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REVIEW

# Progress of Plant Medicine Derived Extracts and Alkaloids on Modulating Viral Infections and Inflammation

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**Abstract:** Viral infectious diseases are serious threats to human health in both developing and developed countries. Although there is the continued development of new drugs from synthetic sources as antiviral agents, medicinal plants continue to provide the basic raw materials for some of the most important antiviral drugs. Alkaloids are a class of pharmacologically active plant compounds that are usually alkaline in nature. In this review, we tried to summarize recent progress in herb-based antiviral research, the advantages of using active plant compounds as antiviral agents, and the inflammatory responses initiated by alkaloids, based on the literature from 2009 to 2019, for the treatment of conditions, including influenza, human immunodeficiency virus, herpes simplex virus, hepatitis, and coxsackievirus infections. Articles are retrieved from PubMed, Google Scholar, and Web of Science using relevant keywords. In particular, the alkaloids from medicinal plants responsible for the molecular mechanisms of anti-inflammatory actions are identified and discussed. This review can provide a theoretical basis and approaches for using various alkaloids as antiviral treatments. More research is needed to develop alkaloidal compounds as antiviral therapeutic agents and potential regulators of the anti-inflammatory response.

**Keywords:** viral infectious diseases, alkaloids, antiviral, anti-inflammatory responses, antiviral therapeutic agents

## Introduction

Viral infectious diseases are a serious threat to human health in both developing and developed countries<sup>1</sup> and are responsible for the death of one million people worldwide each year. Viral diseases cause a substantial health burden with direct and indirect costs, including hospitalization and loss of productivity.<sup>2</sup> The emergence of new diseases, such as the Zika virus and Chikungunya virus, previously unaffected has created significant concerns in healthcare. The pathogenesis of viral infections has provoked various types of complications that target different organs and the immune system and sometimes can even promote tumor progression. Most therapeutic regimens to date have emphasized broad, nonspecific approaches to treat viruses. As specific antiviral therapies become available, better diagnostic approaches to identify specific pathogens will be required.<sup>3</sup>

A considerable number of approved antiviral agents are vaccines, including vaccines against the various serotypes of influenza. However, the efficacy of antiviral vaccines is limited by antigenic drift or viral shift.<sup>4</sup> Recently, synthetic drugs have been used as lifesaving treatments,<sup>5</sup> although they are responsible for

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many harmful effects on the human body. One issue facing synthetic drugs is emerging drug resistance. Despite the development of new drugs from synthetic sources as anti-viral agents, medicinal plants continue to provide the basic raw materials for some of the most important antiviral drugs.<sup>6</sup> Six natural alkaloid derivatives have been approved as antiviral drugs. Among them, tenofovir disoproxil is the orotate salt of a compound first approved as fumarate in 2001.<sup>7</sup> Natural products and natural product structures continue to play a highly important role in the antiviral drug discovery and development process. Among these, herbal essential oils are also continuously under investigation as potential new antiviral agents.

Alkaloids are a class of chemical compounds that are usually alkaline in nature and have at least one nitrogen atom in a heterocyclic ring. Alkaloids possess a wide range of biological activities including antimalarial, antiasthmatic, anticancer, antihypertensive, antispasmodic, antiarrhythmic, analgesic, antibacterial, and antidiabetic effects, as well as having CNS stimulant, muscle relaxant, and vasodilatory properties.<sup>8</sup> According to their chemical structure, alkaloids can be divided into groups, including the piperidine alkaloids, isoquinoline alkaloids, indole alkaloids, terpenoid alkaloids, steroid alkaloids, and quinoline alkaloids. There are numerous examples of bioactive alkaloids that are found both naturally and are available as synthetic products, including quinine, ephedrine, lobeline, theobromine, vincristine, vinblastine, serpentine, reserpine, ergotamine, nicotine, caffeine, vasicine, tubocurarine, curarine, atropine, aconitine, morphine, and piperine. Alkaloids are present in numerous plants. For example, piperidine alkaloids exist in many genera including *Nicotiana*, *Conium*, *Lobelia*, *Pinus*, *Punica*, *Duboisia*, *Sedum*, *Withania*, *Carica*, *Hydrangea*, *Dichroa*, *Cassia*, *Prosopis*, *Genista*, *Ammodendron*, *Lupinus*, *Liparia*, and *Collidium*.<sup>9,10</sup>

In recent years, antiviral treatments using alkaloids have received increasing attention. Interestingly, many researchers have reported that alkaloids can be used to prevent and treat viral diseases. Additionally, alkaloids regulate human immune mechanisms to achieve viral resistance. They do not directly kill viral particles but instead function by promoting humoral immunity, type I IFN production, type I IFN signaling transduction, and other anti-inflammatory mechanisms.<sup>11</sup> Therefore, this review mainly focuses on a summary of recent progress and advantages of herb-based antiviral research and various alkaloids related to anti-HIV, anti-HBV, anti-HCV, anti-IFV, anti-HSV, anti-enterovirus 71, etc. and the anti-

inflammatory responses based on the literature from 2009 to 2019. The present review provides a comprehensive scientific summary of naturally occurring alkaloids that are pharmacologically active against viruses, and related anti-inflammatory effects. The authors hope that this review will provide new possibilities for the anti-virus new drug discovery from these alkaloids.

## Extracts and Alkaloids from Plants Modulating Viral Infections and Inflammation

We performed a literature search using PubMed, Google Scholar, and Web of Science to identify completed and ongoing studies of various classes of alkaloids in viral diseases and publications focused on related anti-inflammatory mechanisms of action (Table 1).

### Extracts and Alkaloids from Plants with Anti-Human Immunodeficiency Virus Type I (HIV-1) Infection Activity Extracts

*Panax ginseng* Meyer (Korean Red Ginseng, KRG) belongs to the family Araliaceae. Korean ginseng has shown therapeutic efficacy toward various diseases, including cancer, diabetes, and atherosclerosis. A recent study has suggested that oral KRG can prolong survival in HIV-1 patients, possibly by slowing the decrease in CD4<sup>+</sup> T-cell counts.<sup>4</sup> Two herbal decoctions (*Betula alba* and *Sutherlandia frutescens*) have interesting immunostimulatory and antimicrobial properties and hence could be useful in the management of HIV/AIDS and associated opportunistic infections.<sup>12</sup> Chloroform and methanol extracts from the roots of *Aerva lanata* (Amaranthaceae family) showed inhibition of recombinant HIV reverse transcriptase (RT) (91% and 89%, respectively) at 1 mg/mL.<sup>13</sup> The findings of another study showed that co-administration of *Moringa oleifera* Lam. (Moringaceae family) leaf powder at traditionally used doses had no clinically significant effect on the steady-state pharmacokinetics of nevirapine in HIV-infected adults.<sup>14</sup> In another study, *Moringa oleifera* Lam. leaf extracts showed potent and selective inhibition of the early stages in HIV-1 infectivity and this study partly explained the benefits and improvement in the quality of life claimed by people living with HIV/AIDS who use this medicinal plant as a supplement.<sup>15</sup> Aqueous and 50% ethanolic extracts prepared from the stem bark of *Acacia catechu* (Mimoso-

