOBn	Qian et al., 2010
115	β-O-β-D-Glc-(1→2)-α-L-Ara	-COOH	Qian et al., 2010
116	β-O-β-D-Glc-(1→3)-β-D-Glc	-COOH	Seebacher et al., 1999
117	β-O-β-D-Glc-(1→2)-β-D-Glc	-COOH	Seebacher et al., 1999
118	β-O-β-D-Glc-(1→4)-β-D-Glc	-COOH	Yan, 2008; Seebacher et al.,1999
119	β-O-β-D-Gal-(1→4)-α-L-Rha	-COOH	Zhao et al., 2011
120	β-O-β-D-Gal-(1→4)-β-D-Glc	-COOBn	Qian et al.,2010
121	β-O-β-D-Gal-(1→4)-β-D-Glc	-COOH	Sha et al., 2008; Yan, 2008; Qian et al., 2010
122	β-O-β-D-Xyl-(1→4)-6-deoxy-α-L-Tal	-COOH	Zhao et al., 2011
123	β-O-β-D-Gal-(1→3)-(2-acetamido-2-deoxy-β-D-Glc)	-COOH	Yan, 2008
124	β-O-2-deoxy-2-acetamido-β-D-Glc(1→4)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
125	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→6)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004

Fig. 2: *Continued*

on that, Qian et al. (2010) obtained a series of oleanolic acid lactone saponins; almost all derivatives exhibited α-glucosidase inhibitory activity. Oleanolic acid lactone showed higher activity than oleanolic acid, with an inhibition ratio of 11.92%. Compound **117** exhibited the strongest inhibitory rate; however, except compounds **55** and **58**, effects of other derivatives did not show any significant differences. The α-glucosidase inhibitory activities of oligoglycosides with their melting points, optical rotation and yields are listed in Table 3.

126	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→3)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
127	β-O-2,3-Di-O-(α-L-Rha)-β-D-Glc	-COOH	Liu, 2010
128	β-O-α-L-Rha-(1→3)-β-D-Glc	-COOH	Liu, 2010
129	β-O-2,3-Di-O-(α-L-Rha)-4,6-Di-O-benzylidene-β-D-Gal	-COOH	Liu, 2010
130	β-O-β-D-Lactin	-CONH$(CH_2)_5$COOH	Qu et al., 2003
131	β-O-β-D-Glc-(1→3)-β-D-Rha-(1→2)-β-D-Ara	-COO-β-D-Glc	Saito et al., 1993
132	β-O-β-D-Glc-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COO-β-D-Glc-(1→6)-β-D-Glc	Guo et al., 2009; Liu, 2010
133	β-O-β-D-Glc-(1→2)-α-L-Ara-(1→3)-α-L-Ara	-COO-β-D-Glc	Li et al., 2006
134	β-O-β-D-Glc-(1→2)-β-D-Glc-(1→6)-β-D-Glc	-COOH	Seebacher et al., 1999
135	β-O-β-D-Glc-(1→3)-β-D-Glc-(1→6)-β-D-Glc	-COOH	Seebacher et al., 1999
136	β-O-α-D-Glc-(1→4)-β-D-Glc-(1→6)-β-D-Glc	-COOH	Seebacher et al., 1999
137	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→6)-β-D-Glc	-COOH	Seebacher et al., 1999
138	β-O-β-D-Glc-(1→3)-α-L-Rha-(1→2)-α-L-Ara	-COOH	Liu, 2010
139	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→4)-2-deoxy-2-acetamido-β-D-Glc-(1→4)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
140	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→6)-2-deoxy-2-acetamido-β-D-Glc-(1→6)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
141	β-O-β-D-Xyl-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COO-β-D-Glc-(1→6)-β-D-Glc	Guo et al., 2009; Liu, 2010
142	β-O-β-D-Xyl-(1→3)-α-L-Rha-(1→2)-α-L-Ara	-COOH	Liu, 2010
143	β-O-β-D-Xyl-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COOH	Liu, 2010
144	β-O-α-L-Rha-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COOH	Liu, 2010
145	β-O-α-L-Rha-(1→2)-β-D-Glc-(1→4)-α-L-Ara	-COOH	Yan, 2008
146	β-O-α-L-Rha-(1→2)-β-D-Glc-(1→3)-α-L-Ala	-COOH	Yan, 2008
147	β-O-α-L-Rha-(1→2)-α-L-Rha-(1→4)-α-L-Ara	-COOH	Yan, 2008
148	β-O-α-L-Rha-(1→2)-α-L-Ara-(1→4)-α-L-Ara	-COOH	Yan, 2008
149	β-O-β-D-Gal-(1→3)-β-D-Xyl-(1→4)-6-deoxy-α-L-Tal	-COOH	Zhao et al., 2011
150	β-O-β-D-Gal-(1→3)-β-D-Glc-(1→4)-2-acetamido-2-deoxy-β-D-Glc	-COOH	Yan, 2008
151	β-O-α-L-Ara-(1→2)-α-L-Ara-(1→6)-2-acetamido-2-deoxy-β-D-Glc	-COOH	Sun et al., 2003
152	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-a-L-Rha-(1→2)-β-D-Xyl	-COO-β-D-Glc-(1→6)-β-D-Glc	Guo et al., 2009; Liu, 2010
153	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COO-β-D-Glc-(1→6)-β-D-Glc	Liu, 2010
154	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-α-L-Rha-(1→2)-β-D-Xyl	-COOH	Liu, 2010
155	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-α-L-Rha-(1→2)-α-L-Ara	-COOH	Liu et al., 2009; Liu, 2010
156	β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-α-L-Rha-(1→2)	-COOH	Liu, 2010

