Recent progress in the antiviral activity and mechanism study of pentacyclic triterpenoids and their derivatives

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Abstract
Viral infections cause many serious human diseases with high mortality rates. New drug-resistant strains are continually emerging due to the high viral mutation rate, which makes it necessary to develop new antiviral agents. Compounds of plant origin are particularly interesting. The pentacyclic triterpenoids (PTs) are a diverse class of natural products from plants composed of three terpene units. They exhibit antitumor, anti-inflammatory, and antiviral activities. Oleanolic, betulinic, and ursolic acids are representative PTs widely present in nature with a broad antiviral spectrum. This review focuses on the recent literatures in the antiviral efficacy of this class of phytochemicals and their derivatives. In addition, their modes of action are also summarized.

KEYWORDS
antiviral, betulinic acid, glycyrrhizin, mechanism, pentacyclic triterpenoid

1 | INTRODUCTION

Viruses exist wherever life is found. They are the most common pathogens leading to infectious and fatal human diseases. According to the 2014 World Health Organization report, over 36.9 million people are living with the human immunodeficiency virus (HIV) infection. The most recent estimate indicates that hepatitis C virus (HCV) causes chronic infection of approximately 3% of the world’s population. In addition to those two viral pathogens, humans also constantly encounter threats from many other emerging and reemerging infectious, zoonotic and devastating viruses, such as the highly pathogenic avian influenza A virus (H5N1 and H7N9), severe acute respiratory syndrome...
coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV), Ebola virus (EBOV), and so on. Given the high mutation rate of viruses and their serious threat to public health, there is a high urgency to develop new antiviral drugs to combat these pathogens. Natural products in the roots, stems, barks, leaves, fruits, and seeds of plants have been used as herbal medicines to treat diseases for more than 3000 years in China. They also have played a significant role in modern drug discovery by serving as prototypes of novel drugs. As mentioned by Newman et al., it has been estimated that over 49% of clinically used antitumor drugs from around the 1940s to the end of 2014 are natural products or their derivatives. Natural product-derived drugs have also been crucial for antiviral drug discovery. From 1981 to 2014, over 40% of antiviral drugs in clinical use are natural products (∼6%) or designed using natural products as prototypes (∼34%).

Among the natural products, triterpenoids and their relatives, also called the steroids, constitute a very large family of compounds with over 20,000 identified molecules. And many new compounds are being discovered in plants, animals, and fungi every year. Most of them exist in nature as free acids, as esters with fatty acids, ferulic acid, etc., or as triterpenoid saponins linked with one or more sugar chains. They are often the main active constituents of many important medicinal plants, such as the ginsenosides in Panax ginseng, glycyrrhizin in Glycyrrhiza uralensis and saikosaponins in Radix Bupleuri. Triterpenoids display a variety of structures with nearly 200 different skeletons known from natural sources or enzymatic reactions, although many are variants of a smaller number of common structural types. Many pentacyclic triterpenoids (PTs) show a wide range of pharmacological activities, and some are marketed as therapeutic agents or dietary supplements. Structurally, PTs have four six-membered rings called A, B, C, D with ring E being five-membered or six-membered. Based on the carbon skeleton, they are divided into six common subgroups: oleanane, lupane, ursane, friedelane, hopane, and gammacerane (Fig. 1).

PTs are a large class of secondary plant metabolites that are constructed by isoprene (2-methylbutadiene) (C₅H₈) units, an abundant natural product in plants. The linear triterpene squalene, the major constituent of shark liver oil, is derived from two farnesyl pyrophosphate units. Under the catalysis of squalene epoxidase, squalene is biosynthetically
FIGURE 2 Chemical structures of lupeol, α-amyrin, and β-amyrin

FIGURE 3 Chemical structures of PTs 1–7

oxidized to 2,3-oxidosqualene and various cyclic products, yielding the dammarenyl, lupenyl, and baccharenyl cation intermediates that eventually give rise to three major products namely: lupeol, α-amyrin, and β-amyrin, respectively (Fig. 2). Many PTs have a hydroxyl group at C3, a 12-ene and a carboxylic acid at C17 or C20. The structural diversity of PTs provides a unique group of agents with a variety of pharmacological activities, including antiviral, antitumor, immunomodulatory, anti-inflammatory, and hepatoprotective activities. Presently, the newly discovered PTs are a subject of annual review, reflecting the increasing importance of this class of compounds. The available reviews cover the chemistry, antitumor activity, anti-inflammatory activity, bioavailability, and other pharmacological activity.

Recently, the antiviral activities of PTs are attracting increasing attention. In Japan, Stronger Neo-Minophagen C™ (SNMC), a preparation containing glycyrrhizin (glycyrrhizic acid, 1) has been used in the treatment of chronic hepatic diseases for over 40 years. Glycyrrhetinic acid (GA, 2) (Fig. 3), a PT derivative of the β-amyrin type, is obtained from the hydrolysis of glycyrrhizin 1, which is isolated from the herb liquorice and shows inhibition on a variety of
viruses including hepatitis B virus (HBV) and HIV. In 1989, saponin B1 and B2, two oleanane-type triterpenoids isolated from soybean seeds, have been reported to have activity against HIV at concentrations greater than 2 and 0.5 mg/mL, respectively. Three years later, Chen et al. reported that salaspermic acid (3), another oleanane-type triterpenoid derivative isolated from *Tripterygium wilfordii*, can block the replication of HIV in H9 lymphocytes (IC₅₀: 10 μM). Afterwards, Fujioka et al. found that betulinic acid (BA, 4), isolated from the leaves and barks of *Syzygium claviflorum*, also showed significant activity against HIV (EC₅₀: 1.4 μM). Since then, more and more natural PTs have been reported to have antiviral activity. It is well known that lipids, a class of hydrophobic biomolecules, are important for cellular life, especially during virus entry into the host cell. It was reported that the promiscuous antiviral activities of natural PTs might be related to the effect of lipid metabolism.

