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•Review•

A review of structural modification and biological activities of oleanolic acid

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[ABSTRACT] Oleanolic acid (OA), a pentacyclic triterpenoid, exhibits a broad spectrum of biological activities, including antitumor, antiviral, antibacterial, anti-inflammatory, hepatoprotective, hypoglycemic, and hypolipidemic effects. Since its initial isolation and identification, numerous studies have reported on the structural modifications and pharmacological activities of OA and its derivatives. Despite this, there has been a dearth of comprehensive reviews in the past two decades, leading to challenges in subsequent research on OA. Based on the main biological activities of OA, this paper comprehensively summarized the modification strategies and structure-activity relationships (SARs) of OA and its derivatives to provide valuable reference for future investigations into OA.

[KEY WORDS] Oleanolic acid; Derivatives; Pentacyclic triterpenoid; Structural modification; Biological activities.
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Introduction

Oleanolic acid (OA), a pentacyclic triterpenoid, exists widely in the plant kingdom, either as a free molecule or in a glycosidic form. Its chemical structure is depicted in Fig. 1. OA is abundant in plants, such as leaf gallbladder and *Ligustrum lucidum*. It is an isomer of ursolic acid (UA), with the sole distinction being the shift of a methyl group from the C-20 to the C-19 position in OA. Both OA and UA exhibit similar biological activities. OA is known for its extensive pharmacological effects, such as antitumor [1], anti-HIV [2], antibacterial [3], anti-inflammatory [4], hepatoprotective [5], antidiabetic [6], anti-atherosclerotic properties [7]. However, literature frequently cites OA's limited activity, with an absolute oral bioavailability of just 0.7%, attributed to its low permeability and water solubility [8]. Malabsorption and extensive metabolic clearance may be responsible for the low oral bioavailability of OA [9]. Structural modifications of OA primarily target the C-3 hydroxyl group, A and C rings, the C-12, 13 double bond, and the C-28 carboxyl group. The main purpose of these modifications is to increase its activities, improve its bioavailability, reduce the side effects of itself or its derivatives, and improve its selectivity or targeting. Design strategies include combination principles, prodrug approaches, and the incorporation of specific pharmacophores. This paper reviews recent advancements in the structural modification of OA and its derivatives, categorized by their biological activities. It summarized the fundamental structure-activity relationship (SAR), which provides a reference for future drug development.

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These authors have no conflict of interest to declare.

Structural Modification and Biological Activities of OA

Antitumor activity of OA and its derivatives

In 2017, Salvador *et al*. reviewed the latest research on semisynthetic derivatives of oleanane, arbutane, and quinone methyl ether with anticancer activities [10]. This review highlighted the progress in understanding the anticancer properties of OA and its derivatives from 2012 to early 2017. The current paper builds upon this foundation, providing an updated overview of the antitumor research related to OA in recent years.

In 2020, WANG *et al*. took OA as the lead compound, implementing structural modifications such as the transform-

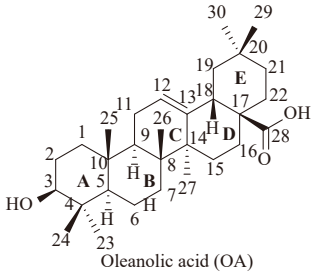


Fig. 1 Structure of OA.

ation of A ring C-2, C-3 into a ketoxime group and the esterification and amidation of the C-28 carboxyl group. This led to the design and synthesis of OA derivatives **1a**–**1j** [11], as shown in Fig. 2. *In vitro* pharmacological activity tests revealed that these target compounds exerted a certain inhibitory effect on SGC7901 and A549 cells at specific concentrations. Notably, modifications at the C-28 carboxyl group, either forming esters or amides, significantly enhanced their antitumor activity [11]. It was observed that the formation of an ester at the C-28 carboxyl group generally resulted in increased activity proportional to the length of the ester chain. Conversely, amide formation at this site typically yielded stronger activity than the corresponding ester. Among these compounds, **1j** demonstrated the most potent antitumor activity against SGC7901 and A549 cells, with IC_{50} values of 10.76 and 13.28 μmol·L^{-1}, respectively [11].

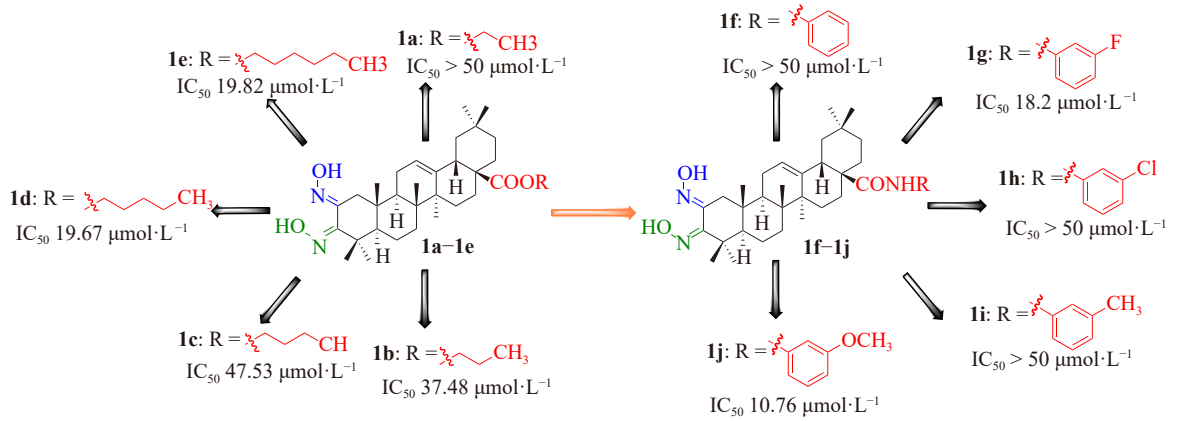


Fig. 2 Structures of OA derivatives 1a–1j.

The potential of polar substituents at the C-28 position of OA to enhance its anticancer efficacy has been a topic of interest. In this context, WEI *et al.* in our research group designed and synthesized a series of novel OA-coupled 1,2,3-triazole derivatives by employing a Cu(I)-catalyzed Huisgen 1,3-dipolar cycloaddition reaction, as illustrated in Fig. 3 [12]. The anticancer activities of these compounds against a group of five human cancer cell lines were assessed by the MTT method. Compared with OA, most derivatives exhibited strong inhibitory activities against all five cancer cell types, with some even surpassing 5-fluorouracil (5-FU). For instance, compound **2f** possessed a strong inhibitory activity against HT1080 cells with an IC_{50} value of 3.51 μmol·L^{-1}, about sevenfold more effective than 5-FU. Moreover, **2f** showed minimal cytotoxicity to most normal cells, indicating its selective inhibition of cancer cell growth. Pharmacological experiments further revealed that **2f** significantly induced the apoptosis of HT1080 cells, positioning it as a promising lead candidate for future research. The analysis of SAR indicated that compounds with *para*-substitution on the aromatic ring were more active than those without substitution or with *ortho*- or *meta*-substitution. Additionally, compounds featuring electron-absorbing groups on the aromatic ring generally exhibited higher activity than those with no substitution or electron-donating groups at the same position.

OA derivatives modified by *N*-benzyl tetrazolium are known for their potent biological activities, such as inhibition of tumor cell proliferation, cell cycle arrest, induction of cell apoptosis and differentiation, and enhanced hydrogen bond formation with purine, pyrimidine, and other base structural fragments [13]. SUN *et al.* synthesized compounds **3a**–**3o**, as shown in Fig. 4. With cisplatin as a positive control, this study targeted human gastric cancer MKN-45 cells, human breast cancer MCF-7 cells, and rat glioma C6 cells to assess the *in vitro* antitumor activity using the MTT method [14]. Particularly, derivative **3l**, which features a nitro group (-NO_2) in the *ortho*-position of the benzene ring, exhibited the most potent antitumor effect. Against MKN-45 and C6 cells, **3l** achieved inhibition rates of 50.3% and 69.3%, respectively, which are approximately four and nine times greater than those of OA. Furthermore, when the *meta*-position of the benzene ring was substituted by a fluorine (-F)

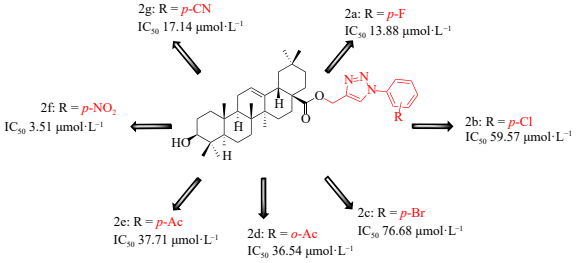


Fig. 3 Structures of OA derivatives 2a–2g.

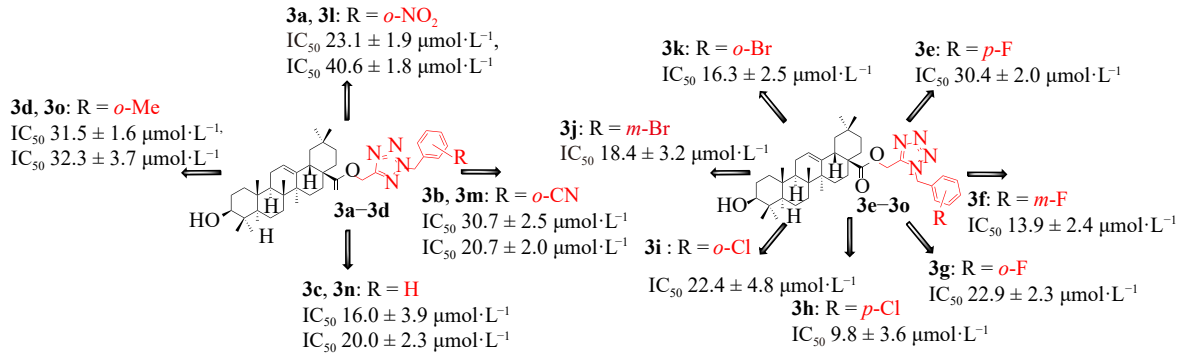


Fig. 4 Structures of OA derivatives 3a–3o.

atom, compound **3f** showed an inhibitory effect on C6 cells approximately ten times that of OA. These results suggest that the conjugation of various benzyl-substituted tetrazoles at the C-28 position of OA significantly enhances its antitumor activity *in vitro*.

Cancer stem cells (CSCs) play an important role in tumorigenesis, tumor recurrence, invasion, and metastasis, and drug resistance [15]. Research has shown that various natural products and their analogs, identified as potential anti-CSC lead compounds [16-19], share a common feature: the presence of Michael acceptors. These active Michael receptors target specific proteins critical in maintaining CSCs. Building on this understanding, researchers synthesized a range of OA derivatives with Michael receptors. The structures of some of these derivatives are illustrated in Fig. 5. Through preliminary *in vitro* screenings using MTT assays and *in vivo* toxicity evaluations, OA derivatives **4c** and **4d** were selected as lead compounds. Both compounds significantly inhibited the proliferation of cancer cells *in vivo* without exhibiting notable toxic effects on normal tissues. They displayed considerable cytotoxicity against cancer cells, especially melanoma cells (A375 and B16F10). Compound **4d** exhibited a more potent inhibitory effect on B16F10 cells, with an IC_{50} of 0.6744 ± 0.064 μmol·L^{-1}. Compound **4c** demonstrated superior antiproliferative activity against A375 cells, with an IC_{50} of 0.8274 ± 0.070 μmol·L^{-1}. Importantly, compounds **4c** and **4d** induced the production of reactive oxygen species (ROS), thereby ablating a variety of CSCs at low concentrations [20].

Triterpenoid saponins containing *N*-acetyl glucosamine, although rare in nature, have demonstrated significant cytotoxicity or antiproliferative activity [21-26]. WANG *et al*., in our research group, previously designed and synthesized a series of diosgenyl glucosaminides and found that saponins with a cinnamyl group exhibited higher antiproliferative activity on cell lines than other derivatives [27]. Inspired by this result, REN *et al*. designed and synthesized *N*-substituted-*β*-D-glucosamine derivatives by a step-by-step glycosylation strategy (Fig. 6). Their cytotoxicity against six different tumor cell lines (HaLa, HepG2, HCT116, MCF-7, A54, and A375-S2) were then evaluated *in vitro* [28]. The results revealed that most compounds effectively inhibited the growth of at least one tumor cell line at micromolar concentrations. Remarkably, their inhibitory activities against HeLa and HepG2 cells were more pronounced against other tested cells. Among these compounds, **5e** stood out for its excellent antiproliferative activity (IC_{50} 6.4 ± 0.3 and 7.7 ± 0.2 μmol·L^{-1} in HeLa and HepG2 cells, respectively), which significantly surpassed the efficacy of 5-FU (IC_{50} 63.4 ± 0.8 and 51.5 ± 0.9 μmol·L^{-1} in HeLa and HepG2 cells, respectively). At the same time, **5e** also showed good selectivity to other cell lines tested.