**Table 1** Medicinal Plants Used as Antiviral Agents

No.	Plant Name	Plant Family	Part Used	Plant Extract Nature	Mechanism Involved (Model)	Ref.
<b>Anti-Human immunodeficiency virus type I (HIV-I):</b>						
1	<i>Panax ginseng</i> Meyer (Korean Red Ginseng, KRG)	Araliaceae	Roots	Capsules	Prolong survival in HIV-I patients, possibly by slowing the decrease in CD4 <sup>+</sup> T-cell count.	[4]
2	<i>Betula alba</i>	Betulaceae	Leaves	Water	Have interesting immunostimulatory and antimicrobial properties and hence could be useful in the management of HIV/AIDS and associated opportunistic infections	[12]
3	<i>Sutherlandia frutescens</i>	Fabaceae	Leaves	Water	Have interesting immunostimulatory and antimicrobial properties and hence could be useful in the management of HIV/AIDS and associated opportunistic infections	[12]
4	<i>Aerva lanata</i>	Amaranthaceae	Roots	Chloroform and methanol	Shows highest inhibition of recombinant HIV RT (91% and 89% respectively) at 1 mg/mL concentration.	[13]
5	<i>Moringa oleifera</i> Lam.	Moringaceae	Leaves	Methanol extract Ethyl ether, methanol and water extract	Co-administration of leaf powder at the traditional dose did not significantly alter the steady-state PK of nevirapine in HIV-infected active against the HIV-I lentiviral vector and inhibited the early events of the viral replication cycle on HeLa cells in a concentration dependent manner with IC <sub>50</sub> of 7.59 µg/mL, 7.72 µg /mL and 7.17 µg /mL, respectively.	[14,15]
7	<i>Acacia catechu</i>	Mimoso	Stem bark	Aqueous and 50% ethanolic extracts	A potential anti-HIV-I activity of A. catechu mediated by the inhibition of the functions of the viral protein and Tat.	[16]
8	<i>Phyllanthus emblica</i>	Euphorbiaceae	Fruit	n-hexane (HX), carbon tetrachloride (CT), chloroform (CF), and aqueous fractions	Anti-HIV activity via inhibition of HIV reverse transcriptase activity	[17]
9	<i>Sutherlandia frutescens</i> (L.) R. Br.	Fabaceae	Leaves	Ground to a uniform powder	Does not causes significant adverse effects in HIV seropositive adults	[18]
10	<i>Pinus yunnanensis</i> Franch	Pinaceae	Pine cones	95% ethanol extract	These data suggest that the pine cone extract from <i>Pinus yunnanensis</i> has potent inhibitory activities against HIV-I <sub>IIIB</sub> , HIV-I <sub>RF</sub> RT inhibitor-resistant strains HIV-I <sub>A17</sub> and HIV-I <sub>AO18</sub> , and HIV-2 <sub>ROD</sub> , and its anti-HIV mechanisms include inhibition of HIV entry and inhibition of reverse transcriptase activity.	[19]
12	<i>Alepidea amatymbica</i>	Umbelliferae	Whole plants	Aqueous extract	Showed significant selective anti-HIV activity	[20]
13	<i>Plectranthus barbatus</i> Andr	Labiatae	Leaves	Ethanol extract	Extract inhibited HIV-I PR and the IC <sub>50</sub> was 62.0 µg/mL. and poor inhibition of HIV-I RT	[21]
14	<i>Sanguisorba officinalis</i>	Rosaceae	Stem	Water extract	Has anti-HIV-I properties	[22]

(Continued)

**Table I** (Continued).

No.	Plant Name	Plant Family	Part Used	Plant Extract Nature	Mechanism Involved (Model)	Ref.
15	<i>Schisandra rubriflora</i>	Magnoliaceae	Fruit	70% aqueous acetone extract	Anti-HIV-I activity that showed inhibitory activity on HIV-I <sub>IIIB</sub> induced syncytium formation	[23]
16	<i>Schisandra chinensis</i> (Turcz.) Baill.	Magnoliaceae	Fruit	Petroleum ether and EtOAc extract	Effects on HIV-I RT and viral replication.	[24]
17	<i>Ephedra sinica</i> Stapf	Ephedraceae	Stem	Water extract	Can induce the replication of latent HIV-I infected U1 cells in vitro, through NF-κB activation	[25]
<b>Anti-hepatitis C virus (HCV):</b>						
17	<i>Acacia nilotica</i>	Fabaceae	Leaves	Methanol extract	To substantiate strong antiviral activity against HCV.	[36]
18	<i>Ruta angustifolia</i>	Rutaceae	Leaves	Dichloromethane extract	Had potent anti-HCV activity with IC <sub>50</sub> of 1.6 ± 0.3 µg/mL	[37]
<b>Anti-Influenza virus:</b>						
19	Elderberry ( <i>Sambucus nigra</i> L.)	Caprifoliaceae	Berries	Concentrated juice	Strong defense against IFV infection, and had a beneficial effect by the stimulating immune response and preventing viral infection.	[42]
20	Elderberry ( <i>Sambucus nigra</i> L.)	Caprifoliaceae	Berries	96% ethanol purified fractions obtained from 50% ethanol, and water extracts	Showed potent dose-dependent complement fixating activity and macrophage stimulating activity, might be responsible for the claimed effect of berry extracts on cold and influenza,	[43,44]
21	Elderberry ( <i>Sambucus nigra</i> L.)	Caprifoliaceae	Flowers	96% EtOH extracts	Posessed high complement fixating activity and macrophage stimulating activity.	[45]
<b>Anti-Herpes simplex virus type (HSV):</b>						
22	<i>Mallotus peltatus</i> (Geist.) Mur. Arg.	Euphorbiaceae	Leaves	Methanolic crude extract	The crude methanolic extract possessed weak anti-HSV activity	[57]
23	Red marine alga <i>Osmundaria obtusiloba</i> (C. Agardh) R. E. Norris	Rhodomelaceae		Acetone extract	Demonstrated that both fractions had potent inhibitory activity against HSV-I (herpes simplex virus type I) and present low toxicity for cell cultures	[58]
24	<i>Phyllanthus urinaria</i> Linnea	Euphorbiaceae	Whole plant	Acetone–water	Inhibited HSV-2 infection but not HSV-1 infection. inhibitor against HSV-2 and could potentially be investigated for combinatorial drug treatment with nucleoside analogues such as ACV in therapeutic management of HSV-2 infection.	[59]
25	<i>Camellia sinensis</i>	Theaceae	Whole plant	Aqueous extract	Showed the most anti-Herpes property at inhibition of HSV-I multiplication at one and two hour that decreased at three hour.	[60]
26	<i>Echium amoenum</i> L	Boraginaceae	Whole plant	Aqueous extract	Had lowest anti-Herpes effect that at two hour was similar antiviral property of <i>Camellia sinensis</i> at three hour.	[60]

(Continued)

**Table I** (Continued).

No.	Plant Name	Plant Family	Part Used	Plant Extract Nature	Mechanism Involved (Model)	Ref.
27	<i>Melissa officinalis</i> Linn.	Labiatae	Leaves	Aqueous extract	Exhibits low toxicity and affects attachment and penetration of acyclovir-sensitive and acyclovir-resistant HSVs in vitro	[61,62]
28	<i>Phyllanthus urinaria</i>	Phyllanthus	Whole plant	Aqueous extracts	Demonstrated the strongest antiviral activities against HSV-1 and HSV-2, with a SI value of more than 33.6	[63]
29	<i>Phyllanthus watsonii</i>	Phyllanthus	Whole plant	Aqueous extracts	The first study that reported the antiviral activity against herpes simplex virus type-I (HSV-1) and HSV-2 in Vero cells	[63]
30	<i>Peganum harmala</i>	Zygophyllaceae	Seed	Methanol extract	Showed a virucidal action for HSV-2 activity, both during the entry of viruses and the release of the newly formed virions.	[64]
<b>Anti-Coxsackievirus B<sub>3</sub> (CVB3):</b>						
31	<i>Rheum palmatum</i>	Polygonaceae	Roots and rhizome	Ethanol extract	Its antiviral activities against CVB <sub>3</sub> in vitro and in vivo	[78]
<b>Anti-Measles virus:</b>						
32	<i>Cajanus cajan</i> (L)	Leguminosae	Whole plant	Aqueous and ethanol extracts	Yielded higher activity against measles virus.	[80]

family) exhibited a dose-dependent inhibition of HIV-1<sub>NL4.3</sub> at concentrations ranging from 0.1 to 10 µg/mL mediated by the inhibition of the functions of the viral protein and Tat.<sup>16</sup> *Phyllanthus emblica* (Euphorbiaceae family) fruit extracts have been found to exert their anti-HIV activity via inhibition of HIV RT activity.<sup>17</sup> The dried leaves of *Sutherlandia frutescens* (L.) R. Br. (Fabaceae family) did not change the HIV viral load, and the CD4 T-lymphocyte counts were similar in the two arms of a clinical study at 24 weeks.<sup>18</sup> A pine cone extract from *Pinus yunnanensis* Franch (Pinaceae family) had potent inhibitory activities against HIV-1<sub>IIIB</sub>, HIV-1<sub>RF</sub>, RT inhibitor-resistant strains HIV-1<sub>A17</sub> and HIV-1<sub>AO18</sub>, and HIV-2<sub>ROD</sub>, and the anti-HIV mechanisms included inhibition of HIV entry and inhibition of reverse transcriptase activity.<sup>19</sup> The aqueous extract from the whole plants of *Alepidea amatymbica* (Umbelliferae family) showed significant selective anti-HIV activity and was found to be non-toxic as judged by observing the cell density and morphology.<sup>20</sup> A *Plectranthus barbatus* Andr (Labiatae family) leaf extract inhibited HIV-1 PR with an IC<sub>50</sub> value of 62.0 µg/mL and showed poor inhibition of HIV-1 RT.<sup>21</sup> A water extract from the stem of *Sanguisorba officinalis* (SOE, Rosaceae family) has anti-HIV-1 properties. SOE acted directly on HIV-1, instead of the cellular

receptors or coreceptors, and exhibited potency against replication-competent HIV-1 strains resistant to specific drugs targeting protease and RT activities.<sup>22</sup> Two members of the Magnoliaceae family, *Schisandra rubriflora* and *Schisandra chinensis* (Turcz.) Baill., have anti-HIV-1 activity. A 70% aqueous acetone extract of *Schisandra rubriflora* fruits showed inhibitory activity on HIV-1<sub>IIIB</sub>-induced syncytium formation.<sup>23</sup> The petroleum ether and ethyl acetate extracts of the fruits of *Schisandra chinensis* (Turcz.) Baill. had effects against HIV-1 RT and viral replication.<sup>24</sup> The water extract of the stem of *Ephedra sinica* Stapf (Ephedraceae family) could induce the replication of latent HIV-1 infected-U1 cells in vitro through NF-κB activation<sup>25</sup> (Table 1).