Synthetic chemists become more interested in these scaffolds due to their potential antiviral properties, leading to the production of a variety of PT derivatives through modifications of the C3-OH, C17-COOH, and other functional groups. Some of these derivatives are used as clinical drugs for the treatment of liver-related diseases, while others are at various phases of clinical trials. For example, the BA derivative Bevirimat (BVM, 5), also known as 3-O-(3′,3′-dimethylsuccinyl) BA (DSB) or PA-457, was found to exhibit remarkable anti-HIV activity against primary and drug-resistant HIV isolates. It represents a unique first in class anti-HIV compound termed maturation inhibitors (MIs). Due to the baseline gag polymorphisms at positions Q369, V370, or T371, which reduced the sensitivity of HIV-1 to Bevirimat (5), it was halted for further development in 2010. Recently, the second class of potent PTs BMS-955176 (6) and GSK-2838232 (7) are under development as oral treatment of HIV infection. However, up to now, there is no review focusing on the activity of PTs against viral infection. The focus of the present review is to summarize the recent advances in the antiviral activities and action models of PTs to aid the antiviral drug development of PTs.

## 2 | PTs AS ANTI-HIV AGENTS

HIV is a lentivirus that could lead to HIV infection and over time acquired immunodeficiency syndrome (AIDS). Because of the lack of CD4-positive T cells, HIV patients are exposed to life-threatening opportunistic infections and cancers without normal immune protection. Fortunately, HIV-1 infection can be effectively managed with a long-term administration of multiple antiviral inhibitors designated as combination antiretroviral therapy (cART). Since Zidovudine (ZDV, also known as azidothymidine, AZT) was launched in 1987 as the first anti-HIV drug that targets HIV reverse transcriptase, so far over 40 formulations have been approved by FDA for HIV therapy. However, none of them is PTs. According to Thomson Reuters, among all chemicals in clinical trials, only four belong to PTs. They are MPC-9055 (the structure has not been reported in literature), Bevirimat (5), BMS-955176 (6), and GSK-2838232 (7). These four compounds are all MIs bearing the scaffold of BA (4). GSK-2838232 (7), an orally active BA derivative, targets against HIV-1 maturation process and it is under phase Iia clinical trial. However, the clinical testing of MPC-9055, Bevirimat (5), and BMS-955176 (6) have been discontinued.

Many PTs and their derivatives have been reported to have fair anti-HIV activity. Most of them usually show weaker anti-HIV activity than the other clinically available drugs. However, they enrich the database of anti-HIV compounds and provide good lead compounds for further drug development due to their diverse chemical structures. According to the life cycle of HIV, the inhibitors of HIV are divided into entry inhibitor, reverse transcriptase (RTase) inhibitor, protease inhibitor, viral MI, and so on. Table 1 summarizes the representative anti-HIV PTs based on their targets.

### 2.1 | Entry inhibitors

Entry of HIV-1 into host cells, the first phase of the viral replication cycle, is an ordered multistep process that involves the attachment of virus to the host cell, the binding of virus to the co-receptor, and the fusion of the cell and viral membranes. HIV-1 uses multiple pathways for entry, such as usurpation of cellular transport pathway, surfing along the cell surface. These processes provide targets for developing novel entry inhibitors to prevent HIV infection in the first step.
TABLE 1  Summary of anti-HIV PTs based on their targets

| Classification          | PTs                                                                 |
|-------------------------|----------------------------------------------------------------------|
| Entry inhibitors        | Glycyrrhizin (1) and its analog 8; RPR103611 (9); IC9564 (10)       |
| Reverse transcriptase inhibitors | Mimusopic acid (11); 12                                                 |
| Protease inhibitors     | UA (13) and its derivatives 14–15; 16                               |
|                         | OA (17) and its derivatives 18–20                                    |
| Maturation inhibitors   | MPC-9055; Bevirimat (5); BMS-955176 (6); GSK-2838232 (7); 23         |
| Bifunctional inhibitors | BA derivatives 24–25                                                  |

FIGURE 4  Chemical structures of PTs 8–25 with anti-HIV activity

Glycyrrhizin (1), a well-known triterpenoid saponin isolated from licorice root, has been reported to possess anti-HIV-1 infection activity by blocking the adsorption of HIV-1 particles onto CD4-positive T cells.\(^\text{51,52}\) Compound 8 (Fig. 4), an analogue of glycyrrhizin with a heteroannular diene structure at the C and D rings, was demonstrated to be as active as glycyrrhizin against HIV-1 infection. HIV-1-induced cytopathogenicity was completely inhibited by this compound...
at the concentration of 0.16 mM in MT-4 and MOLT-4 cells. However, the underlying mechanism of this kind of compounds remains unclear.

RPR103611 (9), a BA derivative with aminooctanoyl amino-3(S)-hydroxy-6-methylheptanoic acid side chain at C17-COOH, has been shown to be a potent inhibitor against envelope-mediated membrane fusion of HIV-1. IC₅₀ values of compound 9 varied in the range of 40–100 nM in most cell systems, with selective indexes in excess of 100. The transmembrane glycoprotein gp41 was initially reported to be the target of RPR103611 (9), because the I84S mutation of gp41 of CXCR4-dependent HIV-1 LAI was sufficient for drug resistance against RPR103611 (9). Further study illustrated that both the sequence of gp41 loop and the stability of the gp120-gp41 complex can affect the antiviral efficacy of RPR103611 (9).

IC9564 (10), the stereoisomer of RPR103611 (9), was found to be equally active with an EC₅₀ value of 0.4 µM. The two BA derivatives 9 and 10 can block the adsorption of HIV to host cells. In addition, compound 9 and its isomer 10 showed the highest activity in the MAGI and fusion assays of H9 lymphocyte.

2.2 | RTase inhibitors

HIV RTase catalyzes the replication of virus RNA into DNA. Inhibition of RTase enzyme disrupts this essential process for virus replication and infection. Therefore, RTase has long been an obvious target in the battle against HIV.

Mimusopic acid (11), a triterpene analogue isolated from the seeds of Mimusops elengi, has been reported to possess weak HIV-RTase inhibitory activity with IC₅₀ at micromolar level. Pengsuparp et al. reported that 1-beta-hydroxyaleuritolic acid 3-p-hydroxybenzoate (12), isolated from the roots of Maprounea africana, also had anti-HIV-1 RTase activity with an IC₅₀ value of 3.7 µM.