The poor water solubility of OA leads to low oral absolute bioavailability, and modifications to its hydrophobic scaffold alone cannot significantly improve its solubility [29]. Interest has grown in OA derivatives containing *N*-acetylglucosamine (such as compound **6a**, Fig. 7) moiety because of their notable cytotoxicity [30-33]. To investigate the effect of glucose isomers on their cytotoxic activity, LIN *et al.* synthesized a series of *N*-acyl, *N*-alkoxycarbonyl, and *N*-alkylcarbamoyl derivatives of 2′-deoxy-glucosyl bearing oleanolic

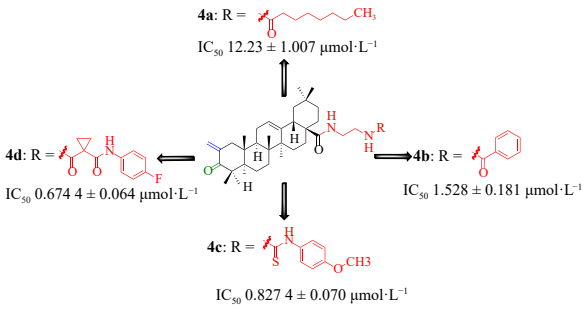


Fig. 5 Structures of OA derivatives 4a–4d.

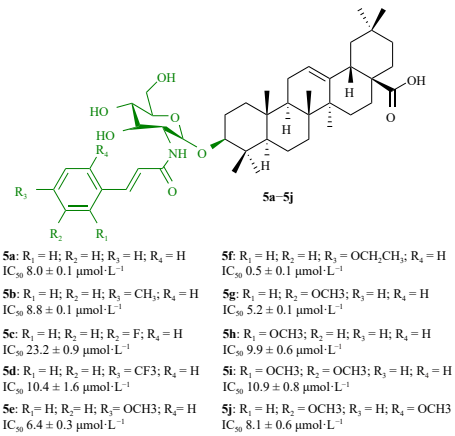


Fig. 6 Structures of OA derivatives 5a–5j.

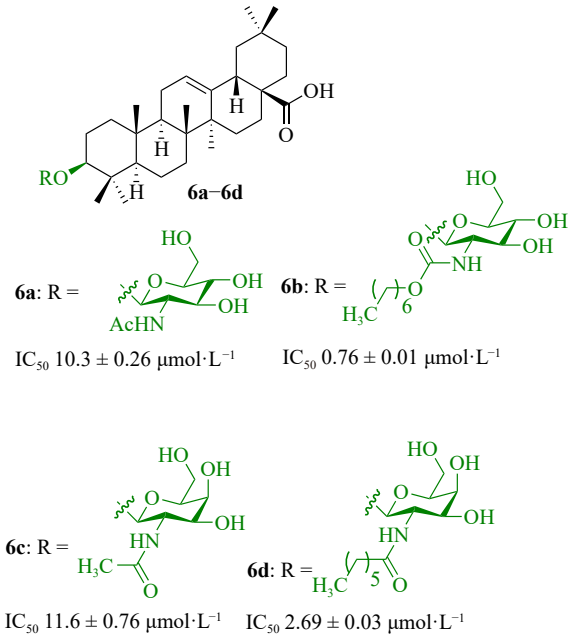


Fig. 7 Structures of OA derivatives 6a–6d.

saponins and evaluated their activies against HL-60, PC-3, and HT29 tumor cancer cells [34]. They also experimented with varying the length of the carbon chains in these derivatives to improve interaction with target organelles, followed by evaluation of antitumor activity against HL-60, PC-3, and HT29 tumor cells. The SAR analysis revealed that the activity of the 2′-amino group, amides, and urea derivatives followed the order: amino > amide > urea. Some amides and carbamates exhibited stronger growth inhibition than compound **6a**, exceeding its cytotoxicity for the first time. The cytotoxic effects of amides, carbamates, and urea compounds with the same carbon chain length on HL-60 cells were almost the same. Increasing the length of the carbon chain enhanced the cytotoxicity of the derivatives, peaking at 11 carbons for amides and nine carbons for carbamates. Compound **6b** emerged as the most cytotoxic against HL-60 cells (IC_{50} 0.76 ± 0.01 μmol·L^{-1}). Additionally, compounds **6c** and **6d**, containing galactosamine, displayed almost equivalent cytotoxicity to glucosamine compounds with the same carbon length, indicating that the configuration of C-4 in the sugar chain had no significant effect on cytotoxicity.

To obtain OA derivatives with stronger biological activity and fewer side effects, Medina-O'Donnell *et al*. synthesized a group of OA derivatives [35]. The cytotoxic effects of 18 triterpene derivatives were assayed on three cancer cell lines (B16-F10, HT29, and HepG2) and compared with their impacts on three non-tumor cell lines from the same or similar tissues (HPF, IEC-18, and WRL68). The findings revealed that almost all triterpenic acid diamine conjugates exhibited lower toxicity to non-neoplastic HPF cells, with survival rates ranging from 81% to 94%. The most significant cytotoxic results were observed with diamine conjugates of OA possessing the shortest diamine chain (IC_{50} 0.76 ± 0.03 μmol·L^{-1}) on the B16F10 cell line, which was around 140-fold more effective than their corresponding precursors (Fig. 8).

Low to intermediate intracellular concentrations of nitric oxide (NO) stimulate oncogenic pathways, while high levels of NO may exert antioncogenic effects. Consequently, numerous studies have investigated OA derivatives with an NO donor for their anticancer properties [36]. The inhibitory effect of OA on the A549 cancer cell line (IC_{50} 6.4 μmol·L^{-1}) was stronger than that on the other four cancer cell lines (MDA-MB-231, KB, KB-VIN, and MCF-7). After adding a NO-donating nitroxyl group to OA at the end of the ester side chain containing two, four, or six carbons, OA derivatives **8b**–**8d** (Fig. 9) were synthesized, and **8b** proved effective against all five cancer cell lines [37]. **8b** exhibited stronger cytotoxicity than OA (IC_{50} from 4.7 to 6.4 μmol·L^{-1}), suggesting that NO donors can increase the potency of OA and broaden its activity spectrum. Compound **8c** was less potent, while compound **8d** was noncytotoxic (IC_{50} > 10 μmol·L^{-1}) against all five cancer cell lines, suggesting that the linker length may affect cytotoxicity. Compared with OA, 3-acetyl-OA (**8a**) was somewhat more potent against the five cancer cell lines (A549, MDA-MB-231, KB, KB-VIN, and MCF-7), particularly KB-VIN. Compound **8f** showed high and comparable potency against all five cancer cell lines (IC_{50} from 4.8 to 5.4 μmol·L^{-1}), while compounds **8e** and **8g** also exhibited cytotoxicity (except for **8e** against the KB-VIN cell line, an MDR cell line overexpressing P-glycoprotein), and compound **8f** exhibited similar cytotoxicity toward KB and KB-VIN cells. Compounds **8h** and **8j** were insoluble in DMSO at 10 μmol·L^{-1}; thus, their cytotoxicity could not be determined. Compounds **8i**, **8k** and **8l** were not cytotoxic (IC_{50} > 10 μmol·L^{-1}). These data indicate that OAc-3 may be a key functional group for enhancing the cytotoxicity of OA-NO hybrids. Compounds **8c** and **8f**, both containing a nitric oxide donor, markedly inhibited EGFR-LTC kinase (IC_{50} 0.03 and 0.02 μmol·L^{-1}, respectively), further underscoring the impact of NO donors in enhancing the cytotoxicity of this triterpene. However, altering the OAc-3 of **8f** to another ester or benzyl group (**8h**–**8l**) resulted in the loss of the inhibitory activity of the kinase, highlighting the importance of both the structure of triterpenes and the existence of an NO donor in inhibiting EGFR-LTC kinase [37].

In view of the anticancer effect of high-level NO, several OA derivatives have shown significant anticancer activities [38-42]. In this vein, ZHANG's research group made structural modifications to OA's C-3 position to develop new NO-releasing OA derivatives with superior antitumor activity to

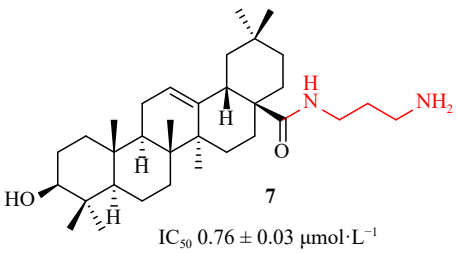


Fig. 8 Structures of OA derivative 7.

OA [43]. These derivatives were designed to be activated by cytochrome P450 (CYP) enzymes, which are differentially expressed in normal and tumor hepatocytes. Among these derivatives, compounds **9a**–**9f** (Fig. 10) released more NO in SMMC-7721 cells, and their inhibitory effects on the proliferation of SMMC-7721 and HepG2 cells were stronger than those of OA and other compounds. Compound **9c** with the highest activity showed potent anti-hepatoma activity while exerting minimal effects on normal hepatocytes. The addition of an NO scavenger significantly reduced the inhibitory activity of **9c** on cancer cells, suggesting that NO might contribute to the antitumor activity of **9c**.

Several derivatives of pentacyclic triterpenoids have been recognized for their significant antitumor activities both *in vitro* and *in vivo* [44-47]. Given that the mitochondrial function of cancer cells is different from that of normal cells [44], targeting mitochondria has become a strategy for cancer therapy [45, 46]. Several derivatives of pentacyclic triterpenoids [47] showed significant antitumor activity *in vitro* and *in vivo*. In particular, triterpenes featuring a piperazinyl spacer and a rhodamine B moiety have been identified as mitogen agents with high cytotoxicity [48-52]. SRB analysis unveiled that all these triterpene homopiperazine-rhodamine adducts exhibited high cytotoxicity to a range of human tumor cell lines, but their cytotoxicity to non-malignant cells was significantly lower, and these compounds were even more cytotoxic than previously prepared piperazinyl analogs [53]. Compound **10** (Fig. 11) stood out as the most cytotoxic in the series.

OA and cinnamic acid (CA) are two natural products with anticancer effects. CA has demonstrated inhibitory effects on various cancer types, including lung cancer, prostate cancer, melanoma, and glioblastoma [54-56]. In order to improve the anticancer activity of OA, WANG *et al*. designed and synthesized a series of new OA-CA esters by a molecular hybridization strategy [57]. The cytotoxicities of these newly synthesized compounds to HeLa, MCF-7, and L-O2 cell lines were assessed *in vitro* using the MTT method. Among these compounds, **11a** (Fig. 12) exhibited the highest selectivity and cytotoxicity to HeLa cells (IC_{50} 1.35 μmol·L^{-1}) but had no inhibitory activity on MCF-7 cells (IC_{50} > 100 μmol·L^{-1}) and L-O2 cells (IC_{50} > 100 μmol·L^{-1}). Conversely, **11b** displayed the most potent selective inhibition on MCF-7 cells (IC_{50} 1.79 μmol·L^{-1}).

CHENG's team reported several pharmacophore-based OA derivatives (Fig. 13) that were coupled with antitumor drug 5-FU to evaluate their antitumor activities [58]. The results revealed that monosubstituted hybrids **12a** and **12b** possessed notable antiproliferative activities, while disubstituted hybrids **12c** and **12d** displayed no antitumor activities. Hybrid **12b** showed potential selectivity to tumor cells (K562, IC_{50} 22.99 μmol·L^{-1}) and moderate antiproliferative activities against MDR cell lines A549/T (IC_{50} 43.07 μmol·L^{-1}) and Bel-7402/FU (IC_{50} 31.42 μmol·L^{-1}), which were comparable to its effect on A549 (IC_{50} 50.54 μmol·L^{-1}) and Bel-7402 cell lines (IC_{50} 43.82 μmol·L^{-1}).

Antiviral activity of OA and its derivatives

Influenza A (IAV) and B (IBV) viruses are significant contributors to upper respiratory tract infections [59]. Pentacyclic triterpenes and their derivatives from plants showed inhibitory activity on the entry of IAV virus *in vitro*. In particular, compound **13a** had strong anti-H1N1 entry activity with an IC_{50} of 4.05 μmol·L^{-1} [59]. OA has emerged as a promising scaffold for developing new influenza virus entry inhibitors [60]. It is reported that the anti-influenza activity of OA can be markedly improved by conjugating its 17-COOH or 3-OH groups with oligosaccharides [59, 61-63]. Expanding on this concept, SU *et al*. conjugated different saccharide moieties with 28-COOH of OA using a triazole linker, assessing the anti-influenza activity of these compounds *in vitro* [60]. Among them, compound **13b** (Fig. 14), an OA-glucose conjugate, demonstrated the strongest inhibitory activity against influenza A/WSN/33 (H1N1) virus with an IC_{50} value of 5.47

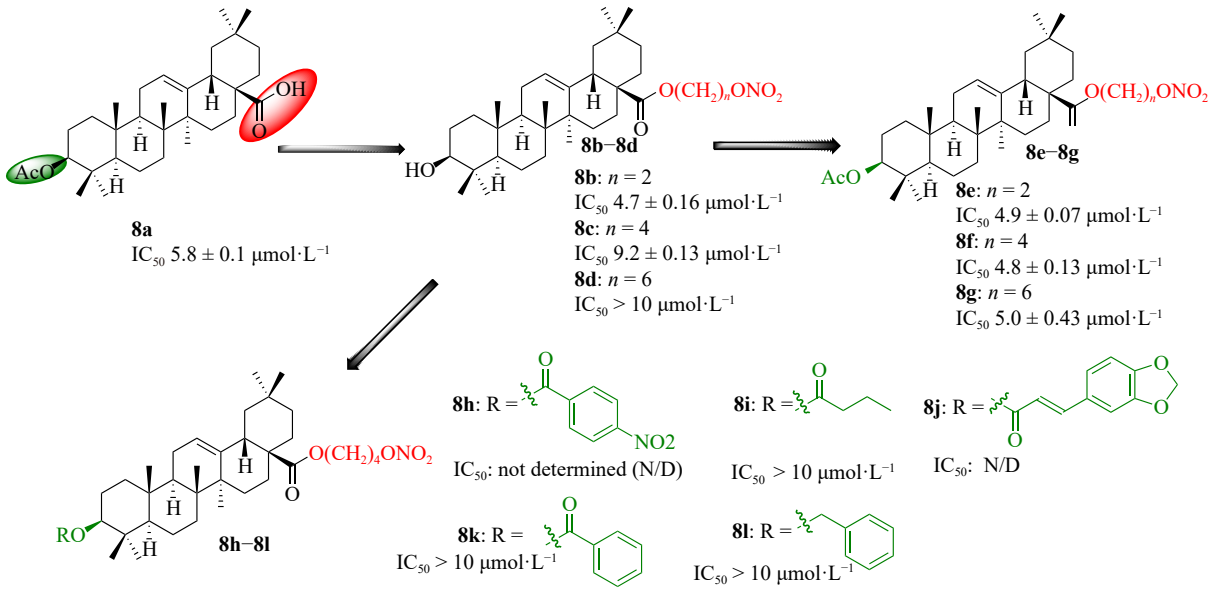


Fig. 9 Structures of OA derivatives 8a–8l.