Fig. 2: *Continued*

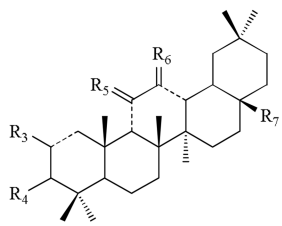
3.3. Antibacterial effect

Compound **49** that originated from *Lactuca scariola* L. exhibited broad spectrum antibacterial and antifungal activities against *Staphylococcus aureus*, *Escherichia coli*, *Penicillium digitatum* and *Aspergillus niger* (Yadava and Jharbade 2007). In subsequent work for discovering antifungal agents from natural resources, several glycoconjugates of oleanolic acid including **49** were efficiently designed and synthesized. All of them exhibited potent fungicidal activity against four fungi at a

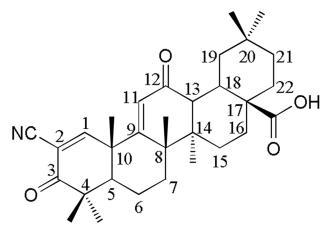
157	-β-D-Xyl β-O-β-D-Glc-(1→4)-β-D-Glc-(1→3)-α-L-Rha-(1→2) -β-D-Glc-(1→4)-α-L-Ara	-COOH	Liu et al., 2009; Liu, 2010
158	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→4)-2-deoxy- 2-acetamido-β-D-Glc-(1→4)-2-deoxy-2-acetamido-β -D-Glc-(1→4)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004
159	β-O-2-deoxy-2-acetamido-β-D-Glc-(1→6)-2-deoxy- 2-acetamido-β-D-Glc-(1→6)-2-deoxy-2-acetamido-β -D-Glc-(1→6)-2-deoxy-2-acetamido-β-D-Glc	-COOH	Wang, 2004

Notice: [a]) Gal refers to galactosyl; [b]) Glc refers to glucosyl; [c]) Xyl refers to xylosyl; [d]) Ara refers to arabinosyl; [e]) Rha refers to rhamnosyl; [f]) Tal refers to talopyranoside; [g]) Man refers to mannosyl.

Fig. 2: The C_3-OH or/and C_{17}-COOH oligoglycosides of oleanolic acid (**1–159**).