### Essential Oils

*Leoheo domatiophorus Chaowasku*, D.T. Ngo and H.T. Le. *L. domatiophoroides* a medium-sized to large trees shrub species, are widely distributed in rainforests of central Vietnam. Le et al have reported that the essential oil resulted in being completely ineffective against tested viruses HIV-1 with EC<sub>50</sub> values over 100 µg/mL.<sup>26</sup> *Paramignya trimera* (Oliv.) Guillaum is a woody species and is widely distributed in the South of Vietnam. *Limnecitrus littoralis* Swingle is a knotty shrub species, naturally distributed in Indonesia

and Vietnam. The parts of *L. littoralis* have been used to treat fevers and colds in Vietnamese traditional medicine. The oils isolated from *P. trimera* and *L. littoralis* were completely ineffective against HIV-1 viruses.<sup>27</sup> *Atalantia sessiliflora* is one of the species of the genus *Atalantia* found in Vietnam. The oil was completely ineffective against tested HIV-1 viruses.<sup>28</sup>

### A Quinolizidine-Type Alkaloid

*Sophora alopecuroides* L. is a medicinal plant widely distributed in Western and Central Asia, especially in China. *Sophora alopecuroides* L. has been used for decades to treat fever, bacterial infections, heart disease, rheumatism, and gastrointestinal diseases. Aloperine (**1**), a quinolizidine-type alkaloid, was first isolated from the seeds and leaves of *Sophora alopecuroides* L. To evaluate the anti-HIV activity of aloperine, HIV-1 NL4-3 NanoLuc-sec virus infection of MT4 cells was performed in the presence of various concentrations of aloperine. Aloperine showed anti-HIV activity with an EC<sub>50</sub> value of  $1.75 \pm 0.59 \mu\text{M}$ . BMS-806-resistant, Env-mediated cell-cell fusion, such as that mediated by YU2-T198P and 8x, may be inhibited by aloperine.<sup>29</sup>

### An Isoquinoline-Type Alkaloid

Emetine (**2**) is an alkaloid that possesses a monoterpenoid-tetrahydroisoquinoline skeleton. Emetine occurs in three plant families, including Alangiaceae, Icacinaceae, and Rubiaceae, and the major source of emetine is *Psychotria ipecacuanha* Stokes (Rubiaceae). Emetine is an anti-HIV agent that blocks HIV-1 infection in primary and established cells at noncytotoxic levels and its effects are mediated by reverse transcription inhibition. Emetine also blocked HIV-1 infection of a variant strain harboring an NRTI-resistance mutation.<sup>30</sup> The isoquinoline alkaloids laurolitsine (norboldine, **3**) isolated from the family Lauraceae belong to the aporphinic group, which contain only one benzyl tetrahydroisoquinoline group. Laurolitsine showed a significant inhibitory effect on HIV-1 integrase with an IC<sub>50</sub> value of 16.3 mM.<sup>31,32</sup>

### Quinoline-Type Alkaloids

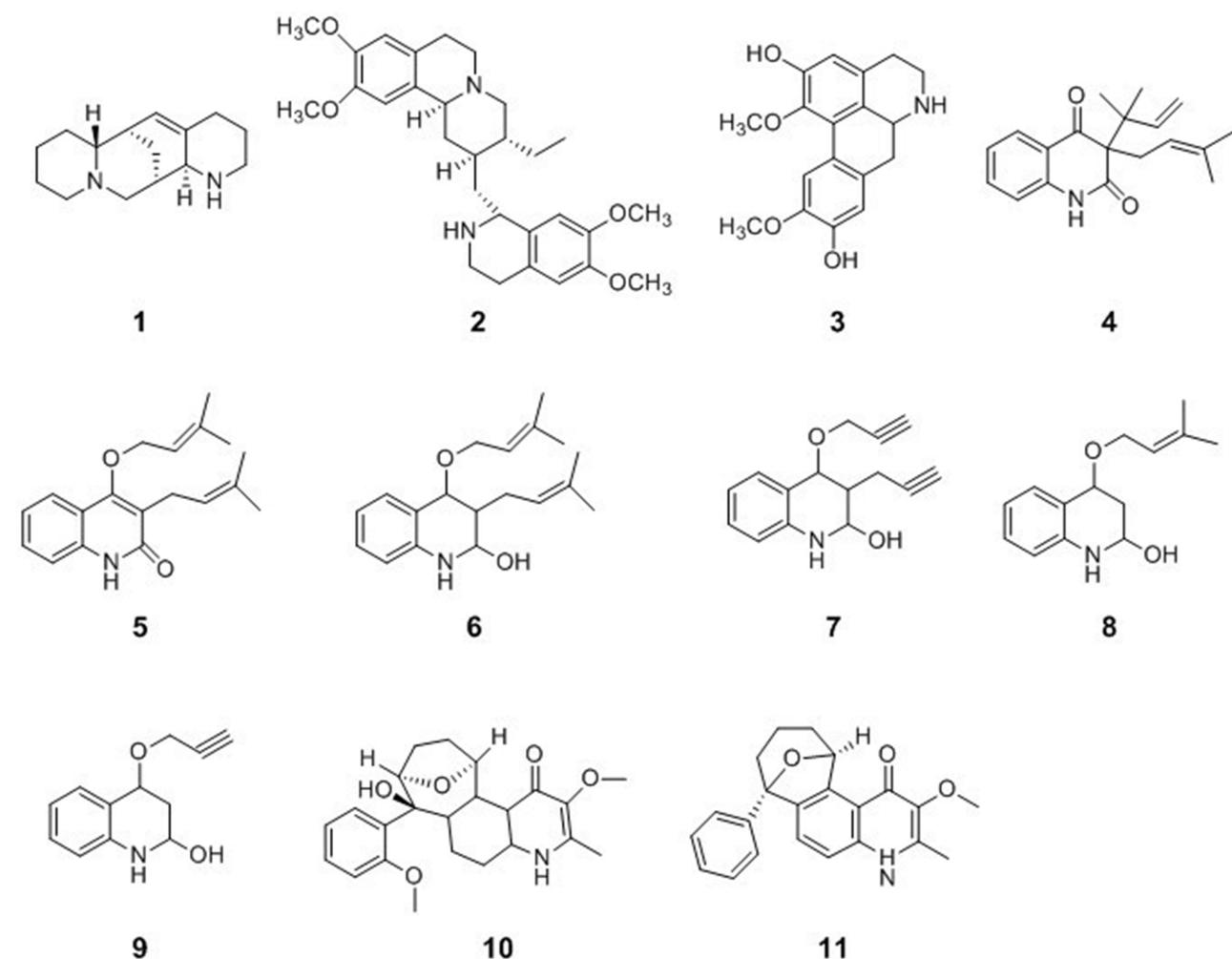
Buchapine (**4**), a quinoline alkaloid, was isolated from a methanolic extract of the epigeal parts of *Haplophyllum bucharicum*, *Haplophyllum tuberculatum*, and *Euodia roxburghiana*. 3-(3-Methyl-2-butenyl)-4-[(3-methyl-2-butenyl)oxy]-2(1H)-quinolinone (**5**) was also isolated from *H. tuberculatum* and *E. roxburghiana*. Compounds **4** and **5** exhibited anti-HIV activities against HIV-1 in cultured human lymphoblastoid CEM-SS cells with IC<sub>50</sub> values of 29.0  $\mu\text{M}$

and 26.9  $\mu\text{M}$ , respectively. Buchapine derivatives of quinoline 2,4-diol were synthesized and tested for their anti-HIV potential in the human CD4+ T cell line CEM-GFP. Compounds **6–9** have displayed good anti-HIV activities with IC<sub>50</sub> values of 8.76, 11.60, 8.95, and 19.34  $\mu\text{M}$ , respectively.<sup>33</sup> The methanol extract of *Melochia odorata* yielded four quinoline alkaloids, including waltherione A (**10**) and waltherione A (**11**). Compounds **10** and **11** showed significant antiviral activity in an in vitro anti-HIV cytoprotection assay at concentrations of 56.2 and 0.83  $\mu\text{M}$ , respectively, and inhibited HIV P24 formation by more than 50% at concentrations of 1.7 and 0.95  $\mu\text{M}$ , respectively<sup>34</sup> (Figure 1).