2.3 | Protease inhibitors

The HIV polyprotein that contains several viral proteins joined together must be cleaved into the individual functional proteins. This cleavage is catalyzed by HIV protease, a symmetric homodimer. Inhibition of HIV protease can prevent the enzyme from cutting the viral protein molecules down to their proper sizes, which makes HIV protease a promising drug target.

Ursolic acid (UA, 13) and its hydrogen malonate (14) isolated from the stems of Cynomorium songaricum have activity in inhibiting HIV-1 protease with EC₅₀ value at micromolar level. The glutaryl hemiesters 15–16 of BA and UA were shown to have anti-HIV-1 protease activity at the concentration of 4 µM. Oleanolic acid (OA, 17) from Xanthoceras sorbifolia was found to completely inhibit HIV-1 protease activity at the concentration of 100 µg/µL. Chemical modifications of oleanane-type triterpene at C3-OH and/or C17-COOH increase the anti-HIV protease activity. The most potent compounds 18–20 showed anti-HIV protease activity with IC₅₀ in the range of 1.7–4.0 µM. In addition, escin Ia (21) and Ib (22), two triterpenes saponins isolated from Aesculus chinensis, also exhibit HIV-1 protease inhibitory activity.

2.4 | Maturation inhibitors

MIs are an emerging class of anti-HIV-1 compounds that can block HIV-1 maturation by specifically interfering with Gag processing cascade. In the final step of the viral replication cycle, p17 matrix protein (MA), p24 capsid protein (CA), nucleocapsid protein (NC), and p6 protein are released from the Gag polyprotein precursor (Pr55Gag), which represents a novel target for potential intervention of HIV-1. Inhibition of Gag leads to defective core condensation and the release of noninfectious virus particles from host cells, thus leading to the release of noninfectious particles.

Bevirimat (5) and MPC-9055 are the first-generation MIs to be studied in humans. Recently several second-generation HIV-1 MIs that show improved potency against viruses containing Bervirimat-resistant Gag polymorphisms are developed in clinical trials for HIV patients.
The introduction of a 3,3-dimethylsuccinyl group at the hydroxyl of C3 of OA (17) generated the most potent compound 23 3-O-3',3'-dimethylsuccinate that has greatly increased the potency without significant cytotoxicity. Compound 23 was shown to have anti-HIV-1 activity at subnanomolar concentrations with a therapeutic index of 22,400. Similarly, the introduction of a 3,3-dimethylsuccinyl group at the same position of BA (4) leads to the discovery of Bevirimat (5). Compound 5 greatly increased the anti-HIV activity of BA with an IC$_{50}$ value of less than 0.35 nM and a selective index of more than 20,000.

MPC-9055 (the structure has not been reported in literature), an orally bioavailable small molecule for HIV therapy, was developed by Myrexis. It blocks HIV-1 replication by interrupting the processing of the viral capsid protein 25 to p24, which condenses to form the conical core structure surrounding the viral genome. A phase I clinical trial of MPC-9055 in healthy volunteers was completed in 2008. The primary objective of the study was to evaluate the safety, tolerability, and pharmacodynamics of MPC-9055. Results show that the overall safety profile was favorable and the observed Pharmacokinetics (PK)/Pharmacodynamics (PD) profile supported continued research and development.

First-generation MIs are ineffective against some naturally occurring variations (polymorphisms) in the Gag protease polyprotein; however, the second-generation inhibitors have been developed to better tolerate gag polymorphisms. BMS-955176 (6) is an orally active second-generation HIV MI under development by Bristol-Myers Squibb for the treatment of HIV infection. This compound had been in phase IIb clinical trial, but was discontinued. By blocking the maturation of the virus, it prevents viral reproduction in host CD4 T cells with the EC$_{50}$ of 1.9 nM against HIV-1 wild-type (WT) and the EC$_{50}$ of 2.7 nM against HIV-1 WT with the V370A variant of Gag protein. GSK-2838232 (7), another anti-HIV inhibitor, is also under clinical investigation.

### 2.5 Bifunctional inhibitors

BA derivatives with modifications at both C3-OH and C17-COOH of BA (4) can block the virus fusion and virus maturation simultaneously as a novel type of bifunctional inhibitors. By combining the anti-HIV-1 entry pharmacophore from IC9564 (10) and the anti-HIV-1 maturation pharmacophore from Bevirimat (5), bifunctional anti-HIV compounds N-[3-O-(3',3'-dimethylsucciny)-lup-20(29)-en-28-oyl]-L-leucine (LH15, 25), and N-[3-O-(3',3'-dimethylsucciny)-lup-20(29)-en-28-oyl]-11-aminoundecanoic acid (LH55, 26) were obtained to double strike the life cycle of HIV. They presented the best activity against NL4-3 with IC$_{50}$ value of 0.016 and 0.0065 μM, respectively.

### 3 PTs AS ANTI-HCV AGENTS

HCV is an enveloped, positive-stranded RNA virus in the genus hepacivirus, and belongs to the flaviviridae family. There are at least six distinct genotypes with multiple subtypes in each genotype class, which is important for the prediction of therapy response. HCV has an error-prone replication process for the RNA genome of about 9.6 kb in full length. It encodes a single polyprotein of more than 3000 amino acids, which is cleaved by viral and host enzymes into ten mature individual proteins, including three structural proteins (core, E1, E2) and seven regulatory proteins (p7, NS2, NS3, NS4A, NS4B, NS5A, NS5B). According to Thomson Reuters, more than 100 anti-HCV drugs have been launched. However, none of them is PTs. Only ME 3738 (35), a PT, had been in Phase I clinical trials. Table 2 summarizes the representative anti-HCV PTs based on their targets.