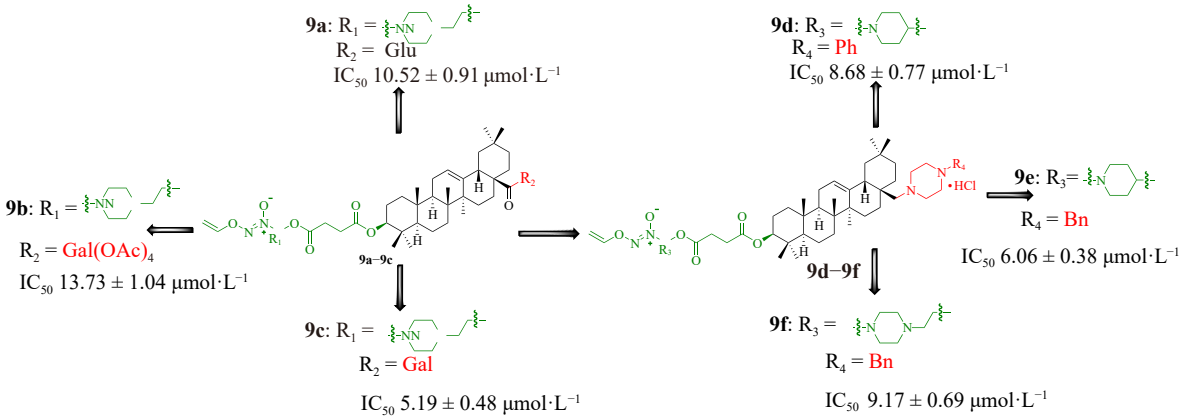


Fig. 10 Structures of OA derivatives 9a–9f.

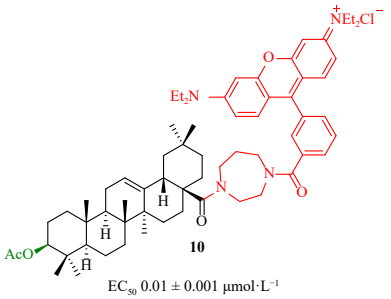


Fig. 11 Structures of OA derivative 10.

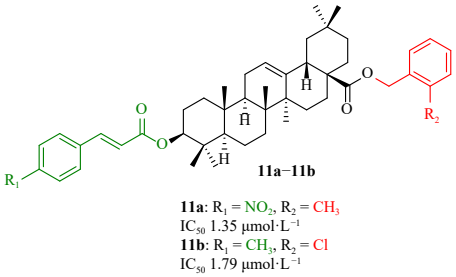


Fig. 12 Structures of OA derivatives 11a and 11b.

μmol·L^{-1} and showed no obvious cytotoxic effect on MDCK (Madin-Darby canine kidney) cells at 100 μmol·L^{-1}. Further broad-spectrum anti-influenza experiments revealed that **13b** was potent against five different strains, including IAV and IBV, with IC_{50} values in the low micromolar range. Hemagglutination inhibition (HI) assays and docking experiments indicated that **13b** might interfere with influenza virus infection by targeting the hemagglutinin (HA) protein.

The development of hepatitis C virus (HCV) entry inhibitors represents an emerging approach that satisfies a tandem mechanism for use with other inhibitors in a multifaceted cocktail. Screening of Chinese herbal extracts revealed that OA displayed a weak capability to inhibit HCV entry with an IC_{50} value of 10 μmol·L^{-1} [64]. Chemical exploration of this triterpene compound revealed its pharmacophore requirements for blocking HCV entry, with rings A, B, and E being conserved while ring C and ring D being tolerant to some modifications [64]. Hydroxylation at 16-C (**14a**, Fig. 15) significantly enhanced its potency for inhibiting HCV entry, with an IC_{50} value of 1.4 μmol·L^{-1}. Further modification by conjugation of this new lead with a disaccharide at 28-COOH removed the undesired hemolytic effect and, more importantly, increased its potency by about 5-fold (IC_{50} 0.3 μmol·L^{-1}) (**14b**, Fig. 15). Alternatively, the combination of two pharmacophores is a potential strategy to increase the activity of **14a**. Unexpectedly, **14c**, the **14a** dimer bearing a triazole linker, exhibited significantly higher potency with an IC_{50} value of 10.3 nmol·L^{-1}, almost two orders of magnitude more potent than **14a** (IC_{50} 1.4 μmol·L^{-1}). **14c** was the most potent compound based on the HCVpp entry assay. Mechanistically, these functional triterpenes interrupt the interaction between the HCV envelope protein E2 and its receptor CD81 by binding to E2, thus blocking the recognition process between the virus and the host cell.

YANG *et al*. have made significant strides in the devel-

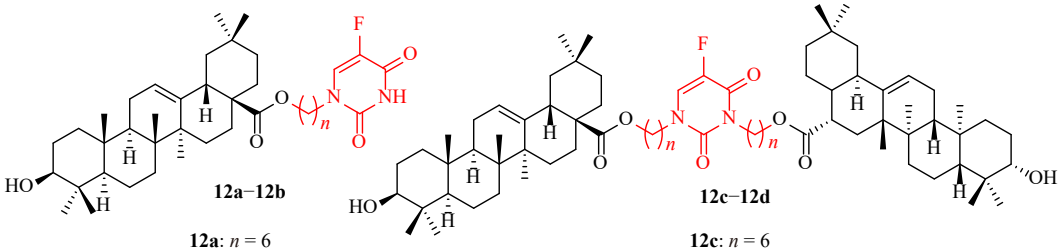


Fig. 13 Structures of OA derivatives 12a–12d.

opment of novel antiviral strategies with their work on multivalent OA protein conjugates, which function as non-glycosylated mucin mimics for the capture and entry inhibition of influenza viruses [65]. They synthesized an OA derivative, compound **15** (Fig. 16), featuring an amine terminal group, by esterification of carboxylic acid and then grafted it onto human serum albumin (HSA) using the diethyl squarate strategy. The resulting conjugate exhibited remarkable agglutination properties, strong capture efficiency, and a high-affinity constant for viral particles. These attributes suggest that the protein conjugate may be used as an anti-infection barrier to prevent the virus from invading host cells.

Medina-O'Donnell *et al*. evaluated how the derivatives of OA conjugated with one or two amino acids and an acyl group affect the inhibition of HIV-1 protease [66]. Their *in vitro* studies suggested that the inclusion of a carboxyacyl group generally enhanced the inhibition of HIV-1 protease, especially when a phthaloyl group was present, with IC_{50} values below 5 μmol·L^{-1}. Among these derivatives, three 3-phthaloyl OA compounds (**16**, Fig. 17) displayed submicromolar IC_{50} values, indicating an activity level 60- and 100-fold greater than OA. These findings suggest that the conjugation of OA with one or two amino acids and a phthaloyl group improves its efficacy as an HIV-1 protease inhibitor, pointing to these triterpene derivatives as potential antiviral agents against HIV. The study also yielded several key insights into the mechanisms of OA derivatives in inhibiting HIV-1 protease. For instance, it was observed that coupling short-chain *ω*-amino acids (*γ*-aminobutyric acid or 6AHA) to the scaffold (OA) at the C-28 position enhances the inhibitory effect on HIV1 protease. Conversely, the presence of long-chain omega-amino acids, like 11AUA, attenuates this effect. The results of docking studies showed that the strong inhibitory activity of 3-phthaloyl OA derivatives may be attributed to their ability to form more hydrogen bonds, which facilitates the placement of ligands in a more favorable position in the proteases. However, the presence of long-chain amino acids may prevent ligands from establishing favorable contacts with the active sites of the enzyme, resulting in a loss of activity unless phthaloyl groups are present.

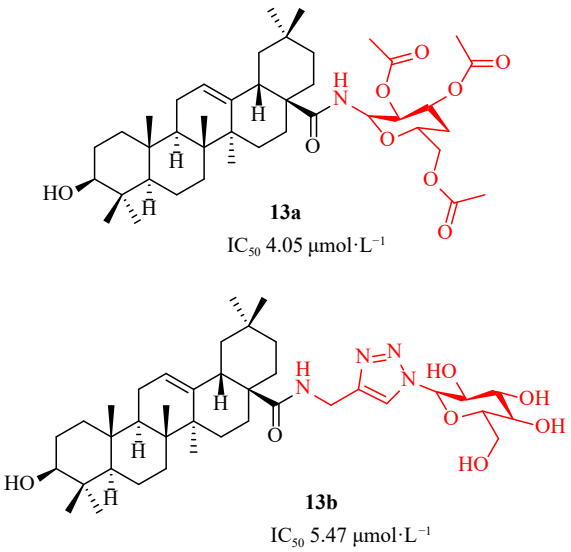


Fig. 14 Structures of OA derivatives 13a and 13b.

LI *et al*. synthesized a series of pentacyclic triterpene derivatives modified by coupling with various polyphenols on C-28 and evaluated the antiviral activity of M against influenza A H1N1 virus in MDCK cells [67]. Three of these compounds **17a**, **17b**, and **17c** (Fig. 18) showed strong anti-influenza efficacy, surpassing the standard antiviral drug oseltamivir. Importantly, these compounds exhibited no toxicity to MDCK cells at a concentration of 100 μmol·L^{-1}. Compound **17c**, in particular, is one of the most representative conjugates in this series. It showed the strongest inhibitory activity against influenza A/WSN/33 (H1N1) viruses with an IC_{50} value of 5.80 μmol·L^{-1} and a stronger affinity with HA with a KD value of 15.6 μmol·L^{-1}. Further investigations, including hemagglutination inhibition (HI) assays, surface plasmon resonance, and molecular simulations, indicated that showed that these conjugates bind closely to the viral envelope HA (K_d 15.6 μmol·L^{-1}) to prevent the influenza virus from invading host cells.

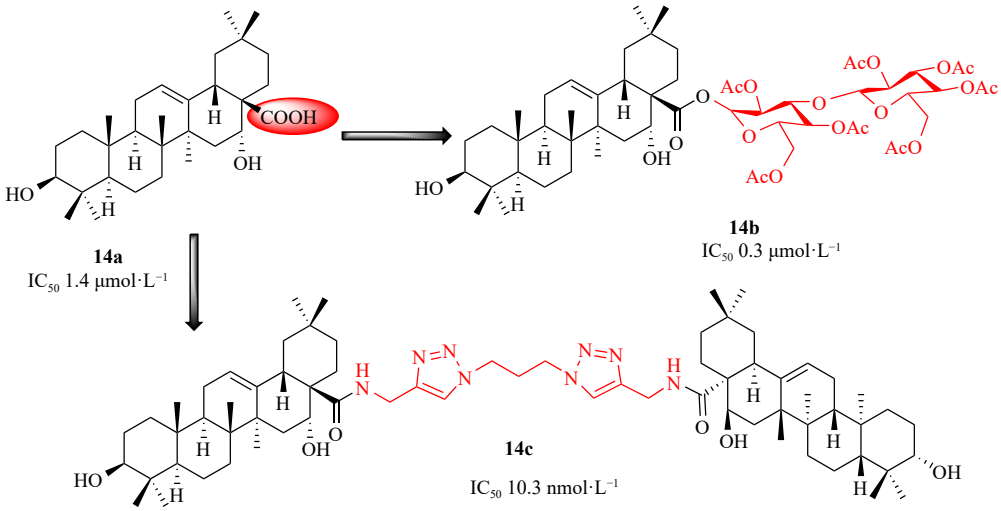
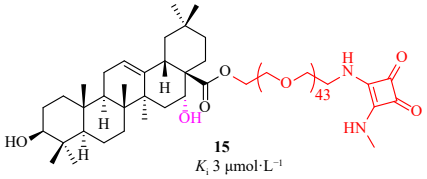
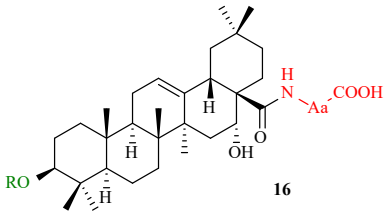


Fig. 15 Structures of OA derivatives 14a–14c.