## Extracts and Alkaloids from Plants with Anti-HBV Infection Activity

### Matrine-Type Alkaloids

*Sophora flavescens* is a species of plant in the genus *Sophora*. Ku shen (the root) or kushenin (a flavonoid compound) are typical traditional Chinese medicines that are derived from this plant. *Sophora flavescens* is commonly used for the treatment of viral hepatitis, cancer, viral myocarditis, gastrointestinal hemorrhage, and skin diseases (such as colpitis, psoriasis, and eczema). Five matrine-type alkaloids, flavesine G (**12**), flavesine J (**13**), alopecurine B (**14**), oxymatrine (**15**), and sophoridine (**16**), were isolated from the roots of *Sophora flavescens*. Compounds **12–16** were evaluated for their anti-HBV activities in HepG2.2.15 cells. Compounds **12–16** significantly inhibited HBsAg secretion by 37.2%, 44.3%, 46.0%, 38.3%, and 40.2%, respectively, at noncytotoxic concentrations of 0.2 or 0.4 mM, which suggested that these alkaloids had comparable potencies to matrine (34.7% at a concentration of 1.0 mM), and were more active than the positive control lamivudine (31.5% at a concentration of 1.0 mM).<sup>35</sup> Five matrine-type alkaloid dimers, flavesine A (**17**), flavesine B (**18**), flavesine D (**19**), and flavesine E (**20**), were isolated from the roots of *Sophora flavescens*. Compounds **17–20** were evaluated for their anti-HBV activities in HepG2.2.15 cells using real-time PCR. The results revealed that compounds **17–20** exhibited inhibitory effects on the expression of HBV DNA in HepG2.2.15 cells with IC<sub>50</sub> values of  $44.85 \pm 7.30$ ,  $86.60 \pm 4.30$ ,  $74.28 \pm 0.31$ , and  $70.62 \pm 0.93 \mu\text{M}$ , respectively, while the IC<sub>50</sub> value of the positive control PFA (foscarnet) was  $105.53 \pm 8.57 \mu\text{M}$ .<sup>36</sup> Three matrine-based alkaloids, sophaline B (**21**), sophaline C (**22**), and sophaline D (**23**), were isolated from the



**Figure 1** Chemical structures of natural plant alkaloids with anti-HIV properties.

seeds of *Sophora alopecuroides*. Compound **21** possesses a previously unknown 6/5/6/6 ring system. Compounds **21–23** were tested for their antiviral activities against HBV in HepG2.2.15 cells. The results of the assays showed that compounds **21–23** significantly inhibited HBsAg secretion by more than 50% at noncytotoxic concentrations of 0.2 or 0.4 mM.<sup>37</sup>

#### Steroidal-Type Alkaloids

*Solanum erianthum* D. Don, a medicinally important plant of Solanaceae, contains steroidal alkaloids. The steroidal alkaloid glycoside solamargine (**24**) was isolated from the methanolic extract of the leaves of *Solanum erianthum* D. Don. Compound **24** demonstrated strong inhibition of the DNA replication of HBV with an IC<sub>50</sub> value of 2.17 µM, and also showed potent activity against HBsAg with an IC<sub>50</sub> value of 1.57 µM. Compound **24** is a promising lead molecule

in the search for drugs with multiple mechanisms for the treatment of HBV<sup>38</sup> (Figure 2).

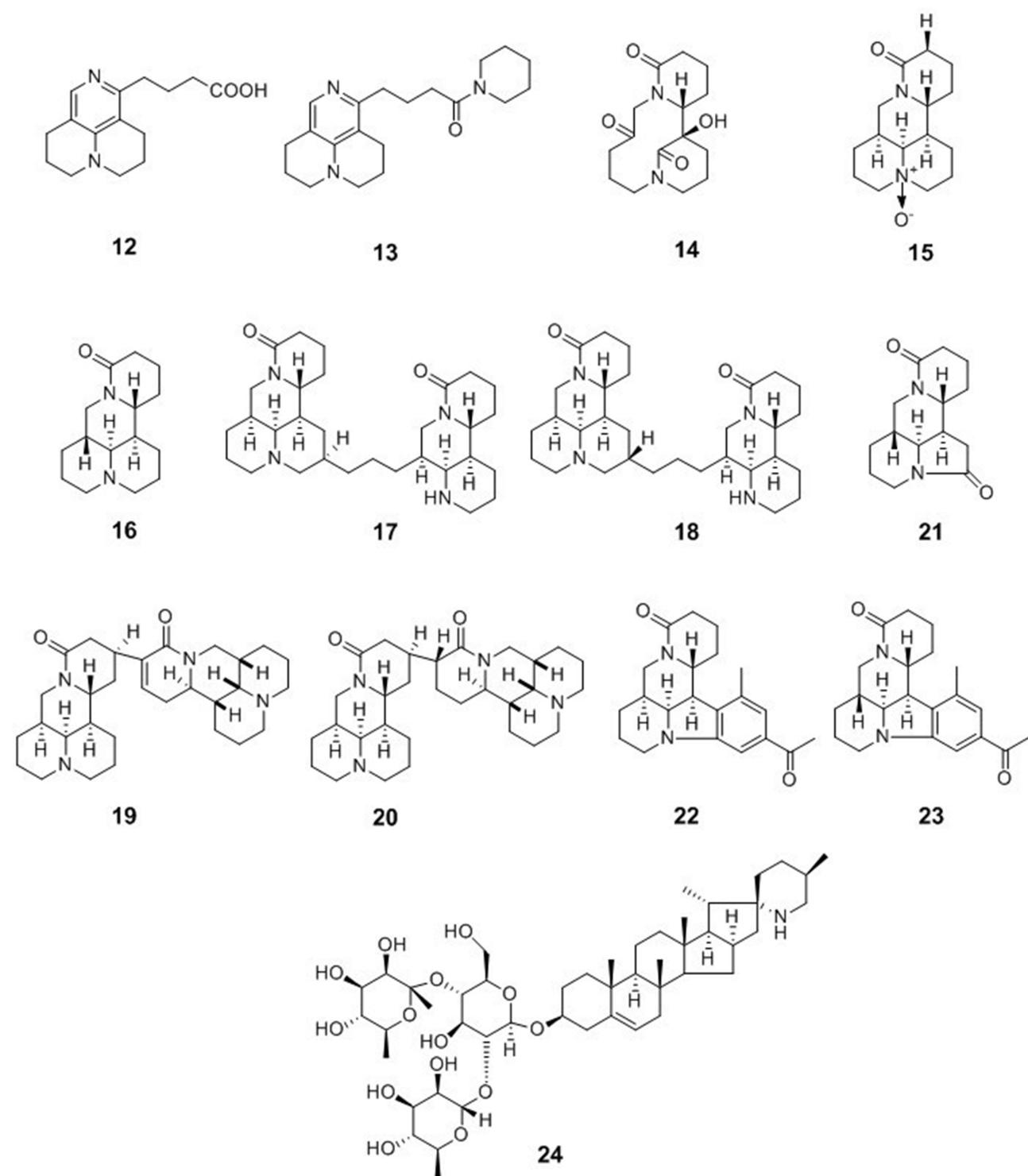
#### Extracts and Alkaloids from Plants with Anti-Hepatitis C Virus (HCV) Infection Activity

##### Extracts

*Acacia nilotica* belongs to the family Fabaceae. A methanolic extract from the leaves of *Acacia nilotica* had strong antiviral activity against hepatitis C virus (HCV).<sup>39</sup> A dichloromethane extract of *Ruta angustifolia* leaves had a potent anti-HCV activity with an IC<sub>50</sub> value of 1.6 ± 0.3 µg/mL<sup>37</sup> (Table 1).