#### 3.1 Entry inhibitors

It was proposed that HCV glycoproteins could be essential drug targets for the development of HCV entry inhibitors. The core structure of E2 protein was solved in 2013. As a result, many agents are investigated as anti-E2 inhibitors to interrupt the interaction between E2 and CD81, thus inhibiting HCV entry. Small molecules are designed and synthesized to mimic the interacting space and hydrophobic feature of the helix D region of CD81,
TABLE 2  Summary of anti-HCV PTs based on their targets

| Classification     | Pentacyclic triterpenes                                      |
|--------------------|-------------------------------------------------------------|
| Entry inhibitors   | OA (17) and its derivatives (27–32)                        |
| Protease inhibitors| OA (17) and its derivatives (33–34)                        |
| Immunomodulator    | ME 3738 (35)                                                |
| Other inhibitor    | Glycyrrhizin (1)                                            |

FIGURE 5  Chemical structures of PTs 26–35 with anti-HCV activity

PTs showed fair activity in anti-HCV entry assays. OA (17) and echinocystic acid (EA, 26) (Fig. 5), two naturally occurring oleanane-type triterpenes, and their derivatives displayed potent activity against HCV entry. Yu et al. reported that OA (17) only showed weak anti-HCV entry activity (10 μM: ∼65%). However, a small modification of the structure by introduction of a hydroxyl group at C-16 to provide its analogues 26 leads to significantly enhanced activity with an IC50 value of 1.4 μM in HCVpp model. With this lead compound, a comprehensive structure–activity relationship (SAR) study was conducted. Introducing a disaccharide to this lead compound at C17-COOH leads to the discovery of compound 27, which showed stronger anti-HCV entry activity with an IC50 of 0.3 μM without the
 FIGURE 6  A proposed mechanism for EA (26)-mediated blocking of HCV entry.\textsuperscript{85}

undesired hemolytic effect. Formation of a triterpene dimer of 26 via a linker results in the discovery of compound 28 with an IC\textsubscript{50} value of about 10 nM.\textsuperscript{85} A series of bivalent oleanane-type triterpenes were further designed and synthesized by optimizing the hydrophobicity, rigidity, and length of the linker. It was found that compound 29 exhibited dramatically enhanced activity with an IC\textsubscript{50} value in the subnanomolar ranges.\textsuperscript{86}

It is well known that the low solubility in biological matrices and the high hydrophobicity of PTs hinder their applications, particularly in the development of therapeutic agents. Given the limited solubility of PTs, a series of triterpene–cyclodextrin (CD) conjugates were synthesized to improve the solubility and maintain the activity of triterpenes.\textsuperscript{87,88} Based on HCVpp/VSVGpp entry assays, the IC\textsubscript{50} value of compound 30 is 0.25 µM, showing the elevation of water solubility and maintain activity of the anti-HCV entry.

To elucidate the anti-HCV pharmacophore of EA (26), a microbial transformation strategy and a ring expansion/opening strategy have been used to explore the SAR.\textsuperscript{89,90} Results showed that most of the metabolites generated by microbial transformation did not exhibit improved anti-HCV activity except compounds 31 and 32, which displayed similar or even a little higher potency than 26 in HCV entry assay. Meanwhile, the ring expansion and ring opening derivatives of EA (26), such as lactones, 3,28-dioic acids, or pentols, showed no improved anti-HCV activity. These studies showed that rings A and C of EA are highly conserved and chemical modification of the two rings abolishes the potency of 26, suggesting that the steric hinder effects of the rigid skeleton play an important role in determination of the anti-HCV entry activity.

In summary, chemical exploration of these triterpene compounds revealed that ring D, right side of ring E, and C17-COOH are tolerant to modifications, while ring A, B, C and the left side of ring E are highly conserved for the anti-HCV entry activity. Introducing a hydroxyl group in ring D at C-16 can enhance the potency of triterpene and remove the hemolytic effect of EA (26) (Fig. 6).

3.2  HCV protease inhibitors

OA (17) was also found to be an HCV protease inhibitor.\textsuperscript{91} Based on this lead compound, 29 OA derivatives were synthesized and tested for their inhibitory activity on hepatitis C viral protease. The derivatives of dicarboxylic acid hemiesters showed potent activity against HCV protease. Of the dicarboxylic acid hemiesters, two compounds 34 and 35 with relatively short carbon chains showed much lower cytotoxicity than OA but maintained the inhibitory activity on HCV protease.
3.3 Immunomodulator

22β-methoxyolean-12-ene-3β,24(4β)-diol (ME 3738, 35), a derivative of soyasapogenol B, inhibits HCV replication by inducing oligoadenylate synthetase 1 gene expression and enhancing the effect of interferon (IFN)-α to increase IFN-stimulated gene expression. In vitro assay, 35 reduces HCV core antigen (HCVcAg) and HCV-RNA levels in mouse livers. Moreover, ME 3738 was also found to be an inducer of interleukin 6 (IL-6). It can stimulate the production of IL-6 and protect mouse from acute liver injury/failure induced by concanavalin A (Con A) and prevent the development of alcoholic fatty liver.

Phase I trial of 35 was carried out in 2001 and it showed that ME 3738 strongly reduced positive and negative RNA strand levels, as measured by real-time Polymerase Chain Reaction (PCR).

3.4 Other HCV inhibitors

Glycyrrhizin (1) has been shown to have the inhibitory activity against various viruses, including HIV, herpes simplex virus (HSV), vesicular stomatitis virus (VSV), HBV, and so on. Compound 1 also showed anti-HCV protease activity with IC_{50} value of 16.7 ± 2.4 μM. A synergistic effect between compound 1 and IFN alpha-2a against HCV has been observed, providing a new treatment along with IFN for HCV infection. It was suggested that the active constituent 1 triggered NFκB pathway and led to induction of IL-8 secretion and antiviral activity against a series of DNA and RNA viruses.

4 PTs AS ANTI-INFLUENZA AGENTS

Influenza viruses belong to the Orthomyxoviridae family, an RNA-type virus with diverse antigenic characteristics. As common pathogens, influenza viruses can cause serious diseases in humans and animal species. Currently, four types of influenza viruses, influenza viruses A, B, C, and D, have been identified. Among them, types A and B generally caused most of the influenza epidemics and outbreaks, leading to serious impact on public health and economy, and type C is generally responsible for sporadic mild upper respiratory symptoms. Neuraminidase inhibitors, including oseltamivir and zanamivir, and M2 ion channel inhibitors, including amantadine and rimantadine, are two classes of clinically used drugs against influenza viruses. However, the high mutation rate of influenza virus results in the emergence of influenza virus strains that are resistant to those drugs, illustrating the urgent need to develop novel anti-influenza drugs.