***Mother Nucleus Structure* - 2**



CDDO

NO.	C_1/C_2	C_9/C_{11}	C_{12}/C_{13}	R_3	R_4	R_5	R_6	R_7	Synthesis Process
160	–	–	–	-H, H	β-OH	=H, H	=H, H	-COO-β-D-Gal	Li et al., 2009
161	–	–	–	-H, H	β-OH	=H, H	=H, H	-COO-β-D-Glc	Li et al., 2009
162	–	–	–	-H, H	β-OH	=H, H	=H, H	-COO-β-D-Xyl	Li et al., 2009
163	–	–	–	-H, H	β-OH	=H, H	=H, H	-COO-β-D-Ara	Li et al., 2009
164	–	–	–	-H, H	β-OH	=H, H	=H, H	-COO-β-D-Glucuronyl	Li et al., 2009
165	–	–	=	-H, H	β-OH	=O	=H, H	-COO-β-D-Glc	Meng et al., 2011
166	=	=	–	-CN	=O	=H, H	=O	-COO-D-Glc$(OAc)_4$	Honda et al., 2002
167	=	=	–	-CN	=O	=H, H	=O	-COO-D-Glc	Honda et al., 2002

Notice: [a]) Gal refers to galactosyl; [b]) Glc refers to glucosyl; [c]) Xyl refers to xylosyl; [d]) Ara refers to arabinosyl.

Fig. 3: A&C carbon rings oligoglycosides of oleanolic acid (**160–167**).

Table 4: Anti-bacterial effect of synthetic oleanolic acid oligoglycosides (%) (Zhao et al. 2011)

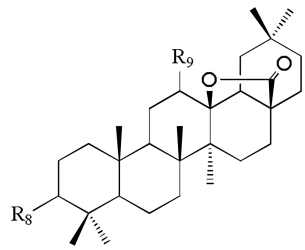
NO.	Mp/°C	$[\alpha]_D^{25}$	*S. sclerotiorum*	*R. solani*	*B. cinerea*	*P. parasitica*
49	—	—	71.90	96.05	75.41	79.21
64	288–290	+6.1	67.35	93.24	77.29	83.54
65	—	—	78.27	95.29	68.42	67.24
66	250–252	+79.8	65.16	96.17	74.59	63.55
119	268–270	+24.6	71.90	95.93	71.44	69.72
122	218–220	−30.7	73.47	93.86	71.73	52.57
149	202–204	−36.8	71.10	88.48	67.17	70.06

Notice: [a]) Mp refers to Melting point; [b]) [α] means to the Specific Rotation of these compounds; due to different test conditions, the data may be various.

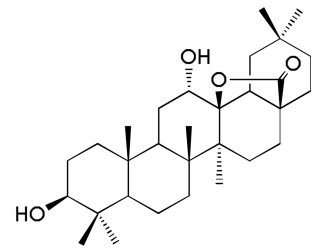
concentration of 50 μg/mL; compounds **49** and **64** possessed better activity against *Botrytis cinerea Pers* and *Phytophthora parasitica Dast* than the others (Zhao et al. 2011). The antibacterial effects of oleanolic acid oligoglycosides with their melting points and optical rotation are listed in Table 4.

3.4. Antitumor effect

The cytotoxic effects of compounds **29** and **30** were evaluated on HeLa, HepG2 and BGC-823 cells *in vitro* by MTT assay, the latter having stronger effects on HeLa cells than oleanolic acid (Meng et al. 2011). Human hepatocellular carcinoma (HCC) is one of the leading causes for mortality in the world (Parkin et al. 2005). An furoxan-based NO releasing derivative of oleanolic acid possessed strong cytotoxicity against HCC *in vitro* and significantly inhibited the growth of HCC tumors *in vivo*, but it showed a very low aqueous solubility (Chen et al. 2008). In order to enhance selectivity and bioactivity, new glycosyl derivatives that derived from furoxan-based NO releasing compound had been synthesized and examined. Among them, compound