##### Quinoline-Type Alkaloids

*Ruta graveolens* L., belonging to the Rutaceae family, is a medicinal plant widely used in the Mediterranean region to treat pain, dermatitis, rheumatism, and other



**Figure 2** Chemical structures of natural plant alkaloids with anti-HBV properties.

inflammatory diseases. Pseudane IX (**25**), arborinine (**26**), and kokusaginine (**27**) were isolated from the leaves of *Ruta angustifolia*. Pseudane IX showed strong anti-HCV activity with an IC<sub>50</sub> value of 1.4 ± 0.2 μM without apparent cytotoxicity. The anti-HCV activity of pseudane

IX was stronger than that of ribavirin (2.8 ± 0.4 μM), which has been widely used for the treatment of HCV infections. Mode-of-action analyses revealed that pseudane IX inhibited HCV at the post-entry step and decreased the levels of HCV RNA replication and viral

protein synthesis. Compounds **26** and **27** also possessed moderate anti-HCV activity with IC<sub>50</sub> values of 6.4 ± 0.7 and 6.4 ± 1.6 μM, respectively.<sup>40</sup>

### Quinolizidine-Type Alkaloids

Myrioneuron alkaloids are a family of nitrogen-containing polycyclic compounds produced by plants of the genus Myrioneuron R. Br. (Rubiaceae). Two pairs of enantiomers, cluster A (**28**) and cluster B (**29**), as well as the cluster A derivative (±)-13α-methoxymyrrifabral A (**30**) were isolated from the aerial parts of *Myrioneuron faberi*. Cluster A (**28**) and cluster B (**29**) possess a cyclohexane-fused octahydroquinolizine skeleton. Compounds **28–30** inhibited replication of HCV with IC<sub>50</sub> values of 4.7, 2.2, and 0.9 μM, respectively, and exhibited less cytotoxicity against liver cells than the positive control telaprevir (VX-950).<sup>41</sup> Aloperine (**1**), a quinolizidine alkaloid with an unusual endocyclic ring system, was extracted from *Sophora alopecuroides*. Aloperine has been identified as a potent HCV inhibitor with an EC<sub>50</sub> value of 4.23 ± 0.99 μM. 12N-4'-Methylpiperazine-1'-sulfonyl aloperine (**31**), based on aloperine as the lead compound, was synthesized and evaluated for its anti-HCV activity. Compound **31** exhibited moderate potency with EC<sub>50</sub> values in the micromolar range against both wild-type and direct-acting anti-viral agent (DAA)-resistant variants, and synergistically inhibited HCV replication in conjunction with approved DAs. Furthermore, compound **31** also had a good oral pharmacokinetic and safety profile.<sup>42</sup>

### Isoquinoline-Type Alkaloids

Berberine (BBR, **32**) is an isoquinoline alkaloid that has been isolated from several plants belonging to the *Berberis* genus and is a traditional component of Chinese and Ayurvedic medicine. BBR is a potent HCV entry inhibitor that specifically impedes HCVcc attachment and entry/fusion steps without inactivating the free virus particles or affecting the expression of host cell entry factors and post-entry viral replication. BBR also effectively inhibited infection by viral pseudoparticles expressing HCV E1/E2 glycoproteins, and molecular docking analysis pointed at a potential interaction with HCV E2. In addition, BBR suppressed HCVcc infection of primary human hepatocytes.<sup>43</sup>

### Matrine-Type Alkaloids

IMB-DM122 (**33**) was designed and semi-synthesized using matrine as the lead compound. Compound **33** was found to be an effective and safe inhibitor of Hsc70 mRNA/protein expression in human hepatocytes. Compound **33** inhibited

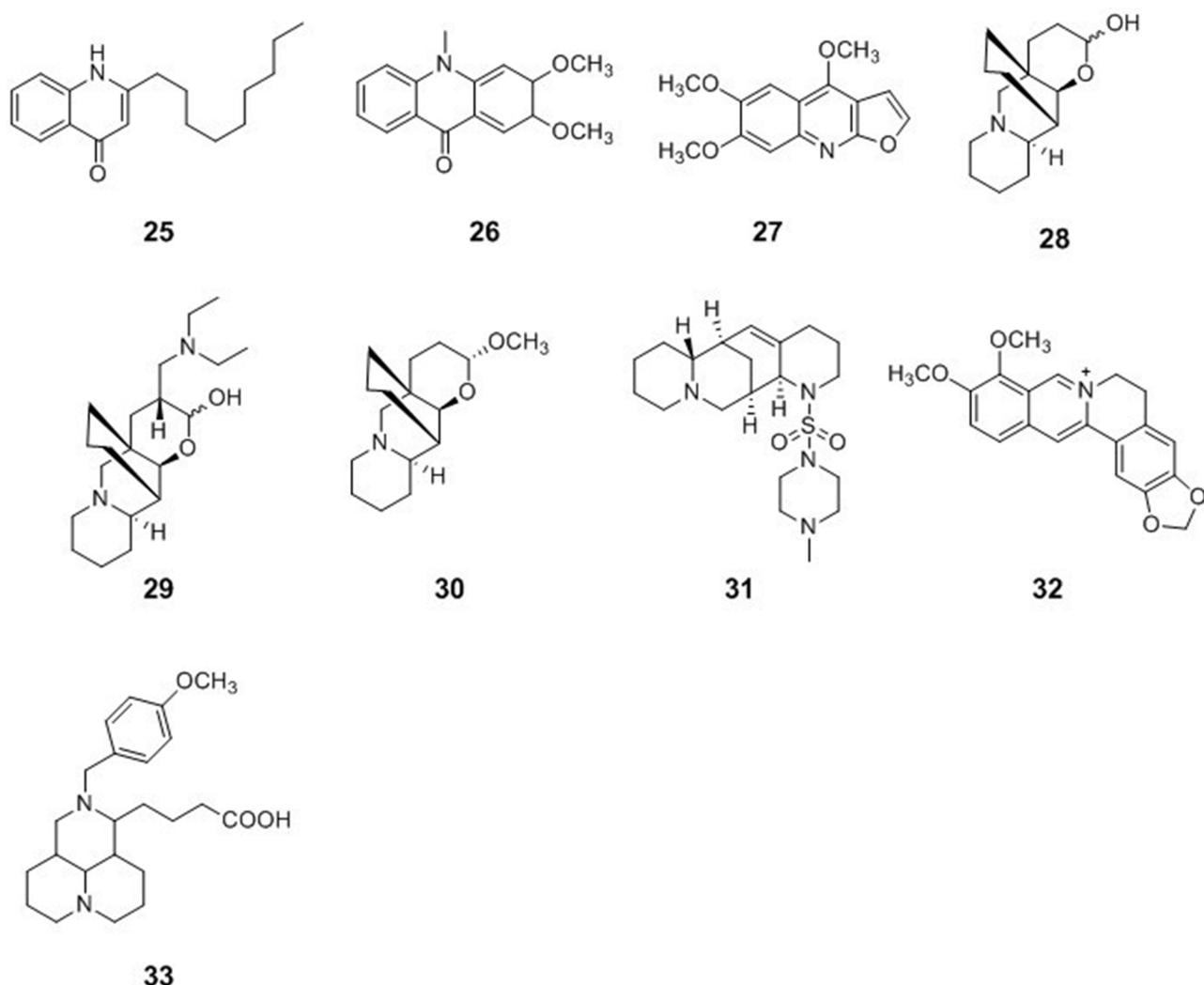
HCV replication through the destabilization of Hsc70 mRNA, and the half-life of host Hsc70 mRNA was reduced by 78% after treatment with **33**. Compound **33** appeared to be highly efficient at inhibiting Hsc70-related HCV replication. In addition, compound **33** showed a good safety profile in vitro as well as in vivo with no indication of harmful effects on liver and kidney functions<sup>44</sup> (Figure 3).

## Extracts and Alkaloids from Plants with Anti-Human Influenza a Virus (IFV) Infection Activity Extracts

Elderberry (*Sambucus nigra* L.) belongs to the family Caprifoliaceae and has traditionally been used for treating influenza and colds. The concentrated juice of elderberry stimulated the immune response and prevented viral infection in human influenza A virus (IFV)-infected mice.<sup>45</sup> The berries of *Sambucus nigra* L. are traditionally used to treat respiratory illnesses, such as colds and influenza. The fractions obtained from 50% ethanol and water extracts showed potent dose-dependent complement fixating activity and macrophage stimulating activity. Studies have also indicated that elderberry's effectiveness against infection may be attributed to immune stimulation.<sup>46,47</sup> The flowers of *Sambucus nigra* L. (elderflowers) are traditionally used for their anti-inflammatory properties. The 96% EtOH extracts from elderflowers possessed high complement fixating activity and macrophage stimulating activity<sup>48</sup> (Table 1).