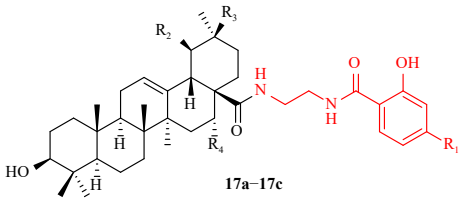
15
K_i 3 μmol·L^{-1}

Fig. 16 Structures of OA derivative 15.



R: phthaloyl group
Aa: ω-amino acid or ω-and α-amino acid
IC_{50} from 0.79 ± 0.01 to 3.1 ± 0.10 μmol·L^{-1}

Fig. 17 Structures of OA derivative 16.



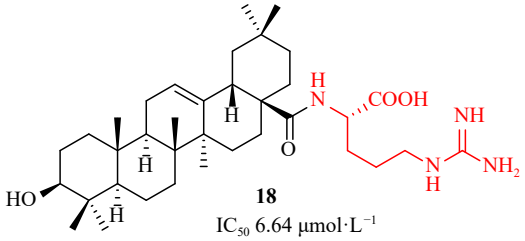
17a: $R_1 = R_2 = R_4 = H$, $R_3 = CH_3$
IC_{50} 7.65 μmol·L^{-1}
17b: $R_1 = R_2 = H$, $R_3 = CH_3$, $R_4 = OH$
IC_{50} 5.84 μmol·L^{-1}
17c: $R_1 = R_3 = R_4 = H$, $R_2 = CH_3$
IC_{50} 5.8 μmol·L^{-1}

Fig. 18 Structures of OA derivatives 17a–17c.

Inspired by the discovery of a series of pentacyclic triterpenes targeting influenza virus HA protein as entry inhibitors, MENG *et al*. designed and synthesized a series of OA analogs by linking different amino acids to the 28-COOH of OA [68]. The antiviral activities of these compounds were evaluated *in vitro*. Among these newly synthesized compounds, **18** (Fig. 19) showed significant antiviral activity against influenza A/WSN/33 (H1N1) viruses. HI assays and docking experiments provided insights into the mechanism of action of these OA analogs. It was observed that they might block the interaction between the influenza virus HA protein and host cell sialic acid receptor by binding to the HA protein, thus blocking virus invasion and producing the same effect as parent compounds.

Hypoglycemic activity of OA and its derivatives

α-Glucosidase inhibitors are a class of oral hypoglycemic drugs used for the treatment of diabetes that delay the absorption of intestinal carbohydrates. α-Glucosidase inhibitors are relatively mature drugs for the treatment of diabetes and have been widely used in the clinic. ZHONG *et al*. synthesized a series of novel anti-α-glucosidase OA analogs and evaluated their biological activities *in vitro* and *in vivo*, as shown in Fig. 20 [69]. The results of α-glucosidase inhibitory activity *in vitro* showed that all the designed compounds had obvious inhibitory activity. The IC_{50} values of compounds **19a**, **19b**, **19c**, and **19d** were 0.33 ± 0.01, 0.98 ± 0.06, 0.69 ± 0.01, and 0.72 ± 0.21 μmol·L^{-1}, respectively. The study of enzyme kinetics indicated that derivatives **19a**–**19d** functioned as non-competitive inhibitors of α-glucosidase. Molecular docking studies further revealed that these four compounds could interact with the hydrophobic region of the active pocket to form hydrogen bonds, thus enhancing their binding affinity to α-glucosidase. Cytotoxicity tests confirmed that the active compounds **19a**–**19d** exhibited no cytotoxicity to normal 3T3 cell lines. The study on the actual pharmacological potential of derivative **19a**–**19d** *in vivo* showed that their hypoglycemic effect was similar to that of acarbose, a positive control.



18
IC_{50} 6.64 μmol·L^{-1}

Fig. 19 Structures of OA derivative 18.

Protein tyrosine phosphatase 1B (PTP1B) is a negative regulatory factor in insulin signal transduction and an effective drug target for the treatment of diabetes and obesity. QIAN *et al*. synthesized a series of oleic acid derivatives and evaluated their inhibitory activity against PTP1B [70]. Among them, compound **20** emerged as the most effective in inhibiting PTP1B (IC_{50} 3.12 μmol·L^{-1}). The structure of compound **20** is shown in Fig. 21. The SAR analysis of these derivatives unveiled that the integrity of the A ring and 12-*ene* part was crucial for maintaining the enzyme inhibitory activity of PTP1B. Furthermore, the distance between the hydrophilic group and the acidic group and between oleanolene and the acidic group played a role in determining the PTP1B inhibitory activity.

Studies have shown that PTP-1B enzymes that deactivate insulin and leptin receptors are involved in glucose and fat metabolism, respectively. Pentacyclic acid triterpenes, such as oleic acid, have been recognized as a class of potent PTP-1B inhibitors. Studies have indicated that the inhibitory activity of these compounds can be significantly enhanced through the substitution of the C-3 hydroxyl, C-12 double bond, or C-28 carboxylic acid groups with aryl or alkyl groups [71]. Based on these studies, Ramírez-Espinosa *et al*. synthesized a series of OA derivatives [72], as shown in Fig. 22. The study highlighted that the presence of carboxylic acid on C-28 and/or its corresponding reduction product methanol derivative (hydrogen bond donor) is essential for maintaining of these compounds against PTP-1B. Moreover, the formation of esters or ethers on C-3 further enhanced this inhibitory activity. In the non-insulin dependent diabetic rat model, OA derivatives showed an enhanced inhibitory effect on PTP-1B activity by increasing their molecular interaction with catalytic or allosteric sites and hypoglycemic effect.

Hypolipidemic activity of OA and its derivatives

Cholesteryl ester transfer protein (CETP) is a key thera-

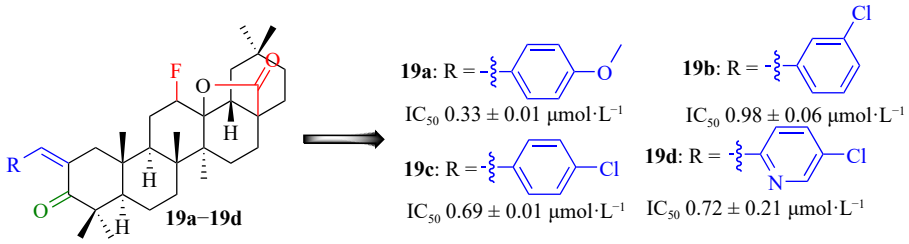


Fig. 20 Structures of OA derivatives 19a–19d.

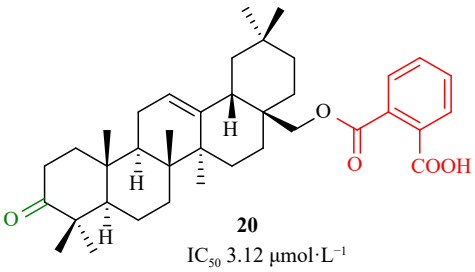


Fig. 21 Structures of OA derivative 20.

peutic target for treating atherosclerotic cardiovascular diseases. Molecular simulation studies have revealed that pentacyclic triterpenoids can simulate the interaction between proteins and ligands by occupying the binding site of the endogenous ligand cholesterol ester (CE). Based on these insights, CHANG *et al*. designed and synthesized a series of new pentacyclic triterpenoid CETP inhibitors [73]. As shown in Fig. 23, compound **22b** (IC_{50} 0.28 ± 0.068 μmol·L^{-1}) stood out with the best biological activity, which validates the authors' molecular design strategy. Molecular dynamics simulations showed that compared with compound **22a** (IC_{50} > 50 μmol·L^{-1}), compound **22b** showed a more stable hydrogen bond interaction with Ser191 and stronger hydrophobic interactions with Val198 and Phe463, which is the main reason for their different CETP inhibitory activity.

Anti-inflammatory activity of OA and its derivatives

Arachidonic acid (AA) plays a critical role in the inflammatory process. It is released from cell membrane phospholipids through the action of phospholipase A2 in response to inflammation-related cell injury. Three key enzymes control the AA pathway: cyclooxygenases (COX-1 and COX-2), which produce prostaglandins (PG) and thromboxane; lipoxygenases (LOX, including 5-LOX and 15-LOX), which generate leukotrienes (LTS) and hydroxy eicosatetraenoic acids (HETE); and cytochrome P450 enzymes (CYPS), which produce epoxide eicosatrienoic acids [74-78]. The products of COX and LOX pathways are key bioactive lipid mediators in the induction of pathophysiological inflammatory conditions requiring drug intervention. In 2019, Vo *et al*. investigated the inhibitory activities of 29 natural oleanane and ursolane pentacyclic triterpenes on four main enzymes involved in the inflammatory process: 5-LOX, 15-LOX-2, COX-1, and COX-2. One of these compounds, 3-*O*-acetyl-*β*-boswellic acid (**23**, Fig. 24), exhibited an obvious inhibitory effect on human 5-LOX-2 (IC_{50} 12.2 ± 0.47 μmol·L^{-1}) [79]. The SAR analysis revealed that the existence of 24 hydroxyl groups was beneficial to the inhibition of 5-LOX and COX-1. The introduction of a carboxylic acid group at position 30 was crucial for the dual inhibitory activity of 5-LOX/COX, and the carbonyl group binding to Cmur11 significantly enhanced the inhibitory activity of 5-LOX. The activity of 5-LOX was markedly

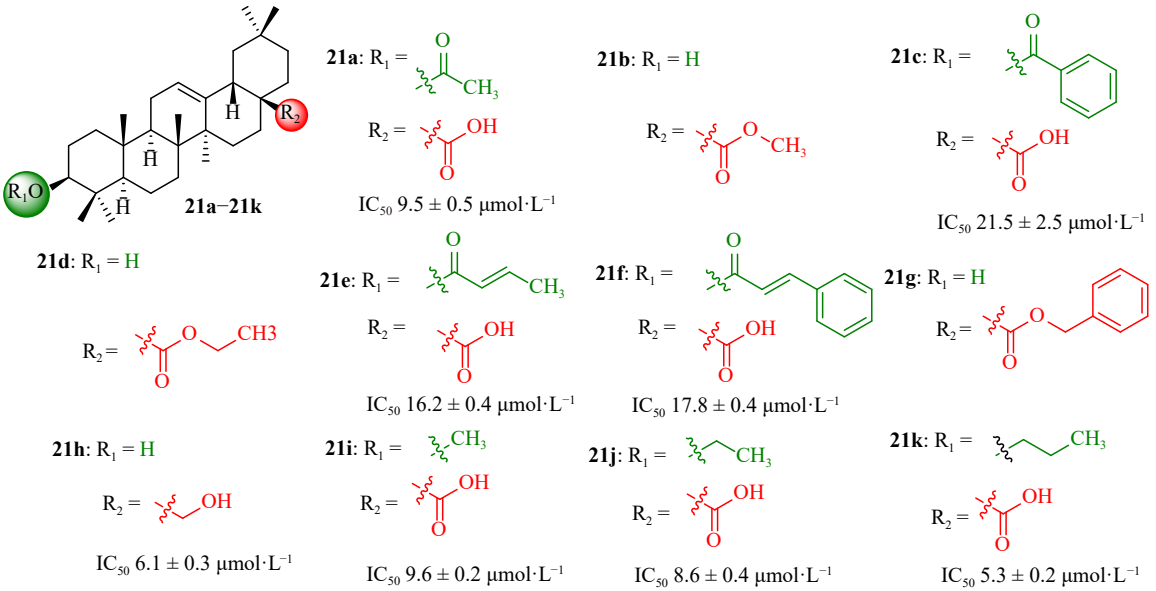


Fig. 22 Structures of OA derivatives 21a–21k.

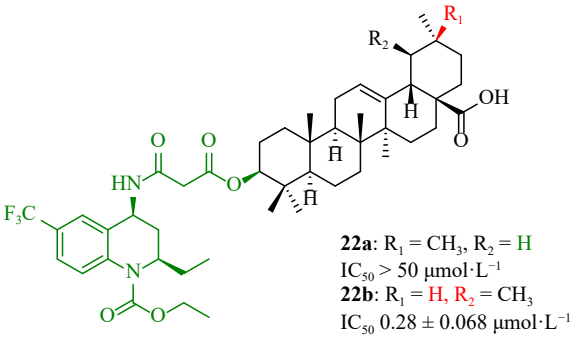


Fig. 23 Structures of OA derivatives 22a and 22b.

inhibited by *α*-hydroxy at C-2 or a carboxylic acid group at C-23. The experimental results uncovered that the types and configurations of polar groups at positions C-2, -3, -11, -24, and -30 were important structural factors in pentacyclic triterpenes due to their potential for anti-inflammatory lead compounds.