4.1 PT-glycoconjugates

Glycyrrhizin (1) has been isolated from the roots of licorice, and showed a broad antiviral spectrum. Wolkerstorfer et al. investigated the mechanism by which 1 inhibits influenza virus infection and found that compound 1 can interact with the membrane of cells, leading to a decrease of cell endocytotic activity and virus uptake. From the lead compound 1, some derivatives were developed. Among them, compounds 36–38 exhibited the most efficient anti-influenza activity (IC_{50}: 4.3–7.2 μM) (Fig. 7). Recently, uralsaponin M (40), a novel triterpenoid saponin isolated from the roots of G. uralensis, was shown to exhibit inhibitory activity against the influenza virus A/WSN/33 (H1N1) in Madin-Darby canine kidney (MDCK) cells with an IC_{50} value of 48.0 μM.

Song et al. reported that the conjugates of PTs with chacotriose could inhibit the entry of highly pathogenic H5N1 influenza A virus into MDCK cells in varying degrees. Compound 41, a 3-O-β-chacotriosyl substituted methyl ursolate derivative, showed potent anti-influenza A (H5N1) virus entry activity with IC_{50} at 6.00–8.54 μM. In another work, both the chacotriosyl and the aglycone moiety have been reported to have an important effect on the activity against influenza virus and the anti-influenza activity could be improved when the disubstituted amide was introduced to the C17-COOH position. The introduction of dimethylamine at the C17-COOH provides the compound 42, which showed the most potent anti-influenza activity (IC_{50}: 0.98 μM).
In view of the broad antiviral spectrum of PTs, our group established an anti-influenza virus drug screening model and screened a mini-library of PT-glycoconjugates. Based on a plaque formation inhibition assay, the acetylated galactose–OA conjugate Y3 (43) and the acetylated galactose–UA conjugate Y5 (44), were found to have the best anti-WSN activity (IC_{50}: 5 μM). In addition, 43 exhibits broad anti-influenza spectrum with the IC_{50} ranging from 2.72...
to 7.41 μM (Table 3). More importantly, the lead compound 43 shows no tendency to induce resistance of influenza viruses, suggesting that it may have the potential to overcome antiviral drug resistance.

The exploration of the mechanism of action indicated that 43 could block the attachment of influenza virus particles to the membrane of host cells by binding to sialic acid receptor-binding pocket on the influenza viral HA protein (Fig. 8).

4.2 PT–CD conjugates

Tri- or multivalent ligands show much higher binding affinity to the homotrimeric influenza HA receptor. Recently, our group designed and synthesized a series of multivalent PT-α-(β, γ-) CD conjugates (45–48) to enhance the affinity between PTs and HA and thus improve their potency against influenza virus. The multivalent OA-β-CD conjugate 46 was found to show the most potent antiviral activity against influenza A virus (IC$_{50}$: 1.6 μM), more potent than the monovalent OA-β-CD conjugate 49 by 60-fold (IC$_{50}$ > 100 μM). Further study on its anti-influenza action mechanism showed that the multivalent PT–CD conjugates could also bind to influenza viral HA protein, and thus inhibit the attachment of influenza virus particle to host cells (Fig. 9).

Recently, per-O-methylated CDs and their derivatives have been found to have improved solubility in organic and water solvents. On the basis of previous work, our group further prepared multivalent PT-functionalized per-(2,3-di-O-methyl)-α-, β-, or γ-CD conjugates and evaluated their in vitro anti-influenza activities. Two conjugates 50 and 51 were identified to exhibit the highest anti-influenza virus activity with IC$_{50}$ at micromolar level (4.7 and 6.5 μM, respectively) and SI > 15.

4.3 Other PTs derivatives

Conjugation of PTs with other bioactive compounds, such as L-ascorbic acid and sialic acid, have also been used as a strategy to prepare new biological PTs. Conjugates 52 and 53 were found to have the most potent antiviral activity against influenza virus. The IC$_{50}$ values for them are 8.7 and 8.3 μM, respectively.

Hong et al. reported that BA (4), isolated from Jujube tree (Zizyphus jujube Mill), exhibited antiviral activity against influenza A/PR/8 virus in vitro and in vivo. Two BA derivatives (54 and 55) isolated from Chinese herbal medicine Schefflera heptaphylla were found to have inhibitory activity on H1N1 influenza A virus (IC$_{50}$ values: 32.2 and 58.4 μM, respectively). Tung et al. reported that betulinic aldehyde 56 isolated from Alnus japonica exhibited anti-influenza...
A proposed mechanism for multivalent PT-CD conjugates mediated blocking of influenza virus entry\textsuperscript{122}

Effect against influenza A/Korea/KBNP-0028/2000 virus (IC\textsubscript{50}: 28.4 μM).\textsuperscript{133} Furthermore, it was reported that 28-O-methoxycinnamoyl betulin \textsuperscript{57} showed high activity against H1N1 influenza A virus and low cytotoxicity with a selectivity index of SI > 100.\textsuperscript{134}

5 | PTs AS ANTI-SARS AGENTS

SARS is an infectious respiratory disease caused by the SARS-CoV. Between 2002 and 2003, an outbreak of SARS started in southern China caused a great number of deaths in many countries, which has drawn massive attention worldwide.\textsuperscript{6} Although SARS is now under control and nearly disappeared, it still could come back. To search for effective inhibitors, more than 10,000 agents including existing drugs, natural products, and synthetic compounds were evaluated for their anti-SARS activity. A variety of PTs and their derivatives have been shown to have anti-SARS-CoV activity.