### Isoquinoline-Type Alkaloids

BBR (**32**), a natural isoquinoline alkaloid, has been evaluated for its antiviral effect against influenza H1N1 in vivo and in vitro. The results showed that BBR strongly suppressed viral replication in A549 cells and in mouse lungs. BBR also relieved pulmonary inflammation and reduced necrosis, inflammatory cell infiltration, and pulmonary edema induced by a viral infection in mice when compared with vehicle-treated mice. BBR suppressed the viral infection-induced up-regulation of components of the TLR7 signaling pathway, such as TLR7, MyD88, and NF-κB (p65), at both the mRNA and protein levels. Furthermore, BBR significantly inhibited the viral infection-induced increases in Th1/Th2 and Th17/Treg ratios, as well as the production of inflammatory cytokines.<sup>49</sup> BBR exhibited antiviral effects on the influenza virus both in vitro and in vivo. The possible therapeutic mechanism of BBR on influenza-induced viral pneumonia might be through inhibition of the virus infection, as well as



**Figure 3** Chemical structures of natural plant alkaloids with anti-hepatitis C virus properties.

improvements in the pathogenic changes by repressing the release of inflammatory substances.<sup>50</sup>

*Papaver rhoes* is a species of flowering plant in the poppy family. Chelanthifoline (34), isolated from the ethyl acetate fraction of Korean *Papaver rhoes* bee pollen, displayed noncompetitive inhibition of H3N2 neuraminidase. Furthermore, compound 34 reduced the severity of virally induced cytopathic effects.<sup>51</sup> Trolline (35) is a representative alkaloid from *Trollius chinensis*. Compound 35 provided an anti-H1N1 viral effect by partially down-regulating the TLR3 and 7 pathways and up-regulating the TLR4 pathway.<sup>52</sup>

#### Indole-Type Alkaloids

*Isatis indigotica* is an important medicinal plant in China. The dried leaves and roots of *Isatis indigotica* are widely used in traditional Chinese medicine for

curing diseases caused by bacteria and viruses, such as influenza and viral pneumonia. Isatibisindosulfonic acid B (36) and isatindosulfonic acid B (37), two indole alkaloid sulfonic acids, were isolated from an aqueous extract of the *Isatis indigotica* root. Compounds 36 and 37 showed antiviral activities against the H3N2 influenza virus with IC<sub>50</sub> values of 33.3 and 33.3 μM, respectively, and the coxsackievirus B3.<sup>53</sup> Three glycosidic bisindole alkaloids, isatindigo-bisindoloside B (38), isatindigobisindoloside E (39), and isatindigobisindoloside F (40), were isolated from an aqueous extract of the *Isatis indigotica* root. Compounds 38–40 showed antiviral activities against both the H3N2 influenza virus and coxsackievirus B3.<sup>54</sup> Five indole alkaloids, oxoglyantrypine (41), nor-quinadoline A (42), deoxynortryptoquivaline (43), deoxytryptoquivaline (44), and tryptoquivaline (45),

were isolated from a culture of the mangrove-derived fungus *Cladosporium* sp. PJX-41. Compounds **41–45** exhibited significant activity against influenza virus A (H1N1), with IC<sub>50</sub> values of 85, 82, 87, 85, and 89 μM, respectively.<sup>55</sup>

### A Pyrrole-Type Alkaloid

Epigoitrin (**46**) is the main alkaloid compound isolated from the wood root of *Isatis indigotica*. Epigoitrin exerts its anti-influenza activity by blocking the virus attachment.<sup>56</sup> Epigoitrin has been shown to reduce the susceptibility to influenza virus via mitochondrial antiviral signaling.<sup>57</sup>

### An Amphetamine-Type Alkaloid

*Ephedra* herbs were used extensively for food and medicine by the Native Americans of the Southwest, especially in dry desert areas. Ephedrine (**47**) alkaid-free *Ephedra* herb extracts have anti-influenza virus activity as shown by the inhibition of MDCK cells infected with the H1N1 influenza virus.<sup>25</sup>

### A Sesquiterpenoid-Type Alkaloid

*Dendrobium nobile* is a medicinal plant from Guizhou province, China. Dendrobine (**48**), a major component of *Dendrobium nobile*, possessed antiviral activity against influenza A viruses, including A/FM-1/1/47 (H1N1), A/Puerto Rico/8/34 H274Y (H1N1), and A/Aichi/2/68 (H3N2) with IC<sub>50</sub> values of 3.39 ± 0.32, 2.16 ± 0.91, and 5.32 ± 1.68 μM, respectively. Compound **48** inhibited early steps in the viral replication cycle and could bind to the highly conserved region of the viral nucleoprotein, subsequently restraining nuclear export of the viral nucleoprotein and its oligomerization<sup>58</sup> (Figure 4).

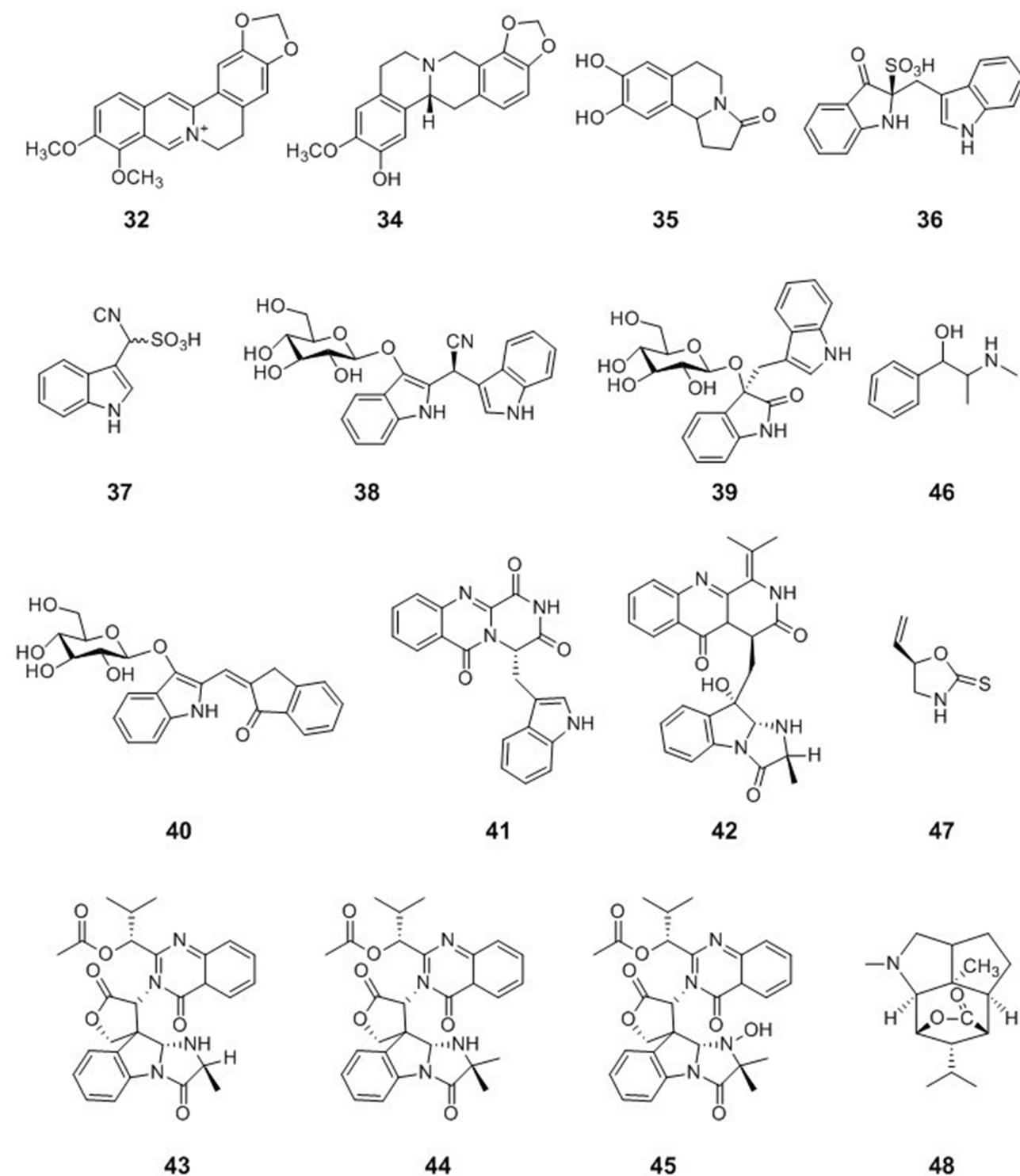
## Extracts and Alkaloids from Plants with Anti-Respiratory Syncytial Virus Infection Activity

Four diterpenoid alkaloids, ajacisine C (**49**), ajacisine D (**50**), ajacisine E (**51**), and isodelectine (**52**), were isolated from *Delphinium ajacis*. Compounds **49–52** were evaluated for their in vitro antiviral activities against the respiratory syncytial virus, and compounds **49–52** exhibited moderate to weak effects with IC<sub>50</sub> values of 75.2 ± 1.1, 35.1 ± 0.6, 10.1 ± 0.3, and 50.2 ± 0.5 μM, respectively<sup>59</sup> (Figure 5).