AMPK exists in the form of a heterotrimeric complex (*α*-, *β*-, *γ*-), which is a key kinase that regulates energy metabolism and stress responses [80]. The activation of AMPK can protect the body from tissue damage caused by acute and chronic inflammation [81]. Importantly, existing AMPK agonists can play an anti-inflammatory role in a variety of inflammatory models [82-86]. It is reported that OA is an activator of AMPK [87-90]. LIU *et al*. found that a variety of natural pentacyclic triterpene saponins and saponins could stimulate the phosphorylation of AMPK and identified *δ*-OA (**24a**) as a powerful AMPK activator [91]. With **24a** as the lead compound, a series of *δ*-OA saponin derivatives were synthesized to discover more effective and anti-inflammatory drugs with pharmacokinetics. The results of cell experiments denoted that saponin **24b** (Fig. 25) could significantly inhibit the secretion of pro-inflammatory cytokines TNF-α and IL-6 stimulated by endotoxin in macrophages. The preliminary mechanism showed that **24b** could stimulate the phosphorylation of AMPK and acetyl-CoA carboxylase (ACC). Compared with that of aglycone, the bioavailability of **24b** was substantially improved. More importantly, **24b** exhibited obvious anti-inflammatory and hepatoprotective effects in a mouse model of fulminant liver failure induced by LPS/D-GalN.

In order to explore the effects of different substituents on anti-inflammatory activity, Bhandari *et al*. synthesized analogs (**25a**−**25m**, Fig. 26) by modifying the structure of OA at the C-3 and C-28 positions. They evaluated their anti-inflammatory effects on the production of NO in macrophages induced by lipopolysaccharide (LPS) [92]. The results revealed that compared with NO synthase inhibitor L-NAME (RAW 264.7 cells, IC_{50} 69.21 ± 2.65 μmol·L^{-1}; J774A.1 cells, IC_{50} 73.18 ± 1.70 μmol·L^{-1}), all synthetic OA analogs could inhibit NO production. Specifically, compounds **25a**, **25g**, **25h**, and **25i** demonstrated a strong ability to inhibit NO production. Among them, **25i** (IC_{50} of RAW 264.7 and J774A.1 cells were 2.66 ± 1.54 and 10.8 ± 2.31 μmol·L^{-1}, respectively) inhibited NO production by 20 times as much as the parent compound, without affecting cell viability. The most potent NO inhibitors (**25a**, **25g**, **25h**, and **25i**) slightly inhib-

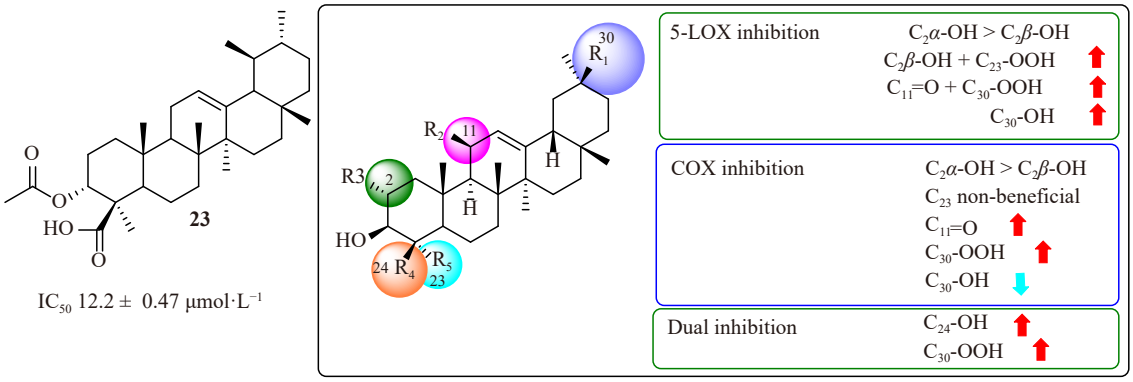
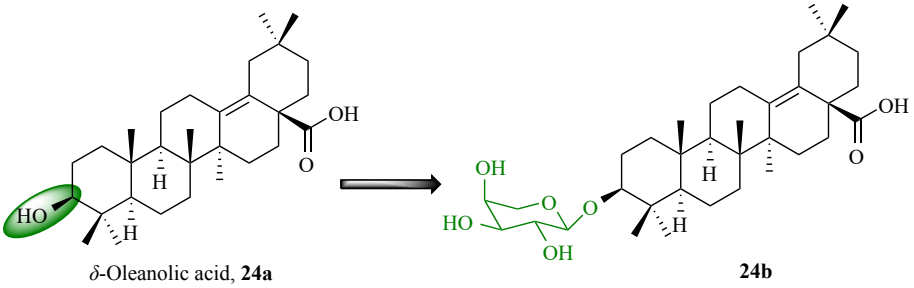


Fig. 24 Structures of OA derivatives 23. 2, 11, 23, 24, and 30 marked in the figure are the labels of the C atoms. R_1−R_5 refer to the groups connected to the C atoms, and the specific groups have been marked in this figure.



δ-Oleanolic acid, **24a** **24b**

Fig. 25 Structures of OA derivatives 24a−24b.

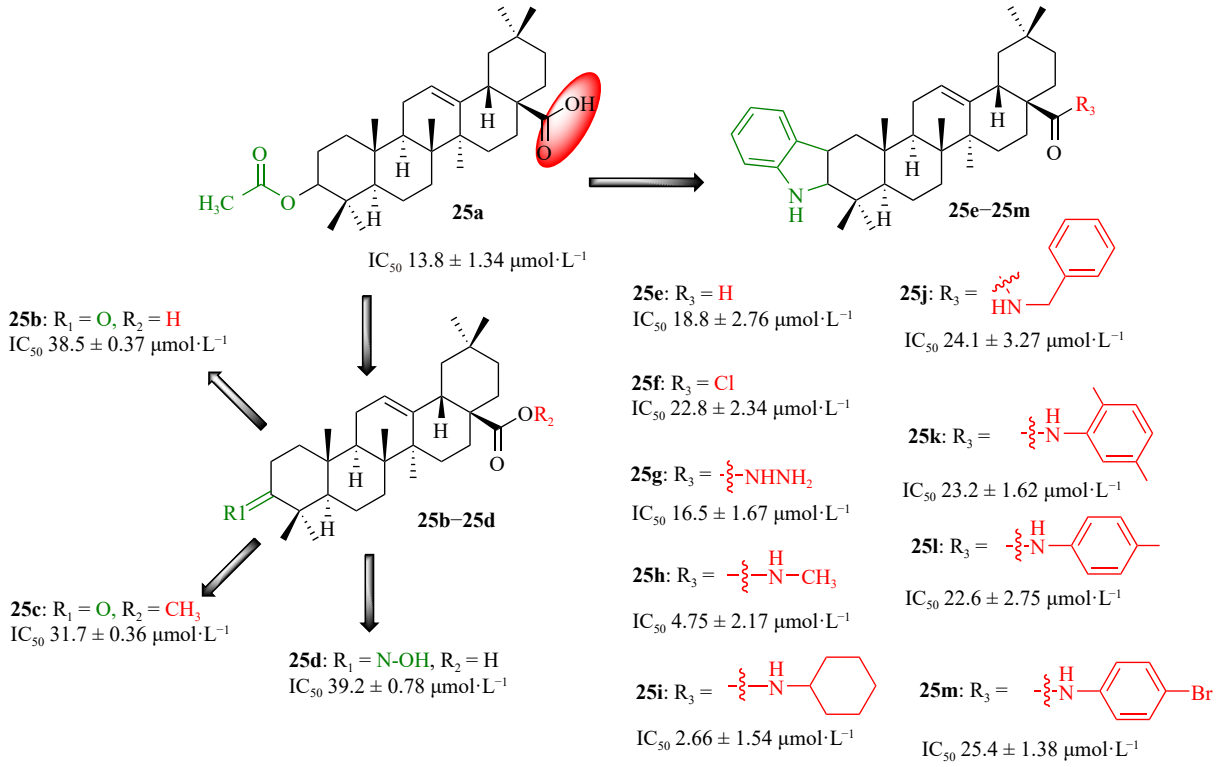


Fig. 26 Structures of OA derivatives 25a–25m.

ited the LPS-induced production of TNF-α (27.9%–51.9%) but had no inhibitory effect on the production of IL-1β (11.1%–37.5%) [92].

In 2021, Jannus *et al*. used an inflammatory model to study the anti-inflammatory effects of diamine-polyethylene glycol derivatives of OA (**26**, Fig. 27) *in vitro* and *in vivo* [93]. They tested the anti-inflammatory activity of compound **26** in RAW264.7 cells. At the same time, the production of NO was monitored. When the concentration of derivative **26** was 11 μg·mL^{-1}, the inhibition rate of NO was more than 75%. Cell cycle analysis showed that the LPS-induced G_0/G_1 phase arrest of RAW264.7 cells was reversed. In addition, through Western blotting analysis, they identified the molecular mechanism by which derivative **26** may be activated: inhibiting the expression of cytokines such as TNF-α, IL-1β, iNOS, and COX-2 and blocking the production of RAW264.7 p-IκBα stimulated by endotoxin. Furthermore, Jannus et al. investigated the *in vivo* anti-inflammatory effects of derivatives **26** and tetradecyl phorbol ester (TPA) in the treatment of acute ear swelling in male BL/6J mice. Compared with diclofenac, derivative **26** had a greater inhibitory effect on swelling and reduced the thickness of the ear by 14%.

Hepatoprotective activity of OA and its derivatives

OA has been used as a dietary supplement and is available over-the-counter as a treatment for liver diseases in humans. YU *et al*. designed and synthesized two new OA prodrugs, **27a** and **27b**, using the slow-release properties of 1,3-cyclopropyl phosphate to modify OA metabolism, as shown in Fig. 28 [94]. The results showed that these prodrugs had strong antioxidant activities and obvious protective effects

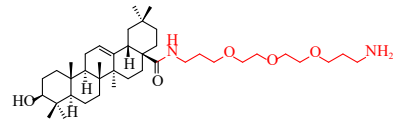


Fig. 27 Structures of OA derivative 26.

against liver injury caused by CCl_4. In terms of metabolism, the study revealed that the half-life of the prodrugs was extended, and their pharmacokinetic parameters significantly changed after direct administration. Further biodistribution studies demonstrated that the concentrations of prodrugs and OA were the highest in the liver, and most of them were excreted *via* the stool. The findings suggest that the incorporation of 1,3-cyclopropyl phosphate into OA to form prodrugs represents an innovative approach to enhance the efficacy and safety profile of the parent drug.

Antibacterial activity of OA and its derivatives

Many compounds with guanidine have significant antibacterial and antifungal activities [95-97]. At physiological pH, the guanidine group is positively charged. One of the antibacterial mechanisms of guanidine ion salts may be the electrostatic interaction between the negatively charged bacterial surface and the positively charged compound, potentially damaging bacterial cells. YU *et al*. synthesized guanidine functionalized OA derivatives in 2019 [98]. The structures of some compounds are shown in Fig. 29, and their antibacterial properties were studied. Compared with the parent molecule, most of the amino and guanidine derivatives of OA showed significantly increased inhibitory activity against methicillin-resistant *Staphylococcus aureus* (MRSA).

A set of OA amide derivatives (Fig. 30) was synthesized

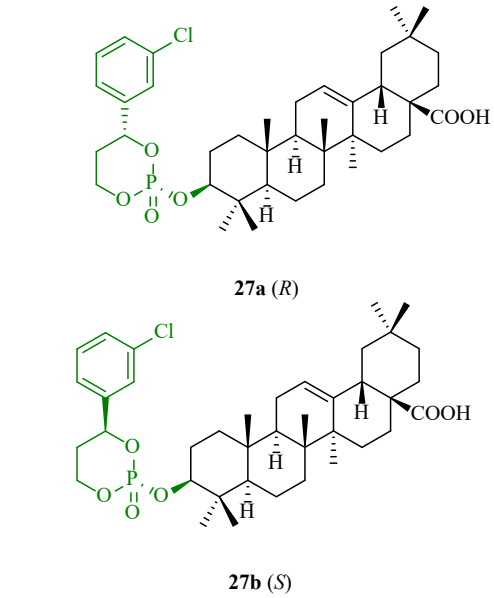


Fig. 28 Structures of OA derivatives 27a and 27b.

by Blanco-Cabra *et al*. [99]. One of these derivatives, **29b**, increased the antibacterial activity of the parent compound *in vitro* while reducing their toxicity to most Gram-positive bacteria, including MRSA. It is noteworthy that OA derivative **29b** increased its antimicrobial activity and reduced the MIC_{50} against MRSA by 87% (MIC_{50} of 10 μg·mL^{-1}) compared with the parent compound (OA, MIC_{50} 75 μg·mL^{-1}). Similarly, another derivative, **29c**, also demonstrated a reduction in MRSA MIC_{50} by 60%. However, bimolecular OA derivatives **29e**–**29g** linked *via* diamines generally lacked antibacterial activity.

In 2020, ZHOU *et al*. reported the effects of OA and its analogs on the *β*-lactamases (NDM-1, KPC-2, and VIM-1) of *Enterobacteriaceae* and *β*-endocrine of *Staphylococcus aureus* [100]. The activity of amidase (*β*-lactamase N1) has a significant inhibitory effect. In the mouse infection model, the efficacy of combining OA and *β*-lactam drugs was evaluated. The results indicated a notable synergistic effect between the two. The survival rate of mice infected with *Staphylococcus aureus* and *Escherichia coli* increased from 25.0% to 75.0% after receiving this combination therapy. In cases where only *β*-lactam drugs were used, the survival rates were 44.4% and 61.1%, while the addition of OA increased these rates to 77.8%. The study's findings suggest that the combination therapy can simultaneously target drug-resistant enzymes and toxins, which can be a promising treatment strategy for drug-resistant bacterial infections.