5.1 | Glycyrrhizin and its derivatives

Among PTs, glycyrrhizin (1) and its derivatives were first reported to have the anti-SARS-CoV activity by Cinatl et al.\textsuperscript{110} Inhibitor 1 presented an EC\textsubscript{50} of 0.37 mM against the replication of SARS-CoV with a SI of 67 in Vero-E6 cells. In addition to inhibiting viral replication, 1 was also able to inhibit the adsorption as well as penetration of the virus at the beginning stage of the life cycle. Compound 1 was more effective when treated after the adsorption process than during the adsorption process (EC\textsubscript{50}: 2.91 mM vs. 0.73 mM, respectively). Moreover, when given both during and after the adsorption period, it showed the most potent activity. It has been shown that the change of the glycoside chain at C3-OH and introduction of heterocyclic fragments or amino acids at C20-COOH into 1 obviously affect the antiviral activity of derivatives. In this case, Hoever et al. evaluated the anti-SARS-CoV activity of 15 PT derivatives.\textsuperscript{111} Compound \textsuperscript{58}, the most potent derivative showing tenfold increase of the bioactivity, was produced through the introduction of 2-
acetamido-\(\beta\)-D-glucopyranosylamine into the carbohydrate chain of 1 (Fig. 10). It inhibited SARS-CoV replication with \(EC_{50}\) and \(CC_{50}\) at 40 \(\mu\)M and 3000 \(\mu\)M, respectively. Compound 57 showed similar effect as 58. Compounds 60–64 were effective against SARS-CoV with \(EC_{50}\) at micromolar level. But these derivatives also demonstrated severe cytotoxicity, resulting in decreased selectivity index ranging from 2 to 5. These results showed that the chemical embellishment by the introduction of CONH bonds into 1 was able to enhance its antiviral effectiveness. Hover also found that 2 (GA), the partial hydrolyzate of 1, exhibited high activity as well as toxicity. Considering the mechanism of their anti-SARS-CoV activity, Hover speculated that the entry process of SARS-CoV into cells was blocked by the attachment of N-acetylglycosamine with the carbohydrates of the S-proteins,\(^{111}\) which was demonstrated to be necessary for viral entry into host cells.

Wu et al. found \(\alpha\)-hederin (65), a derivative of 1, showed anti-SARS-CoV activity at concentrations of <100 \(\mu\)M. The minimal concentration of inhibition toward SARS-CoV was 10 \(\mu\)M.\(^{135}\)

5.2 BA and betulonic acid

Wen et al. evaluated 221 compounds, including two PTs, 4 and betulonic acid (66), for their anti-SARS-CoV activity in Vero-E6 cells based on a cell-based cytopathic effect (CPE) assay (Table 4).\(^{136}\) Comparing with 4 whose \(EC_{50}\) value was over 10 \(\mu\)M, the \(EC_{50}\) value of 66 was 0.63 \(\mu\)M, 2.6-fold lower than that of the positive control (valinomycin, \(EC_{50}\) = 1.63 \(\mu\)M). The \(CC_{50}\) values of compounds 4 and 66 were >100 \(\mu\)M. The SI of compound 66 was 180, indicating that it effectively inhibited viral replication without obvious cytotoxicity. The two compounds were further tested through inhibition assay toward 3CL protease. Compound 4 demonstrated valid inhibitory effect on 3CL protease function with an \(IC_{50}\) value of 10 \(\mu\)M, and its \(K_i\) value was 8.2 \(\pm\) 0.7 \(\mu\)M, indicating a competitive inhibition mode of action. However, the \(IC_{50}\) of 66 was >100 \(\mu\)M. Computer docking analysis revealed that 4 was able to occupy the binding pocket of SARS-CoV 3CL protease. Moreover, the binding was enhanced by the formation of a hydrogen bond between the C3-
TABLE 4  PTs with anti-SARS-associated coronavirus activity

| Compound | EC_{50} (\mu M) | CC_{50} (\mu M) | SI |
|----------|-----------------|-----------------|----|
| Ribavirin | >4095           | >4095           | -  |
| 1        | 729             | >24,303         | >33|
|          | 365             | >24,303         | >67|
|          | 2916            | >24,303         | >8.3|
| 2        | >20             | 20 ± 5          | -  |
| 4        | >10             | 150             | <15|
| 56       | 40 ± 13         | >3000           | >75|
| 57       | 35 ± 7          | 1462 ± 50       | 41 |
| 58       | 139 ± 20        | 215 ± 18        | 2  |
| 59       | 8 ± 2           | 44 ± 6          | 6  |
| 60       | 50 ± 10         | 250 ± 19        | 5  |
| 61       | 5 ± 3           | 15 ± 3          | 3  |
| 62       | 16 ± 1          | 66 ± 8          | 4  |
| 63       | 0.63            | 112             | 180|

TABLE 5  Inhibitory effects of 4, 66–71 on SARS-CoV 3CL protease

| Compound | IC_{50} (\mu M) | Inhibition type |
|----------|-----------------|-----------------|
| 4        | 10              | 8.2 ± 0.7       |
| 66       | >100            | -               |
| 67       | 10.3 ± 0.2      | Competitive (4.2 ± 0.6) |
| 68       | 5.5 ± 0.7       | Competitive (3.1 ± 0.0) |
| 69       | 9.9 ± 0.1       | Competitive (4.0 ± 0.1) |
| 70       | 2.6 ± 0.3       | Competitive (0.8 ± 0.2) |
| 71       | 21.7 ± 1.9      | -               |

OH of 4 and the C = O of Thr24 of the 3CL protease. On the contrary, 66 did not form other intermolecular bonds with the pocket besides the hydrophobic interaction. Their anti-SARS activity could be the result of a combination of two different antiviral mechanisms. One is via protease inhibition and the other is via blocking SARS-CoV entry at the post binding step during the fusion of virus particle to host cell membrane, which is also an important and general antiviral mechanism of PTs.

5.3  Quinone-methide triterpenes

Ryu and co-workers isolated four quinone-methide triterpenes (67–70) from Triterygium regelli. Compound 67 was smoothly converted to its derivatives 71 by hydrogenation under palladium-carbon catalyst. The five compounds were tested for SARS-CoV 3CL protease inhibitory activity (Table 5). The IC_{50} values of four separated quinone-methide triterpenes were below or around 10 \mu M, but the synthesized 71 with a phenol moiety showed lower activity (IC_{50} = 21.7 \mu M). These results demonstrated that the presence of a quinone-methide moiety exerted relatively significant effect in inhibition. Moreover, all isolated inhibitors had the same mode of competitive inhibition. The K_{i} value of the most potent compound 70 was determined to be 0.8 \mu M. The hydroxy group of C3 of 70 formed a firm hydrogen bond with the oxygen atom of the carbonyl group of Cys44 and OH of Thr25 in the pocket, whereas 71 only formed the hydrophobic interaction.
PTs and their derivatives show anti-SARS-CoV activity at different steps of the life cycle, which suggested that PTs can block SARS-CoV replication by a complex mechanism. Though most of them are unclear, SARS-CoV 3CL protease can be an attractive target for the development of anti-SARS-CoV drugs.