## Extracts and Alkaloids from Plants with Anti-Herpes Simplex Virus (HSV) Infection Activity

### Extracts

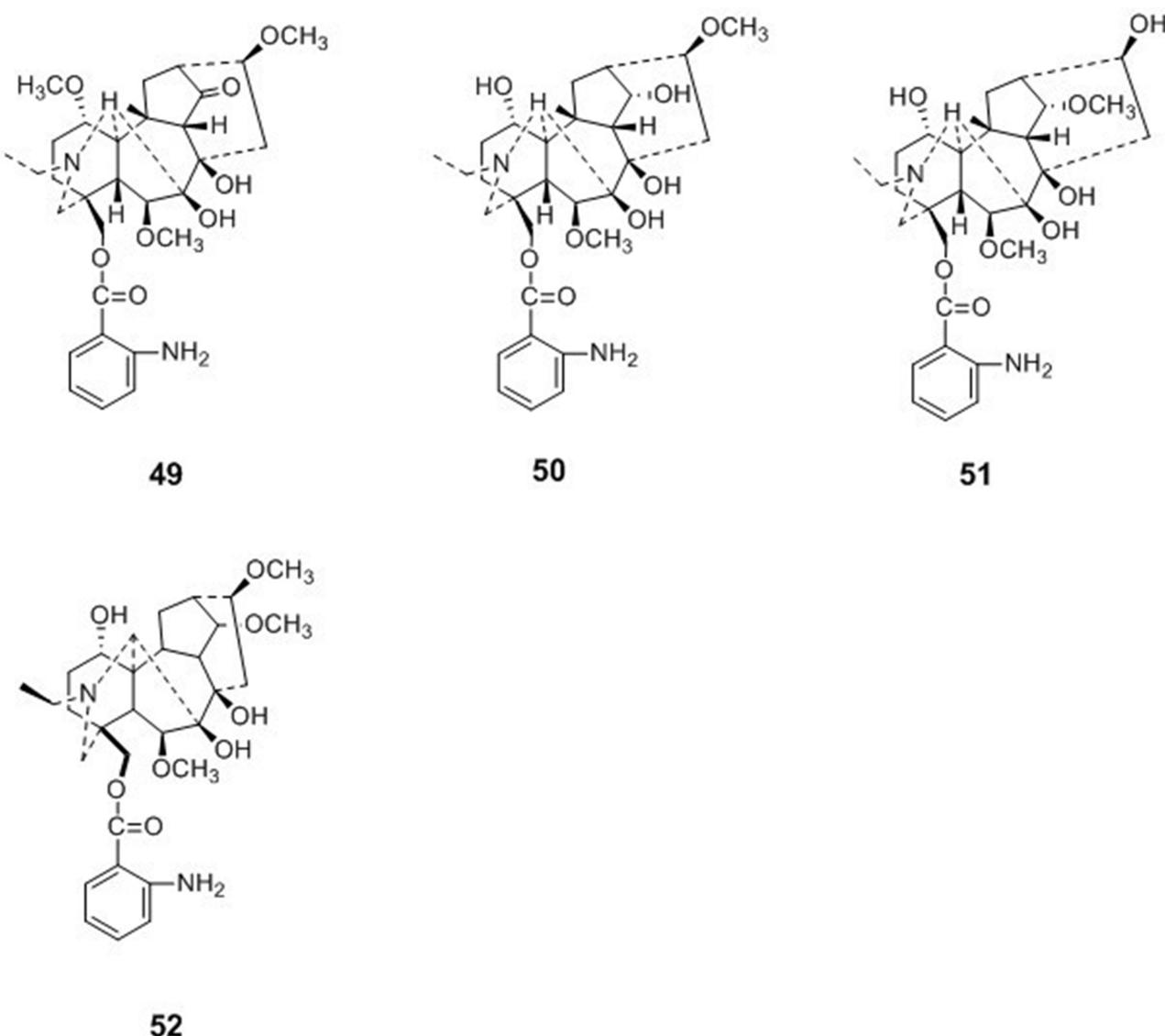
*Mallotus peltatus* (Geist.) Mur. Arg belongs to the family Euphorbiaceae. A methanolic crude extract of *Mallotus peltatus* leaves possessed weak anti-herpes simplex virus (HSV) activity. Conversely, an active fraction A exhibited potent anti-HSV activity against both HSV-1 (EC<sub>50</sub> = 7.8 μg/mL) and HSV-2 (EC<sub>50</sub> = 8.2 μg/mL), probably by inhibiting the early stage of multiplication.<sup>60</sup> The red marine alga *Osmundaria obtusiloba* (C. Agardh) R. E. Norris treated with acetone had potent antiviral activity against HSV-1 and HSV-2 and showed low toxicity toward cell cultures. Although acyclovir has better activity than the algal extract, inhibitors that impact the different steps of viral infection are desirable because they may allow more efficient treatment and prevent the emergence of resistant strains.<sup>61</sup> *Phyllanthus urinaria* linnea (Euphorbiaceae family) is a traditional medicinal plant used to treat various diseases. An acetone extract of the whole plant of *P. urinaria* inhibited HSV-2 infection, but not HSV-1 infection. As an entry inhibitor against HSV-2, this extract could potentially be investigated for combinatorial drug treatment with nucleoside analogs, such as ACV, for the therapeutic management of HSV-2 infections.<sup>62</sup> A *Camellia sinesis* (Theaceae family) aqueous extract of the whole plant was tested for antiviral activity against HSV. The results showed that HSV-1 multiplication was inhibited at 1 and 2 h after treatment and was decreased at 3 h. An aqueous extract of the whole plant of *E. amoenum*, which belongs to the family Boraginaceae, had a low antiherpes effect at 2 h after treatment, which was similar to the antiviral properties of *C. sinesis* at 3 h. *C. sinesis* and *E. amoenum* extracts showed the best antiherpes effect when used 1 h after virus inoculation.<sup>63</sup> An aqueous extract of *Melissa officinalis* Linn (Labiatae family) was examined for its antiviral activity against acyclovir-sensitive HSV-1 and clinical isolates of acyclovir-resistant strains in vitro. The *Melissa* extract interacted directly with free viral particles of two acyclovir-resistant HSV strains with low IC<sub>50</sub> values and high selectivity indices (SI). The *Melissa* extract inhibited HSV-1 attachment to host cells in a dose-dependent manner for acyclovir-sensitive and acyclovir-resistant strains.<sup>64,65</sup> The whole plant of two *Phyllanthus* family members, *Phyllanthus urinaria* and *Phyllanthus watsonii*, demonstrated strong



**Figure 4** Chemical structures of natural plant alkaloids with anti-influenza virus properties.

antiviral activity against HSV-1 and HSV-2 with an SI >33.6. Time-of-addition studies suggested that the extract may act against both the early infection and replication stages. Protein expression studies indicated that *P. urinaria* demonstrated potent inhibitory activity against HSV.<sup>66</sup>

*Peganum harmala* (Zygophyllaceae family) was investigated for its HSV-2 activity and organic extracts of the different plant organs were evaluated for their cytotoxicity toward Vero cells by the MTT test and anti-HSV-2 activity by a plaque reduction assay. Only the methanol seed



**Figure 5** Chemical structures of natural plant alkaloids with anti-respiratory syncytial virus properties.

extract was active with an  $IC_{50}$  value of 13.2  $\mu\text{g}/\text{mL}$  and SI of 161. Additionally, a study of the antiviral mode of action revealed that this extract exerted a virucidal action during both the viral entry and the release of the newly formed virions; however, no cell protection was observed<sup>67</sup> (Table 1).

#### Essential Oils

Researchers have reported that essential oils isolated from *Leioeo domatiophorus* Chaowasku, D.T. Ngo, H.T. Le. *L. domatiophorus*, *Paramignya trimera* (Oliv.) Guillaum and *Limnocitrus littoralis* Swingle were completely ineffective against HSV viruses.<sup>26,27</sup> Another research explored *Mentha suaveolens* essential oil effectiveness

against HSV-1 replication in an in vitro model of infection. They found *Mentha suaveolens* essential oil could reduce HSV-1 replication with  $IC_{50}$  of 0.0051 mg/mL and 0.0014 mg/mL.<sup>68</sup>