Anti-AD activity of OA and its derivatives

The typical symptoms of Alzheimer's disease (AD), such as amnesia or behavioral disorders, are often attributed to a reduction in acetylcholine (ACh) concentration [101-104]. Typically, the breakdown of this neurotransmitter is mediated by acetylcholinesterase (AChE). Butyrylcholinesterase (BuChE) is also believed to play a crucial role in regulating the concentration of ACh in different tissues. It is speculated that BuChE may compensate for the decrease in AChE activity [105, 106]. Therefore, these two enzymes are potential targets for the treatment of AD or at least a tool for achieving a deep-

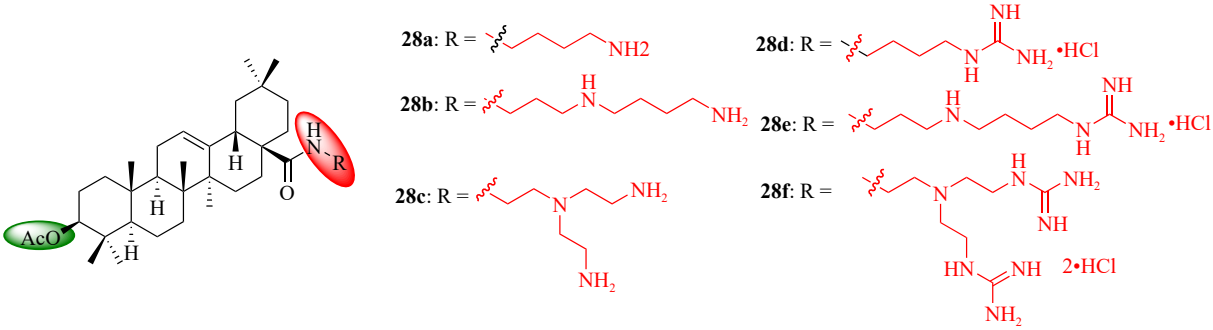
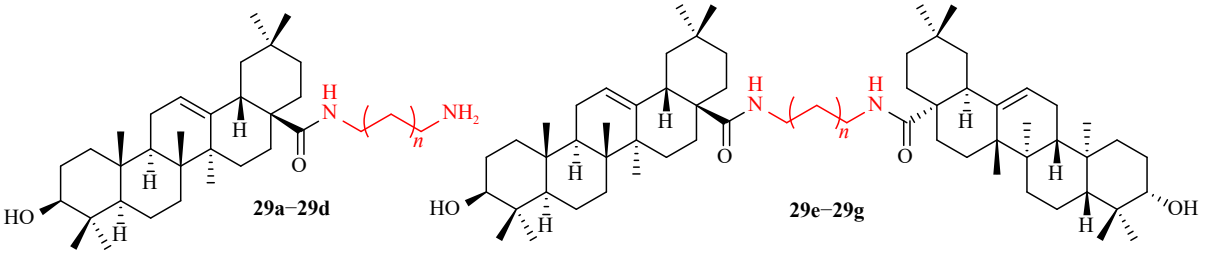


Fig. 29 Structures of OA derivatives 28a–28f (28b–28f, MICs ≤ 0.25 μg·mL^{-1}).



29a: n = 1 (No activity)
29b: n = 4 MIC_{50} = 10 μg·mL^{-1} (against MRSA)
29c: n = 8 MIC_{50} = 30 μg·mL^{-1} (against MRSA)
29d: n = 1, the terminal amine group is NMe_2 (No activity)
29e: n = 1 (No activity)
29f: n = 4 (No activity)
29g: n = 8 (No activity)

Fig. 30 Structures of OA derivatives 29a–29g.

er understanding of AD pathology.

Loesche *et al*. synthesized several OA derivatives, evaluated their inhibitory effects on AChE and BuChE by the Ellman method, and determined the type of inhibition of each active compound [107]. The results showed that several compounds (**30a**–**30e**, as shown in Fig. 31) exerted a stronger inhibitory effect on AChE than OA, which acted as a mixed inhibitor of AChE. Their inhibition constants were K_i 3.46 ± 0.56, 6.37 ± 0.26, 4.22 ± 0.68, and 6.26 ± 2.71 μmol·L^{-1}. Compound **30a** demonstrated the highest activity, which was three times that of OA. Most of the OA derivatives had no inhibitory effect on BuChE, except for compound **30e** (K_i 24.35 ± 9.07 μmol·L^{-1}).

In 2018, according to previous reports on oleanolic-glycoside saponins [108, 109], LI *et al*. in our research group synthesized hederacolochiside E and a series of new derivatives **31a**–**31f** (Fig. 32) in a simple and practical way for the first time [110]. The neuroprotective effects of these compounds on injuries induced by H_2O_2 and $A\beta_{1-42}$ were further evaluated. Compound **31b**, a relatively simple chemical structure, was

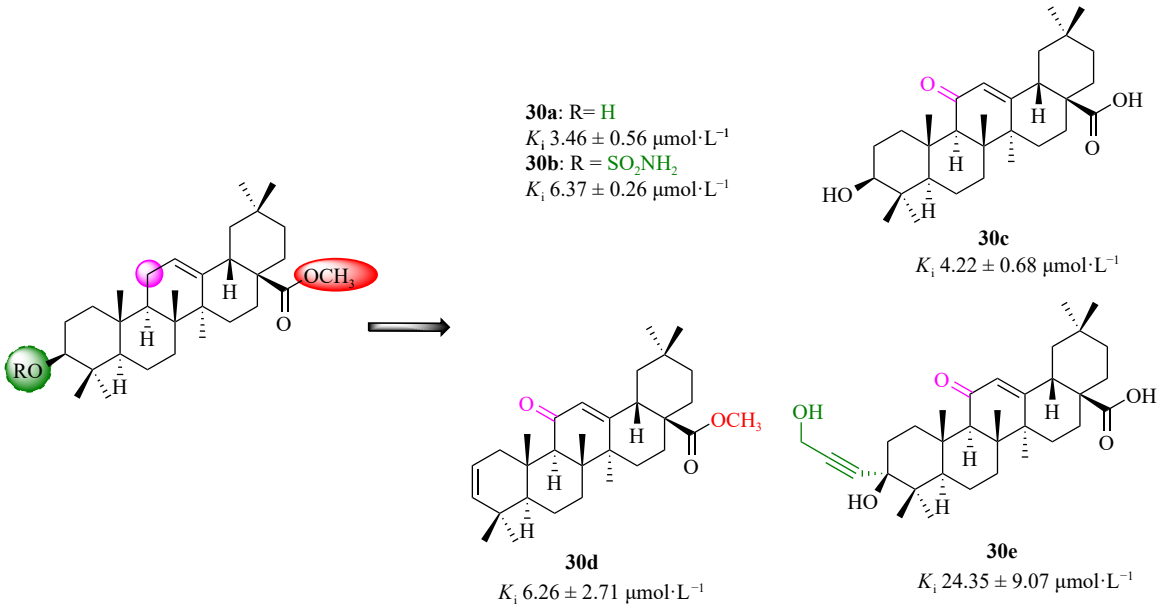


Fig. 31 Structures of OA derivatives 30a–30e.

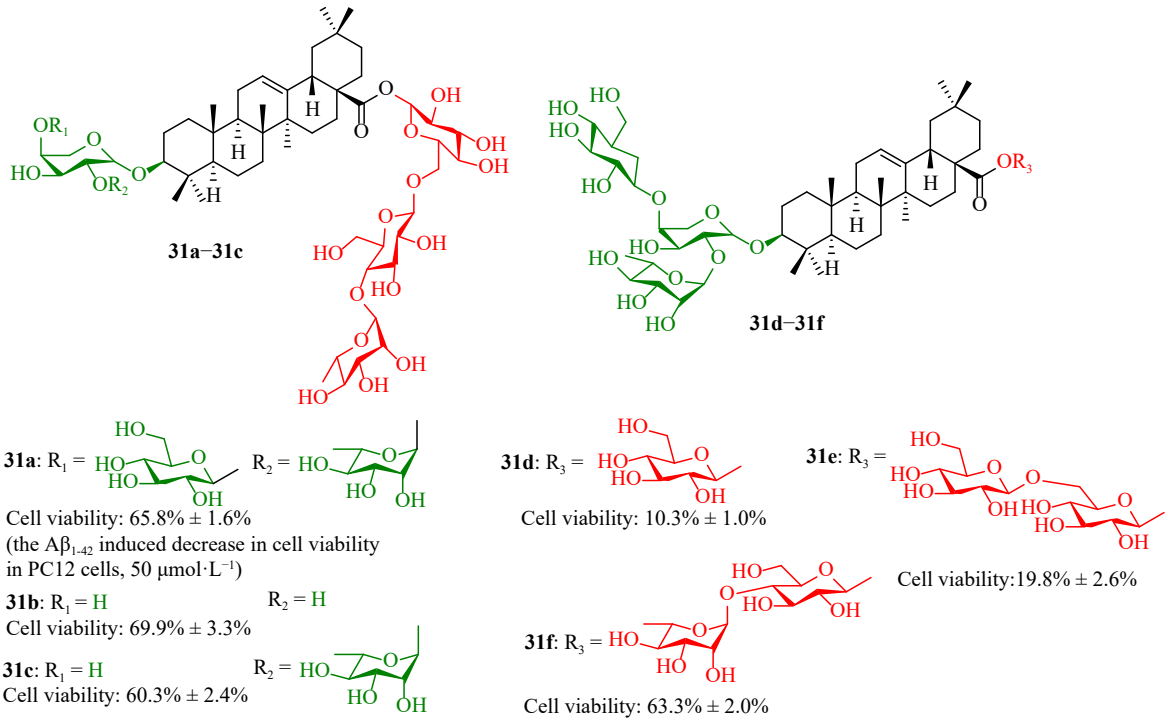
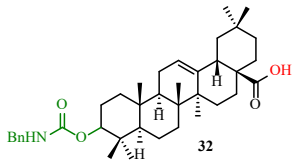


Fig. 32 Structures of OA derivative 31a–31f.

the most active derivative, which exhibited a better neuroprotective effect in the $A\beta_{1-42}$-induced injury model. Moreover, **31a** and **31b** remarkably reduced the release of lactate dehydrogenase (LDH), intracellular ROS level, and the extent of malondialdehyde (MDA) increase resulting from $A\beta_{1-42}$ treatment, indicating that these compounds showed neuroprotective effects in AD models by regulating oxidative stress. The SAR analysis revealed that the rhamnopyranosyl residue at the C-28 position was of vital importance for the neuroprotective activity.

Accumulating evidence suggests that neurotoxic amyloid-beta (Aβ) peptides are one of the major causative factors of AD, particularly $A\beta_{42}$, a major contributing factor to AD pathogenesis. $A\beta_{42}$ is known for its propensity to aggregate, and its accumulation is considered a key biomarker and likely a primary driver of AD [111]. In 2020, LUO *et al*. evaluated the anti-AD biological activity of benzyl-OA carbamate derivatives [112]. They selected compound **32** (Fig. 33) as carbamate compounds, which are nonnative substrates of endogenous lipase enzymes and are cleaved less efficiently than an ester *in vivo*. They found that compound **32** reduced the production of $A\beta_{40}$ and $A\beta_{42}$, with IC_{50} values of 0.57 and 0.65 $\mu mol \cdot L^{-1}$, respectively. The treatment with compound **32** reduced the Aβ level in N2a695 cell-conditioned media by 10%−40%. Furthermore, **32** and OA at 5 $\mu mol \cdot L^{-1}$ exhibited no toxicity against N2a695 cells in an MTT assay.



IC_{50} 0.57 $\mu mol \cdot L^{-1}$, 0.65 $\mu mol \cdot L^{-1}$
(against $A\beta_{40}$ and $A\beta_{42}$, respetively)

Fig. 33 Structures of OA derivative 32.

Conclusion

The utilization of natural products as lead compounds for drug discovery is a well-established and significant aspect of new drug development. OA, a natural product of pentacyclic triterpenes widely existing in nature, is a prime example of this approach. Its unique skeleton and specific chiral methyl configuration are the results of long-term natural evolutionary selection, potentially conferring a higher specificity towards biological cell target proteins. Based on the pharmacological effects of OA, such as antitumor, antiviral, antibacterial, anti-inflammatory, hepatoprotective, hypoglycemia, hypolipidemia, and anti-AD properties, this paper outlines the modification strategies and SARs of OA and its derivatives, drawing on two decades of research, in order to provide a valuable reference for future studies on OA. We can be optimistic that further progress will be made in future research on OA and its derivatives, freeing humans from psychosomatic diseases.