6 | PTs AGAINST OTHER VIRUSES

6.1 | Anti-HBV activity

HBV, belonging to Hepadnaviridae family, is characterized by its high hepatotropism.\(^{138,139}\) HBV infection is a global health threat. There are about 240 million HBV carriers worldwide who are at risk of developing liver cancer.\(^ {140}\) Several agents have undergone clinical trials to treat HBV infection; however, problems arose in clinical trials have challenged the use of those drugs.\(^ {140,141}\) For example, the nucleotide analogs, such as Lamivudine and Adefovir, and IFN are currently used to treat chronic HBV patients, but the frequent relapse after recovery limited their use.\(^ {142}\) Therefore, novel HBV inhibitors are urgently needed.

Glycyrrhizin (1) has been used for treating HBV for many years. In vitro and in vivo experiments have been conducted to test its mechanism of action.\(^{143,144}\) The study showed that treatment with 1 can inhibit the secretion of hepatitis B surface antigen (HbsAg) in vitro. In addition, Romero et al. reported that 1 has a moderate ability to inhibit the HBV DNA release from cells (IC\(_{50}\): 85 \(\mu\)M).\(^ {145}\) Sato et al. determined the SAR of glycyrrhizin (1), GA (2), and GA 3-O-monoglucuronide (72) against HBV. Of the three compounds, compound 2 showed the most potent inhibition activity on HbsAg secretion. However, in the guinea pig study, GA (2) was not detected in the liver fraction even after administration of an excessive dose of glycyrrhizin (1), and glycyrrhizin (1) was the main compound in the liver fraction after intravenous administration, suggesting that glycyrrhizin (1) would play an important role in the treatment of patients with chronic hepatitis B.\(^ {144}\)

The Tibetan herb Potentilla anserine L. has been widely used in China to treat hepatitis B. Compound 73 (Fig. 11) was isolated from the rhizomes of P. anserine L. and has been found to have inhibitory activity on HbsAg and HbeAg secretion and HBV DNA release in vitro (IC\(_{50}\): 90.96, 47.40, and 30.68 \(\mu\)M, respectively). In vivo anti-HBV study indicated that compound 73 could inhibit HBV DNA replication.\(^ {146}\)

Pulsatilla chinensis, another traditional Chinese herb, showed the efficacy of HBV clearance in HBV patient. So far, about 30 components have been isolated from P. chinensis and tested for their HBV clearance activity. Among them, BA (4) and its derivatives were identified as the active components.\(^{147,148}\) Yao et al. found that BA (4) could inhibit the expression of manganese superoxide dismutase (SOD2) and the subsequent generation of reactive oxygen species (ROS), by which compound 4 could inhibit HBV replication in vitro and in vivo.\(^ {142}\)
6.2 Anti-HSV activity

HSV belongs to the *Herpesviridae* family, which causes serious public health problems. World Health Organization reports that 67% of the world population under the age of 50 have HSV-1. Currently, Acyclovir and its derivatives have been approved by FDA to treat HSV infection. However, the toxic side effects and the emergence of drug-resistant HSV virus strains have limited their use. Therefore, novel HSV inhibitors are needed.

The medicinal herb *Rhus javanica* has been reported to have anti-HSV activity. Kurokawa et al. isolated two major anti-HSV compounds, 66 and moronic acid (74) (Fig. 12), from this herb and evaluated their anti-HSV activity in vitro and in vivo. The effective concentrations for 50% plaque reduction of wild-type HSV type 1 (HSV-1) by 66 and 74 were 5.7 μM and 8.6 μM, respectively. The therapeutic index of 74 (10.3–16.3) was larger than that of 66 (6.2). Susceptibility of Acyclovir phosphonoacetic acid-resistant HSV-1, thymidine kinase-deficient HSV-1, and wild-type HSV type 2 to 74 was similar to that of the wild-type HSV-1, indicating that 74 has a broad antiviral spectrum against HSV.

Ikeda et al. studied the SAR of 15 oleanane-type triterpenoids including glycyrrhizin (1) and its sapogenol against HSV-1. The results showed that glycyrrhetic acid (2) and the sapogenol of glycyrrhizin (1) had much more potent anti-HSV-1 activity than glycyrrhizin (1). In addition, it was found that soyasapogenol A (75) showed less anti-HSV activity than soyasapogenol B (76) by 20-fold, suggesting that hydroxylation at C-21 might weaken antiviral activity against HSV-1. It was also found that kudzusapogenol A (77), abrisapogenol B (78), and abrisapogenol C (79) had no anti-HSV-1 activity, suggesting that the C-29 hydroxyl group could abolish the activity against HSV-1. However, kudzusapogenol B (80) and the methyl esters of 2 (81 and 82) exhibited stronger anti-HSV activity, suggesting that a methyl ester group at C-30 could improve the anti-HSV-1 activity.

Furthermore, Gong et al. determined the synergistic anti-HSV-1 effect of betulin (83) and Acyclovir in a drug combination study. The potent and moderate synergistic anti-HSV-1 effects were found for Acyclovir and betulin (83) when their concentrations were higher than 4.4 μM and 0.9 μM, respectively. The synergistic anti-HSV-2 effects were also found when the concentrations of Acyclovir and betulin were 2.0 μM and 19.0 μM, respectively. The synergistic antiviral effect suggested that the action mechanism of betulin is different from that of Acyclovir. Navid et al. explored the action mechanism and found that the PTs could inhibit the early stage of HSV life cycle.
TABLE 6  Anti-enteroviral activity of UA (12)

| Compound | EC$_{50}$ (µM) | CC$_{50}$ (µM) | SI |
|----------|----------------|---------------|----|
| Ribavirin| $>105 \pm 16$ | $>105 \pm 16$ | -  |
| UA       | $1.09 \pm 0.44$ | 220           | 201|