Mother Nucleus Structure - **3**



Dihydroxy-olide

NO.	R_8	R_9	Synthesis Process
168	β-O-benzyl-β-D-Glc	α-O-benzyl-β-D-Glc	Qian et al., 2010
169	β-O-β-D-Glc	α-O-β-D-Glc	Qian et al., 2010
170	β-$OCOCH_3$	α-O-benzyl-β-D-Glc	Qian et al., 2010
171	β-$OCOCH_3$	α-O-b-D-Glc	Qian et al., 2010
172	β-OH	α-O-β-D-Glc	Qian et al., 2010
173	β-O-acetyl-β-D-Glc	-H, H	Cheriti et al., 1994
174	β-O-benzyl-β-D-Glc	α-O-benzyl-β-D-Glc	Qian et al., 2012
175	β-O-β-D-Glc	α-O-β-D-Glc	Qian et al., 2012
176	β-$OCOCH_3$	α-O-benzyl-β-D-Glc	Qian et al., 2012
177	β-$OCOCH_3$	α-O-β-D-Glc	Qian et al., 2012

Notice: Glc refers to glucosyl.

Fig. 4: The functional oligoglycosides of oleanolic acid lactone (**168–177**).

Table 5: IC_{50} values of synthetic oleanolic acid oligoglycosides on cancer cells proliferation (μM)

NO.	HeLa	HepG2	BGC-823	HL-60	SMMC-7721	BEL-7402	A549	A379	References
29	50.42 ± 13.55	> 10	> 10	—	—	—	—	—	Meng et al., 2011
30	22.92 ± 3.82	79.50 ± 9.93	> 10	—	—	—	—	—	Meng et al., 2011
33	—	2.13	—	—	1.18	2.96	—	—	Huang et al., 2010; Huang et al., 2011
59	—	—	—	2.80	—	—	—	—	Huang et al., 2009
60	—	—	—	26.89	—	—	—	—	Huang et al., 2009
61	—	—	—	17.09	—	—	—	—	Huang et al., 2009
93	—	—	—	3.6 ± 0.1	—	—	10.7 ± 4.2	5.0 ± 1.8	Liu, 2010
95	—	—	—	12.9 ± 2.7	—	—	23.5 ± 2.7	11.6 ± 1.8	Liu, 2010
96	—	—	—	2.5 ± 1.1	—	—	12.4 ± 5.5	5.1 ± 1.2	Liu, 2010
97	—	—	—	4.2 ± 1.5	—	—	17.5 ± 3.4	7.7 ± 3.8	Liu, 2010
98	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
99	—	—	—	> 20	—	—	15.2 ± 0.7	15.4 ± 0.9	Liu, 2010
127	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
128	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
129	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
132	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
138	—	—	—	6.1 ± 2.3	—	—	16.7 ± 1.5	12.1 ± 1.1	Liu, 2010
141	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
142	—	—	—	3.4 ± 1.2	—	—	15.4 ± 1.3	8.9 ± 2.4	Liu, 2010
143	—	—	—	4.5 ± 1.5	—	—	11.5 ± 3.1	6.3 ± 2.9	Liu, 2010
144	—	—	—	9.3 ± 0.8	—	—	16.2 ± 3.4	8.4 ± 3.3	Liu, 2010
153	—	—	—	> 20	—	—	> 20	> 20	Liu, 2010
154	—	—	—	2.5 ± 0.9	—	—	7.8 ± 4.4	6.1 ± 1.3	Liu, 2010
155	—	—	—	3.5 ± 1.3	—	—	7.9 ± 1.3	5.9 ± 0.9	Liu, 2010
156	—	—	—	4.6 ± 2.9	—	—	14.7 ± 1.6	5.5 ± 1.7	Liu, 2010
157	—	—	—	3.1 ± 1.8	—	—	6.1 ± 1.1	3.5 ± 0.4	Liu, 2010

Table 6: Haemolytic index of synthetic oleanolic acid oligoglycosides (Seebacher et al. 1999)

NO.	Mp/°C	$[\alpha]_{546}^{20}$	Yield (%)	Haemolytic Index
134	171–175	+18.0	10.00%	22000
135	188–195	+0.8	5.90%	11000
136	179–185	+20.0	7.60%	19500
137	263	+1.4	7.10%	<2000

Notice: [a]) Mp refers to Melting point; [b]) [α] means to the Specific Rotation of these compounds; due to different test conditions, the data may be various; [c]) Yield refers to comparative productivity for the last reaction.