References

[1] Leal AS, Wang R, Salvador JAR, *et al*. Synthesis of novel heterocyclic oleanolic acid deriva-tives with improved antiproliferative activity in solid tumor cells [J]. *Org Biomol Chem*, 2013, **11**(10): 1726-1738.
[2] Mengoni F, Lichtner M, Battinelli L, *et al*. *In vitro* anti-HIV activity of oleanolic acid on infected human mononuclear 893 cells [J]. *Planta Med*, 2002, **68**(2): 111-114.
[3] Fontanay S, Grare M, Mayer J, *et al*. Ursolic, oleanolic and betulinic acids: antibacterial spectra and selectivity indexes [J]. *J Ethnopharmacol*, 2008, **120**(2): 272-276.
[4] Tsai SJ, Yin MC. Antioxidative and anti-inflammatory protection of oleanolic acid and ursolic acid in PC12 cells [J]. *J Food Sci*, 2008, **73**(7): 174-178.
[5] Zhao HZ, Zhou MJ, Duan LF, *et al*. Efficient synthesis and anti-fungal activity of oleanolic acid oxime esters [J]. *Molecules*, 2013, **18**(3): 3615-3629.
[6] Tang C, Chen Y, Bai S, *et al*. Advances in the study of structural modification and biological activities of oleanolic acid [J]. *Chin J Org Chem*, 2013, **33**(1): 46-65.
[7] Luo HQ, Liu JN, Ouyang Q, *et al*. The effects of oleanolic acid on atherosclerosis in different animal models [J]. *Acta Bioch Bioph Sin*, 2017, **49**(4): 349-354.
[8] Jeong DW, Kim YH, Kim HH, *et al*. Dose-linear pharmacokinetics of oleanolic acid after intravenous and oral administration in rats [J]. *Biopharm Drug Dispos*, 2007, **28**(2): 51-57.
[9] Amidon GL, Lennernäs H, Shah VP, *et al*. A theoretical basis for a biopharmaceutic drug classification: the correlation of *in vitro* drug product dissolution and *in vivo* bioavailability [J]. *Pharm Res*, 1995, **12**(3): 413-420.
[10] Salvador JAR, Leal AS, Valdeira AS, *et al*. Oleanane-, ursane-, and quinone methide friedelane-type triterpenoid derivatives: recent advances in cancer treatment [J]. *Eur J Med Chem*, 2017, **142**: 95-130.
[11] Wang Q, Meng YQ. Synthesis and anti-tumor activity of oleanolic acid a ring derivatives *in vitro* [J]. *J Shenyang Univ Chem Technol*, 2020, **34**(2): 125-129.
[12] Wei GF, Luan WJ, Wang S, *et al*. A library of 1,2,3-triazole-substituted oleanolic acid derivatives as anticancer agents: design, synthesis, and biological evaluation [J]. *Org Biomol Chem*, 2015, **13**(5): 1507-1514.
[13] Liu B, Hu GQ, Kang YH. Research progress of the mechanism on antitumor activity of the triazole derivatives [J]. *Pharm Biotechnol*, 2009, **16**(5): 472-476.
[14] Sun KW, Xu YR, Song J, *et al*. Synthesis and *in vitro* antitumor activities of oleanolic acid C-28 tetrazole derivatives [J]. *J Yantai Univ (Nat Sci Eng Edit)*, 2021, **34**(3): 282-288.
[15] Tirino V, Desiderio V, Paino F, *et al*. Cancer stem cells in solid tumors: an overview and new approaches for their isolation and characterization [J]. *FASEB J*, 2013, **27**(1): 13-24.
[16] Sang F, Ding Y, Wang JH, *et al*. Structure-activity relationship study of rakicidins: overcoming chronic myeloid leukemia resistance to imatinib with 4-methylester-rakicidin A [J]. *J Med Chem*, 2016, **59**(3): 1184-1196.
[17] Wang J, Kuang B, Guo X, *et al*. Total syntheses and biological activities of vinylamycin analogues [J]. *J Med Chem*, 2017, **60**(3): 1189-1209.
[18] Liu S, Gao X, Zhang L, *et al*. A novel anti-cancer stem cells compound optimized from the natural symplostatin 4 scaffold inhibits Wnt/b-catenin signaling pathway [J]. *Eur J Med Chem*, 2018, **156**: 21-42.
[19] Zhang BY, Zheng YF, Zhao J, *et al*. Identification of multi-target anti-cancer agents from TCM formula by *in silico* prediction and *in vitro* validation [J]. *Chin J Nat Med*, 2022, **20**(5): 332-351.
[20] Liu XH, Li BL, Zhang Z, *et al*. Synthesis and discovery novel anti-cancer stem cells compounds derived from the natural triterpenoic acids [J]. *J Med Chem*, 2018, **61**(23): 10814-10833.
[21] Liang H, Tong WY, Zhao YY, *et al*. An antitumor compound julibroside J28 from *Albizia julibrissin* [J]. *Bioorg Med Chem Lett*, 2005, **15**(20): 4493-4495.
[22] Liu Y, Yang YT, Wang HH, *et al*. Dammarane-type triterpenoid saponins isolated from *Gynostemma pentaphyllum* ameliorate liver fibrosis *via* agonizing PP2Cα and inhibiting deposition of extracellular matrix [J]. *Chin J Nat Med*, 2023, **21**(8): 599-609.
[23] Krief S, Thoison O, Sevenet T, *et al*. Triterpenoid saponin anthranilates from albiziagrandibracteata leaves ingested by primates in uganda [J]. *J Nat Prod*, 2005, **68**(6): 897-903.
[24] Zou K, Tong WY, Liang H, *et al*. Diastereoisomeric saponins from *Albizia julibrissin* [J]. *Carbohydr Res*, 2005, **340**(7): 1329-1334.
[25] Juang YP, Lin YY, Chan SH, *et al*. Synthesis, distribution

analysis and mechanism studies of *N*-acyl glucosamine-bearing oleanolic saponins [J]. *Bioorg Chem*, 2020, **99**: 103835.
[26] Wang P, Wang J, Guo TT, *et al*. Synthesis and cytotoxic activity of the *N*-acetylglucosamine-bearing triterpenoid saponins [J]. *Carbohydr Res*, 2010, **345**(5): 607-620.
[27] Wang B, Liu Y, Wang YS, *et al*. Syntheses and structure-activity relationship studies of *N*-substituted-*β*-D-glucosaminides as selective cytotoxic agents [J]. *Bioorg Med Chem Lett*, 2012, **22**(23): 7110-7113.
[28] Ren L, Liu Y, Yu GH, *et al*. Synthesis and tumor cytotoxicity of novel *N*-substituted glucosamine bearing oleanolic acid derivatives [J]. *Chem Res Chin Univ*, 2014, **30**(4): 639-643.
[29] Liu QC, Liu HC, Zhang L, *et al*. Synthesis and antitumor activities of naturally occurring oleanolic acid triterpenoid saponins and their derivatives [J]. *Eur J Med Chem*, 2013, **64**: 1-15.
[30] Sun JS, Han XW, Yu B. Synthesis of a typical *N*-acetylglucosamine-containing saponin, oleanolic acid 3-yl-*α*-L-arabinopyranosyl-(1-2)-*α*-L-arabinopyranosyl-(1-6)-2-acetamido-2-deoxy-*β*-D-glucopyranoside [J]. *Carbohyd Res*, 2003, **338**(9): 827-833.
[31] Abdel-Kader M, Hoch J, Berger JM. Two bioactive saponins from *Albizia subdimidiata* from the suriname rainforest [J]. *J Nat Prod*, 2001, **64**(4): 536-539.
[32] Seo Y, Hoch J, Abdel-Kader M, *et al*. Bioactive saponins from *Acacia tenuifolia* from the suriname rainforest [J]. *J Nat Prod*, 2002, **65**(2): 170-174.
[33] Yan MC, Liu Y, Chen H, *et al*. Synthesis and antitumor activity of two natural *N*-acetylglucosamine-bearing triterpenoid saponins: lotoidoside D and E [J]. *Bioorg Med Chem Lett*, 2006, **16**(16): 4200-4204.
[34] Lin YY, Chan SH, Juang YP, *et al*. Design, synthesis and cytotoxic activity of *N*-Modified oleanolic saponins bearing A glucosamine [J]. *Eur J Med Chem*, 2018, **143**: 1942-1958.
[35] Medina-O' Donnell M, Rivas F, Reyes-Zurita FJ, *et al*. Diamine and PEGylated-diamine conjugates of triterpenic acids as potential anticancer agents [J]. *Eur J Med Chem*, 2018, **148**: 325-336.
[36] Monteiro HP, Costa PE, Reis AK, *et al*. Nitric oxide: protein tyrosine phosphorylation and protein *S*-nitrosylation in cancer [J]. *Biomed J*, 2015, **38**: 380-388.
[37] Chen Z, Huang KY, Ling Y, *et al*. Discovery of an oleanolic acid/hederagenin−nitric oxide donor hybrid as an EGFR tyrosine kinase inhibitor for non-small-cell lung cancer [J]. *J Nat Prod*, 2019, **82**(11): 3065-3073.
[38] Serafim RAM, Primi MC, Trossini GHG, *et al*. Nitric oxide: state of the art in drug design [J]. *Curr Med Chem*, 2012, **19**(3): 386-405.
[39] Chen L, Zhang YH, Kong XW, *et al*. Design, synthesis, and antihepatocellular carcinoma activity of nitric oxide releasing derivatives of oleanolic acid [J]. *J Med Chem*, 2008, **51**(15): 4834-4838.
[40] Fu JJ, Liu L, Huang ZJ, *et al*. Hybrid molecule from O_2-(2,4-dinitrophenyl) diazeniumdiolate and oleanolic acid: a glutathione *S*-transferase pi-activated nitric oxide prodrug with selective anti-human hepatocellular carcinoma activity and improved stability [J]. *J Med Chem*, 2013, **56**(11): 4641-4655.
[41] Fu JJ, Zou, ZY, Huang ZJ, *et al*. Identification of nitric oxide-releasing derivatives of oleanolic acid as potential anti-colon cancer agents [J]. *RSC Adv*, 2015, **5**(25): 19445-19454.
[42] Ai Y, Kang FH, Huang ZJ, *et al*. Synthesis of CDDO-amino acid-nitric oxide donor trihybrids as potential antitumor agents against both drug-sensitive and drug-resistant colon cancer [J]. *J Med Chem*, 2015, **58**(5): 2452-2464.
[43] Zou Y, Yan C, Liu JC, *et al*. Synthesis and anti-hepatocellular carcinoma activity of novel O^2-vinyl diazeniumdiolate-based nitric oxide-releasing derivatives of oleanolic acid [J]. *Chin J Nat Med*, 2017, **15**(12): 928-937.
[44] Smith RAJ, Hartley RC, Cocheme HM, *et al*. Mitochondrial pharmacology [J]. *Trends Pharmacol Sci*, 2012, **33**(6): 341-352.
[45] Nunnari J, Suomalainen A. Mitochondria: in sickness and in health [J]. *Cell*, 2012, **148**(6): 1145-1159.
[46] Gogvadze V, Orrenius S, Zhivotovsky B. Mitochondria in cancer cells: what is so special about them [J]. *Trends Cell Biol*, 2008, **18**(4): 165-173.
[47] Miettinen K, Pollier J, Buyst D, *et al*. The ancient CYP716 family is a major contributor to the diversification of eudicot triterpenoid biosynthesis [J]. *Nat Commun*, 2017, **8**: 14153.
[48] Hu S, Wang Z, Hou T. Design, synthesis, and biological evaluation of novel 2-methylpiperazine derivatives as potent CCR5 antagonists [J]. *Bioorg Med Chem*, 2015, **23**(5): 1157-1168.
[49] Lei M, Xiao Z, Ma B, *et al*. Synthesis and biological evaluation of bufalin-3-yl nitrogen-containing-carbamate derivatives as anticancer agents [J]. *Steroids*, 2016, **108**: 56-60.
[50] Teimoori S, Panjamurthy K, Vinaya K, *et al*. Synthesis and antiproliferative activity of novel homopiperazine derivatives in leukemia cells [J]. *Chem Biol Interface*, 2011, **1**: 59-67.
[51] Vanden EJJ, Mayence A, Johnson MT, *et al*. Antitumor and anti-pneumocystis carinii activities of novel bisbenzamidines [J]. *Med Chem Res*, 2005, **14**: 143-157.
[52] Wang N, Switalska M, Wu MY, *et al*. Synthesis and *in vitro* cytotoxic effect of 6-amino-substituted 11H- and 11Me-indolo[3,2-c] quinolines [J]. *Eur J Med Chem*, 2014, **78**(6): 314-323.
[53] Wolfram RK, Fischer L, Kluge R, *et al*. Homopiperazine-rhodamine B adducts of triterpenoic acids are strong mitocans [J]. *Eur J Med Chem*, 2018, **155**: 869-879.
[54] De P, Baltas M, Bedos-Belval F. Cinnamic acid derivatives as anticancer agents-a review [J]. *Curr Med Chem*, 2011, **18**(11): 1672-1703.
[55] Hunke M, Martinez W, Kashyap A, *et al*. Antineoplastic actions of cinnamic acids and their dimers in breast cancer cells: a comparative study [J]. *Anticancer Res*, 2018, **38**(8): 4469-4474.
[56] Su P, Shi YL, Wang JF, *et al*. Anticancer agents derived from natural cinnamic acids [J]. *Anticancer Agents Med Chem*, 2015, **15**(8): 980-987.
[57] Wang R, Yang W, Fan Y, *et al*. Design and synthesis of the novel oleanolic acid-cinnamic acid ester derivatives and glycyrrhetinic acid-cinnamic acid ester derivatives with cytotoxic properties [J]. *Bioorg Chem*, 2019, **88**: 102951.
[58] Liu CM, Huang JY, Sheng LX, *et al*. Synthesis and antitumor activity of fluorouracil: oleanolic acid/ursolic acid/glycyrrhetinic acid conjugates [J]. *Med Chem Commun*, 2019, **10**(8): 1370-1378.
[59] Yu M, Si LL, Wang YF, *et al*. Discovery of pentacyclic triterpenoids as potential entry inhibitors of influenza viruses [J]. *J Med Chem*, 2014, **57**(23): 10058-10071.
[60] Su YQ, Meng LK, Sun JQ, *et al*. Design, synthesis of oleanolic acid-saccharide conjugates using click chemistry methodology and study of their anti-influenza activity [J]. *Eur J Med Chem*, 2019, **182**: 111622.
[61] Li SM, Jia XH, Shen XT, *et al*. Structure-activity relationships of 3-*O*-*β*-chacotriosyl oleanic acid derivatives as entry inhibitors for highly pathogenic H5N1 influenza virus [J]. *Bioorg Med Chem*, 2017, **25**(16): 4384-4396.
[62] Song GP, Shen XT, Li SM, *et al*. Structure-activity relationships of 3-*O*-*β*-chacotriosyl oleanane-type triterpenoids as potential H5N1 entry inhibitors [J]. *Eur J Med Chem*, 2016, **119**: 109-121.
[63] Song GP, Shen XT, Li SM, *et al*. Discovery of 3-*O*-*β*-chacotriosyl oleanane-type triterpenes as H5N1 entry inhibitors [J]. *RSC Adv*, 2015, **5**(49): 39145-39154.
[64] Yu F, Wang Q, Zhang Z, *et al*. Development of oleanane-type triterpenes as a new class of HCV entry inhibitors [J]. *J Med Chem*, 2013, **56**(11): 4300-4319.
[65] Yang Y, He HJ, Chang H, *et al*. Multivalent oleanolic acid human serum albumin conjugate as nonglycosylated neomucin for influenza virus capture and entry inhibition [J]. *Eur J Med Chem*, 2018, **143**: 1723-1731.
[66] Medina-O'Donnell M, Rivas F, Reyes-Zurita FJ, *et al*. Oleanolic acid derivatives as potential inhibitors of HIV-1 protease [J]. *J Nat Prod*, 2019, **82**(10): 2886-2896.
[67] Li HW, Li M, Xu RY, *et al*. Synthesis, structure activity relationship and *in vitro* anti-influenza virus activity of novel polyphenol-pentacyclic triterpene conjugates [J]. *Eur J Med Chem*, 2019, **163**: 560-568.
[68] Meng LK, Su YQ, Yang F, *et al*. Design, synthesis and biological evaluation of amino acids-oleanolic acid conjugates as influenza virus inhibitors [J]. *Bioorg Med Chem*, 2019, **27**(23): 115147.
[69] Zhong YY, Chen HS, Wu PP, *et al*. Synthesis and biological evaluation of novel oleanolic acid analogues as potential *α*-glucosidase inhibitors [J]. *Eur J Med Chem*, 2019, **164**: 706-716.
[70] Qian S, Li HJ, Chen Y, *et al*. Synthesis and biological evaluation of oleanolic acid derivatives as inhibitors of protein tyrosine phosphatase 1B [J]. *J Nat Prod*, 2010, **73**(11): 1743-1750.
[71] Liu QC, Guo TT, Zhang L, *et al*. Synthesis and biological evaluation of oleanolic acid derivatives as PTP1B inhibitors [J]. *Eur J Med Chem*, 2013, **63**: 511-522.
[72] Ramírez-Espinosa JJ, Rios MY, Paoli P, *et al*. Synthesis of oleanolic acid derivatives: *in vitro*, *in vivo* and *in silico* stud-