FIGURE 13  Chemical structures of PTs 84–87 with anti-EV71 activity

TABLE 7  Anti-EV71 activity of 84 against EV71 C3 and C4a

| Compound | EV71 C3 | EV71 C4a |
|----------|---------|---------|
|          | EC$_{50}$ (µM) | CC$_{50}$ (µM) | EC$_{50}$ (µM) | CC$_{50}$ (µM) |
| Ribavirin| –       | >39.96   | –            | >39.96        |
| 84       | 19.79 ± 10 | >39.96   | 33.38 ± 0.61 | >39.96        |

6.3  Anti-EV71 activity

Human enterovirus 71 (EV71) is a single strand RNA virus belonging to *Picornaviridae* family. It possesses a nonenveloped positive-sense ssRNA genome. EV71, the major pathogen of hand, foot, and mouth disease (HFMD), can cause epidemic encephalitis and acute flaccid paralysis (AFP), resulting in cardiopulmonary failure and death in babies under 10 years old. Up to now there is still no effective drug to treat EV71 infection.

Glycyrrhizin (1), as one of the main component isolated from *Glycyrrhiza* spp., has many kinds of antiviral activity. Wang's study first recognized the medicinal effectiveness of 1 against EV71. Compound 1 can inhibit EV71 replication in a dose-dependent manner and the concentrations required for 1 to inhibit EV71 infection were in the millimolar ranges. 1 reduced infectious EV71 production by 34% and 60% at 3 mM and 5 mM, respectively. In addition to the identification of 1 as the antiviral component of *G. uralensis* against EV71, Wang et al. also revealed the distinct mechanisms of 1 blocking EV71 infection by targeting an event(s) after cell entry.

UA (12) is a PT isolated from the aqueous extract of *Ocimum basilicum* (also known as *sweet basil*), an herb commonly used in traditional Chinese medicine. In Chiang’s report, 12 demonstrated the strongest activity against EV71 ($EC_{50} = 1.09$ µM; SI = 201) in a dose-dependent manner. The SI value of greater than 200, strong activity and low cytotoxicity indicated its potential use for treating infection of EV71 (Table 6). Furthermore, the action of 12 against EV71 was from −2 to 24 hr, indicating that its inhibitory effect occurred in the infection and replication process. Therefore, it may have the potential preventive effect as well as treatment effect.

SONG et al. reported that hederasaponin B (84) (Fig. 13) from *Hedera helix* has the anti-EV71 activity. Compound 84 could significantly decrease the formation of visible CPE in Vero cells, demonstrating its effective anti-EV71 C3 and C4a activity without obvious cytotoxicity (Table 7). In addition, western blot assay showed that 84 was able to reduce the expression of viral VP2 protein, thus demonstrating the inhibitory effect of the synthesis of viral capsid protein. By comparison, Ribavirin showed no anti-EV71 C3 and C4a activity. These results indicated that 84 is a promising drug candidate against various subgenotypes of EV71 because of its broad spectrum of antiviral activity.
Zhao et al. evaluated six newly synthesized PTs for their anti-EV71 activity. They analyzed their inhibitory effects on the expression of VP1 protein through western blot analysis and reverse transcription (RT) PCR. Compounds 85, 86, and 87 demonstrated more potent anti-EV71 activity than their parent compounds while no significant cytotoxicity was found.

6.4 | Anti-EBV activity

Epstein–Barr virus (EBV) is one of the major pathogens of infectious mononucleosis in humans. It is generally linked with two malignancies, endemic Burkitt’s lymphoma and nasopharyngeal carcinoma (NPC). The number of EBV-associated diseases is increasing, requiring the development of effective vaccines for protection as well as novel antiviral agents for treatment.

Lin et al. reported that glycyrrhizin (1) exhibited activity against EBV replication in superinfected Raji cells in a dose-dependent manner (IC\(_{50}\) = 0.04 mM, CC\(_{50}\) = 4.8 mM, SI = 120). Time of addition studies showed that the anti-EB effect of 1 was closely associated with an event post virus cell entry rather than the direct inactivation of the virus and the blocking of virus adsorption. The antiviral mechanism appeared to be at the early step of EBV replicative cycle. Different from the mechanism of nucleoside analogs targeting viral DNA polymerase, 1 and its derivatives represent a new type of anti-EBV agents.

Chang and co-workers first reported moronic acid (76), which was isolated from the galls of Brazilian propolis and Rhus chinensis, as an agent against EB virus. Compared with other triterpenes, 76 has a novel anti-EB mechanism. During the immediate-early stage of the lytic cycle of EBV, the transcription of viral lytic genes can be activated by Rta and Zta, two transcription factors expressed by EB virus. It was found that compound 76 can inhibit the functions of Rta by activating a promoter that contains a Rta-response element, thus reducing the expression of Zta and EA-D (an EBV early protein) (EC\(_{50}\) = 3.15 \(\mu\)M, CC\(_{50}\) = 46.67 \(\mu\)M, SI = 14.8). Because the target of compound 76 is Rta, one of the important transcription factors of EBV, this compound can be used as a new lead for the development of anti-EBV drugs.

7 | CONCLUSIONS

PTs are a class of plant metabolites with high structural diversity. They provide important sources of lead compounds in drug research and development. Some PTs and their derivatives have been used to prevent and treat chronic hepatic diseases in many countries, such as China and Japan. In addition, they generally show no or weak toxicity. However, the value of PTs in preventing and treating viral diseases has only partially been exploited. Up to now, only Bevirimat (5), BMS-955176 (6), and GSK-2838232 (7) have undergone phase Ib clinical trial as HIV MIs. Recently, many research groups have investigated PTs as potential therapeutic agents in the treatment of virus infections. Many natural PTs and their semisynthetic derivatives have been reported to have activity against HIV, HCV, influenza, and other viruses. The investigation of the molecular basis of their antiviral activity is also progressing rapidly. However, their precise targets and action mechanism are usually unclear, which limits their further development. In addition, the poor aqueous solubility is another major drawback for various applications, in particular, the development of drugs. Those intensive explorations will lead to the design of new PTs as potent antiviral inhibitors with better antiviral activity profiles and lower IC\(_{50}\) values.

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