Table 7: Inhibitory activity against production of nitric oxide in mouse macrophages (Honda et al. 2002)

NO.	Yield (%)	IC_{50}(nM)
166	75%	0.07
167	62%	10.1

Notice: [a]) Mp refers to Melting point; [b]) [α] means to the Specific Rotation of these compounds; due to different test conditions, the data may be various; [c]) Yield refers to comparative productivity for the last reaction.

33 showed better aqueous solubility, produced high levels of NO, and displayed strong cytotoxicity selectively against HCC *in vitro* and *in vivo*, but little acute toxicity to mice (Huang et al. 2010, 2011). Liu et al. (2010) evaluated the antitumor effect of several saponins on HL-60, A549 and A375 cell lines; natural compounds **132**, **141** and **152** displayed no cytotoxicities, while synthetic compounds **143**, **154** and **156** exhibited potent properties that explain the importance for keeping derivatives' C_{28}-COOH free. The IC_{50} values of oleanolic acid oligoglycosides against eight cell lines are listed in Table 5.

3.5. Hemolytic activity

Another well-known and characteristic property is their haemolytic activity, which was also used as a bioassay for saponin drugs. 3-O-Monoglucoside of oleanolic acid had a higher haemolytic activity than sapogenin. Elongation of the carbohydrate residue with a further glucose unit in position 2, 4, or 6 of the sugar moiety decreased haemolytic potency, whereas a linkage in position 3 raised it. The Haemolytic Indexes of trisaccharide saponins **134–137** were lower than that of the corresponding disaccharide; then Seebacher et al. (1999) deduced that influence of the carbohydrate moiety on haemolytic activity of disaccharides and trisaccharides of oleanolic acid strongly depended on the linkage between the glucose units and on their configurations. The effects varied for different positions in the sugar residue (Li et al. 2006). Hemolytic Index of oleanolic acid oligoglycosides with their melting points, optical rotation and yields are listed in Table 6.

3.6. Other effects

Compound **166** was demonstrated to have potent inhibitory activity against production of NO induced by interferon-γ in mouse macrophages; this potency was about 6 times and 1.5 times higher than that of CDDO and dexamethasone, respectively, while **167** exhibited only moderate effects. It seemed that the more polar the compound, the less its potency was (Honda et al. 2002). The inhibitory activities of compounds **166** and **167** against the production of nitric oxide are listed in Table 7.

4. Conclusion and prospect

Studies on synthetic oleanolic acid oligoglycosides and their bioactivities drew considerable attention in the past several years. The present paper reviewed glycosylated modifications of oleanolic acid at C_3-OH and C_{17}-COOH, of the carbons at ring A/C, and of the functional groups of oleanolic acid lactone. Among 177 synthetic oleanolic acid oligoglycosides, C_3-OH and C_{17}-COOH oligoglycosides of oleanolic acid accounted for the majority (about 90%). This article presented the audience both structural and bioactive information of synthetic oleanolic acid oligoglycosides with physical properties and biological activities. Several compounds' structural novelty and bioactive potential confirmed their value for further investigation.

Different from oleanolic acid, effects of synthetic oleanolic acid oligoglycosides mainly focused on antiosteoporosis, antidiabetes, antibacterial, anticancer and hemolytic. To some extent, reported results verify the feasibility of galactosylated modification of oleanolic acid; however, as it possesses relatively wide biological activities, how to establish a comprehensive and systematic method for assessing these synthetic derivatives' bioactivies and discussing their structure-activity relationships is worth studying. Furthermore, a growing number of patents involving pentacyclic triterpenoids and application to different therapeutic targets indicates that the functional molecules are coming up through introduction of various substituents at different positions of pentacyclic triterpenoids (Anderson et al. 2011, 2012a,b,c; Jiang et al. 2011; Shode et al. 2012). In a word, as an effective natural product and drug, oleanolic acid presents a promising lead compound for further development.

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