ies for PTP-1B inhibition [J]. *Eur J Med Chem*, 2014, **87**: 316-327.
[73] Chang YZ, Zhou SX, Li EQ, *et al*. Fragment-based discovery of novel pentacyclic triterpenoid derivatives as cholesteryl ester transfer protein inhibitors [J]. *Eur J Med Chem*, 2017, **126**: 143-153.
[74] Braca A, Dal PF, Marzocco S, *et al*. Triterpene derivatives as inhibitors of protein involved in the inflammatory process: molecules interfering with phospholipase A2, cycloxygenase, and lipoxygenase [J]. *Curr Drug Targets*, 2011, **12**(3): 302-321.
[75] Chan KY, Mohamad K, Ooi AJ, *et al*. Bioactivity-guided fractionation of the lipoxygenase and cyclooxygenase inhibiting constituents from *Chisocheton polyandrus* Merr [J]. *Fitoterapia*, 2012, **83**(5): 961-967.
[76] Chung LY, Soo WK, Chan KY, *et al*. Imiyabir, lipoxygenase inhibiting activity of some Malaysian plants [J]. *Pharm Biol*, 2009, **47**(12): 1142-1148.
[77] Martel-Pelletier J, Lajeunesse D, Reboul P, *et al*. Therapeutic role of dual inhibitors of 5-LOX and COX, selective and non-selective non-steroidal anti-inflammatory drugs [J]. *Ann Rheum Dis*, 2003, **62**(6): 501-509.
[78] Chen XC, Ly Y, Liu Y, *et al*. Identification of a cytochrome P450 from *Tripterygium hypoglaucum* (Levl.) Hutch that catalyzes polpunonic acid formation in celastrol biosynthesis [J]. *Chin J Nat Med*, 2022, **20**(9): 691-700.
[79] Vo NNQ, Nomura Y, Muranaka T, *et al*. Structure-activity relationships of pentacyclic triterpenoids as inhibitors of cyclooxygenase and lipoxygenase enzymes [J]. *J Nat Prod*, 2019, **82**(12): 3311-3320.
[80] Hardie DG, Schaffer BE, Brunt A. AMPK: an energy-sensing pathway with multiple inputs and outputs [J]. *Trends Cell Biol*, 2016, **26**(3): 190-201.
[81] Antonioli L, Colucci R, Pellegrini C, *et al*. The AMPK enzyme-complex: from the regulation of cellular energy homeostasis to a possible new molecular target in the management of chronic inflammatory disorders [J]. *Expert Opin Ther Targets*, 2016, **20**(2): 179-191.
[82] Pilon G, Dallaire P, Marette A. Inhibition of inducible nitric-oxide synthase by activators of AMP-activated protein kinase: a new mechanism of action of insulin-sensitizing drugs [J]. *J Biol Chem*, 2004, **279**(20): 20767-20774.
[83] Nath N, Giri S, Prasad R, *et al*. 5-Aminoimidazole-4-carboxamide ribonucleoside: a novel immunomodulator with therapeutic efficacy in experimental autoimmune encephalomyelitis [J]. *J Immunol*, 2005, **175**(1): 566-574.
[84] Prasad R, Giri S, Nath N, *et al*. 5-Aminoimidazole-4-carboxamide-L-beta-4-ribofuranoside attenuates experimental autoimmune encephalomyelitis *via* modulation of endothelial-monocyte interaction [J]. *J Neurosci Res*, 2006, **84**(3): 614-625.
[85] Nath N, Khan M, Paintlia MK, *et al*. Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis [J]. *J Immunol*, 2009, **182**(12): 8005-8014.
[86] Myerburg MM, King JD, Jr Oyster NM, *et al*. AMPK agonists ameliorate sodium and fluid transport and inflammation in cystic fibrosis airway epithelial cells [J]. *Am J Respir Cell Mol Biol*, 2010, **42**(6): 676-684.
[87] Wang JY, Ma H, Zhang XY, *et al*. A novel AMPK activator from Chinese herb medicine and ischemia phosphorylate the cardiac transcription factor FOXO3 [J]. *Int J Physiol Pathophysiol Pharmacol*, 2009, **1**(2): 116-126.
[88] Wang X, Liu R, Zhang W, *et al*. Oleanolic acid improves hepatic insulin resistance *via* antioxidant, hypolipidemic and anti-inflammatory effects [J]. *Mol Cell Endocrinol*, 2013, **376**(1-2): 70-80.
[89] Liu J, Zheng LH, Wu N, *et al*. Oleanolic acid induces metabolic adaptation in cancer cells by activating the AMP-activated protein kinase pathway [J]. *J Agric Food Chem*, 2014, **62**(24): 5528-5537.
[90] Nie H, Wang Y, Qin Y, *et al*. Oleanolic acid induces autophagic death in human gastric cancer cells *in vitro* and *in vivo* [J]. *Cell Biol Int*, 2016, **40**(7): 770-778.
[91] Liu L, Li HB, Hu KW, *et al*. Synthesis and anti-inflammatory activity of saponin derivatives of *δ*-oleanolic acid [J]. *Eur J Med Chem*, 2021, **209**: 112932.
[92] Bhandari P, Patel NK, Gangwal RP, *et al*. Oleanolic acid analogs as NO, TNF-α and IL-1β inhibitors: synthesis, biological evaluation and docking studies [J]. *Bioorg Med Chem Lett*, 2014, **24**(17): 4114-4119.
[93] Jannus F, Medina-O'Donnell M, Neubrand VE, *et al*. Efficient *in vitro* and *in vivo* anti-inflammatory activity of a diamine-PEGylated oleanolic acid derivative [J]. *Int J Mol Sci*, 2021, **22**(15): 8158.
[94] Yu ZJ, Sun WZ, Peng WB, *et al*. Pharmacokinetics *in vitro* and *in vivo* of two novel prodrugs of oleanolic acid in rats and its hepatoprotective effects against liver injury induced by CCl_4 [J]. *Mol Pharm*, 2016, **13**(5): 1699-1710.
[95] Saczewski F, Balewski Ł. Biological activities of guanidine compounds [J]. *Expert Opin Ther Pat*, 2009, **19**(10): 1417-1448.
[96] Castagnolo D, Schenone S, Botta M. Guanylated diamines, triamines, and polyamines: chemistry and biological properties [J]. *Chem Rev*, 2011, **111**(9): 5247-5300.
[97] Wexselblatt E, Esko JD, Tor Y. On guanidinium and cellular uptake [J]. *J Org Chem*, 2014, **79**(15): 6766-6774.
[98] Yu SA, Khalitova RR, Nedopekina DA, *et al*. Antimicrobial properties of amine- and guanidine-functionalized derivatives of betulinic, ursolic and oleanolic acids: synthesis and structure/activity evaluation [J]. *Steroids*, 2020, **154**: 108530.
[99] Blanco-Cabra N, Vega-Granados K, Moya-Andérico L, *et al*. Novel oleanolic and maslinic acids derivatives as a promising treatment against bacterial biofilm in nosocomial infections: an *in vitro* and *in vivo* study [J]. *ACS Infect Dis*, 2019, **5**(9): 1581-1589.
[100] Zhou YL, Guo Y, Sun XD, *et al*. Application of oleanolic acid and its analogues in combating pathogenic bacteria *in vitro*/*vivo* by a two-pronged strategy of *β*-lactamases and hemolysins [J]. *ACS Omega*, 2020, **5**(20): 11424-11438.
[101] Perry EK, Perry RH, Blessed G, *et al*. Changes in brain cholinesterases in senile dementia of alzheimer type [J]. *Neuropathol Appl Neurobiol*, 1978, **4**(4): 273-277.
[102] Whitehouse PJ, Price DL, Clark AW, *et al*. Alzheimer-disease-evidence for selective loss of cholinergic neurons in the nucleus basalis [J]. *Ann Neurol*, 1981, **10**(2): 122-126.
[103] Bartus RT, Dean RL, Beer B, *et al*. The cholinergic hypothesis of geriatric memory dysfunction [J]. *Science*, 1982, **217**(4558): 408-414.
[104] Coyle JT, Price DL, Delong MR. Alzheimers-disease a disorder of cortical cholinergic innervation [J]. *Science*, 1983, **219**(4589): 1184-1190.
[105] Harrell LE. Cholinesterases and cholinesterase inhibitors [J]. *Arch Neurol*, 2001, **58**(3): 516.
[106] Mesulam MM, Guillozet A, Shaw P, *et al*. Acetylcholinesterase knockouts establish central cholinergic pathways and can use butyrylcholinesterase to hydrolyze acetylcholine [J]. *Neuroscience*, 2002, **110**(4): 627-639.
[107] Loesche A, Köwitsch A, Lucas SD, *et al*. Ursolic and oleanolic acid derivatives with cholinesterase inhibiting potential [J]. *Bioorg Chem*, 2019, **85**: 23-32.
[108] JS Seo, TK Kim, YH Leem, *et al*. SK-PC-B70M confers antioxidant activity and reduces Ab levels in the brain of Tg2576 mice [J]. *Brain Res*, 2009, **1261**: 100-108.
[109] Gülçin I, Mshvildadze V, Gepdiremen A, *et al*. Antioxidant activity of saponins isolated from ivy: alpha-hederin, hederasaponin-C, hederacolchiside-E and hederacolchiside-F [J]. *Planta Med*, 2004, **70**(6): 561-563.
[110] Li HN, Liu Y, Zhang ZP, *et al*. Synthesis, biological evaluation and structure-activity relationship studies of hederacolchiside E and its derivatives as potential anti-Alzheimer agents [J]. *Eur J Med Chem*, 2018, **143**: 376-389.
[111] Selkoe DJ, Hardy J. The amyloid hypothesis of Alzheimer's disease at 25 years [J]. *EMBO Mol Med*, 2016, **8**(6): 595-608.
[112] Luo WJ, Ip FCF, Fu GM, *et al*. A pentacyclic triterpene from *Ligustrum lucidum* targets *γ*-secretase [J]. *ACS Chem Neurosci*, 2020, **11**(18): 2827-2835.

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