#### Indole-Type Alkaloids

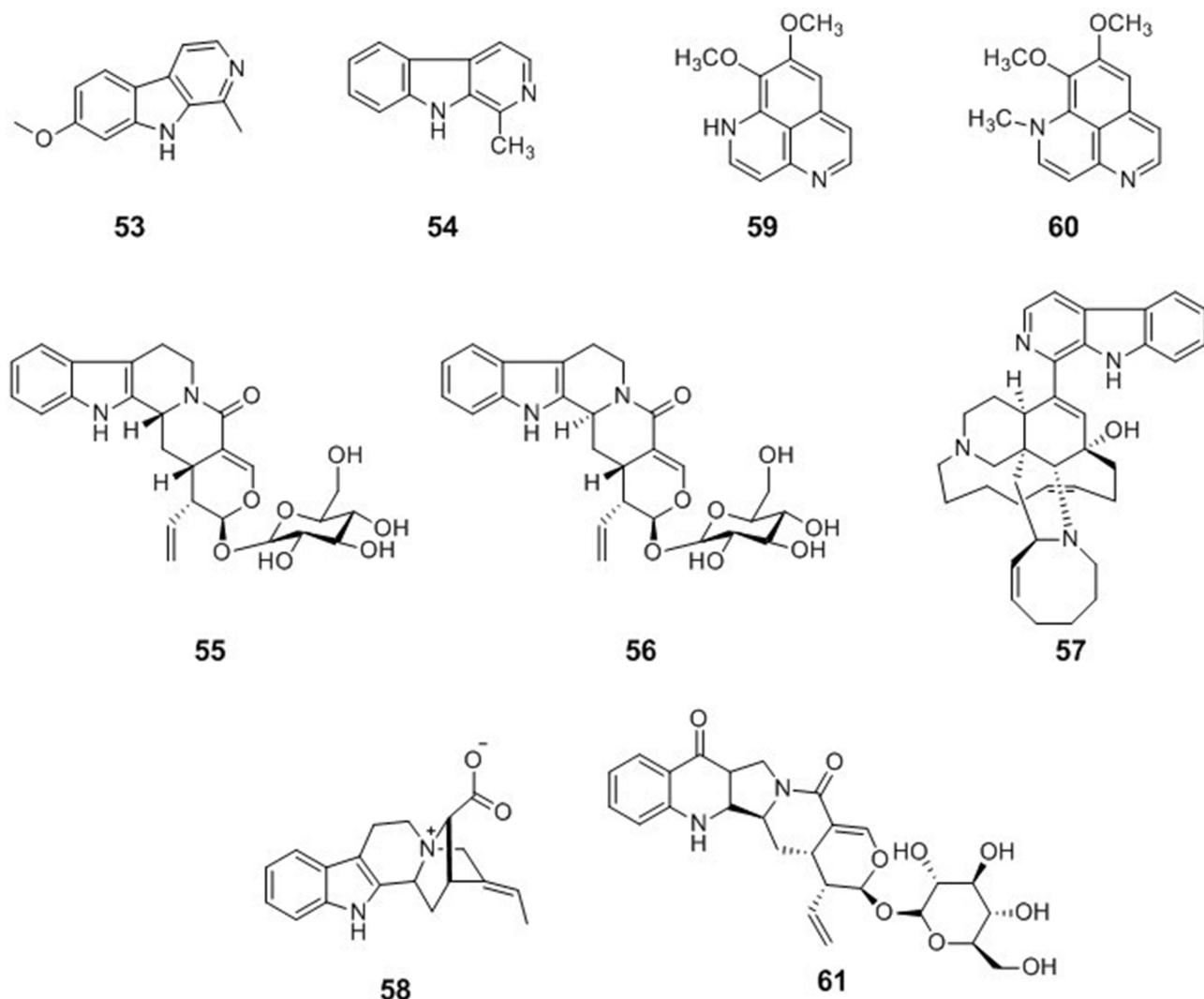
Harmine (**53**) was isolated from *Peganum harmala*, *Banisteriopsis caapi*, and *Passiflora incarnata*. Compound **53** exhibited activity against HSV-2 with an  $IC_{50}$  value of 0.1  $\mu\text{g}/\text{mL}$ .<sup>69</sup> The combination of harmine with acyclovir showed a combination index of 0.5, which indicated that these two compounds have a synergic effect. This suggests that harmine may be used with acyclovir to improve the treatment of genital herpes in immunocompromised

patients.<sup>67</sup> Harman (**54**) was isolated from *Simira eleiezeriana* and *Simira glaziovii* and was evaluated against HSV-1 and HSV-2. Harman showed good results with an EC<sub>50</sub> value of 4.90 µM and a SI of 11.8 for HSV-1, and an EC<sub>50</sub> value of 71.8 µM and SI of 24.7 for HSV-2.<sup>70</sup> Vincosamide (**55**) and strictosamide (**56**) belong to a class of indole alkaloids and were isolated from the root bark of *Nauclea latifolia* Smith. Compounds **55** and **56** inhibited both acyclovir-sensitive and acyclovir-resistant HSV-2 strains.<sup>71</sup> Manzamine A (**57**) was isolated from the sponges *Pachypellina sp.* and *Haliclona sp.* and had an anti-HSV-2 activity with a minimal effective concentration of 0.05 µg/mL.<sup>72</sup> 17-nor-Excelsinidine (**58**), an akuammigine-type alkaloid, was identified from *A. scholaris*. Compound **58** was tested against HSV in an HSV-transfected Vero cell line, and against adenovirus in an adenovirus-transfected HepG-2 cell line, and showed higher

activity than acyclovir, with EC<sub>50</sub> values of 6.97 µg/mL against HSV and 3.32 µg/mL against adenovirus.<sup>73</sup>

### Quinolone-Type Alkaloids

Aaptamine (**59**) was isolated from the marine sponge *Aaptos spitos* collected in the waters of Malaysia. Compound **59** showed potential anti-HSV-1 activity with 71.4 ± 0.4% protection from infection at 25 µg/mL with an EC<sub>50</sub> value of 7.0 ± 0.1 µg/mL, along with low cytotoxicity.<sup>74</sup> 4-Methylaaptamine (**60**) was isolated from the marine sponge *Aaptos sp.* (collected in Abrolhos, Bahia, Brazil). Compound **60** had an anti-HSV activity with an EC<sub>50</sub> value of 2.4 µM, which is more potent than acyclovir.<sup>75</sup> Pumiloside (**61**) was isolated from the root bark of *Nauclea latifolia* Smith. Compound **61** inhibited both acyclovir-sensitive and acyclovir-resistant HSV-2 strains<sup>71</sup> (Figure 6).



**Figure 6** Chemical structures of natural plant alkaloids with anti-herpes simplex virus properties.

### An Isoquinoline-Type Alkaloid

BBR (32) and the plants that contain this compound, including *Coptidis rhizome* and Ching-Wei-San, have all shown anti-HSV effects. BBR may interfere with the viral replication cycle sometime after virus penetration, and no later than the viral DNA synthesis step, and the activity was not affected by the preparation processes.<sup>75</sup>

### Extracts and Alkaloids from Plants with Anti-Dengue Virus Infection Activity

Hirsutine (62), an indole alkaloid of *Uncaria rhynchophylla*, has been identified as a potent anti-dengue (DENV) compound exhibiting high efficacy and low cytotoxicity. Hirsutine showed antiviral activity against all DENV serotypes. Time-of-drug-addition and time-of-drug-elimination assays indicated that hirsutine inhibited the viral particle assembly, budding, or release step but not the viral translation and replication steps in the DENV lifecycle. A subgenomic replicon system was used to confirm that hirsutine does not restrict viral genome RNA replication. Hirsutine is a DENV inhibitor and a potential candidate for treating dengue fever.<sup>76</sup>

The natural alkaloid anisomycin (63) was isolated from *Streptomyces griseolus*. At noncytotoxic concentrations, anisomycin strongly inhibited the replication of reference strains and clinical isolates of all DENV serotypes and Asian and African strains of ZIKV in Vero cells. Compound 63 is a potent and selective inhibitor of DENV and ZIKV in-vitro that impairs a post-entry step of viral replication, and low-dose anisomycin treatment provided some minimal benefit in a mouse model<sup>77</sup> (Figure 7).

### Extracts and Alkaloids from Plants with Anti-Tobacco Mosaic Virus and Cucumber Mosaic Virus Infection Activity

Two C19-diterpenoid alkaloids, hypaconitine (64) and mesaconitine (65), have been isolated from the ethanol extract of the root of *Aconitum carmichaelii* Debx. In an in-vitro anti-viral activity test, compounds 64 and 65 had inactivation efficacy values of 82.4 and 85.6, respectively, against TMV at 500 µg/mL. Compound 65 had an inactivation activity of 52.1% against CMV at 500 µg/mL, which was almost equal to that of the commercial drug ningnanmycin.<sup>78</sup>

Phenanthroindolizidine alkaloids are a group of pentacyclic natural products isolated mainly from *Cynanchum*, *Pergularia*, and *Tylophora* species. Hypoestestain 1 (66) is a phenanthroindolizidine alkaloid that has exhibited

cytotoxic activity, but its antiviral activity has not been investigated. A series of 13a-substituted hypoestestain analogs were designed to target TMV RNA. Compounds 67–72 exhibited good to excellent antiviral activities against TMV both in vitro and in vivo and had higher activity at 500 and 100 µg/mL than commercial ningnanmycin<sup>79</sup> (Figure 7).

### Extracts and Alkaloids from Plants with Anti-Enterovirus 71 Infection Activity

#### Matrine-Type Alkaloids

Sophoridine (73) is one of the most abundant alkaloids in *Sophora flavescens Aiton* (Leguminosae). Compound 73 inhibited EV71 infection in Vero cells. Compound 73 was highly effective against EV71 when Vero cells were pre-treated with Sophoridine for 2 h. Sophoridine was highly effective at inhibiting EV71 attachment when Sophoridine concentrations were over 250 µg/mL.<sup>80</sup>

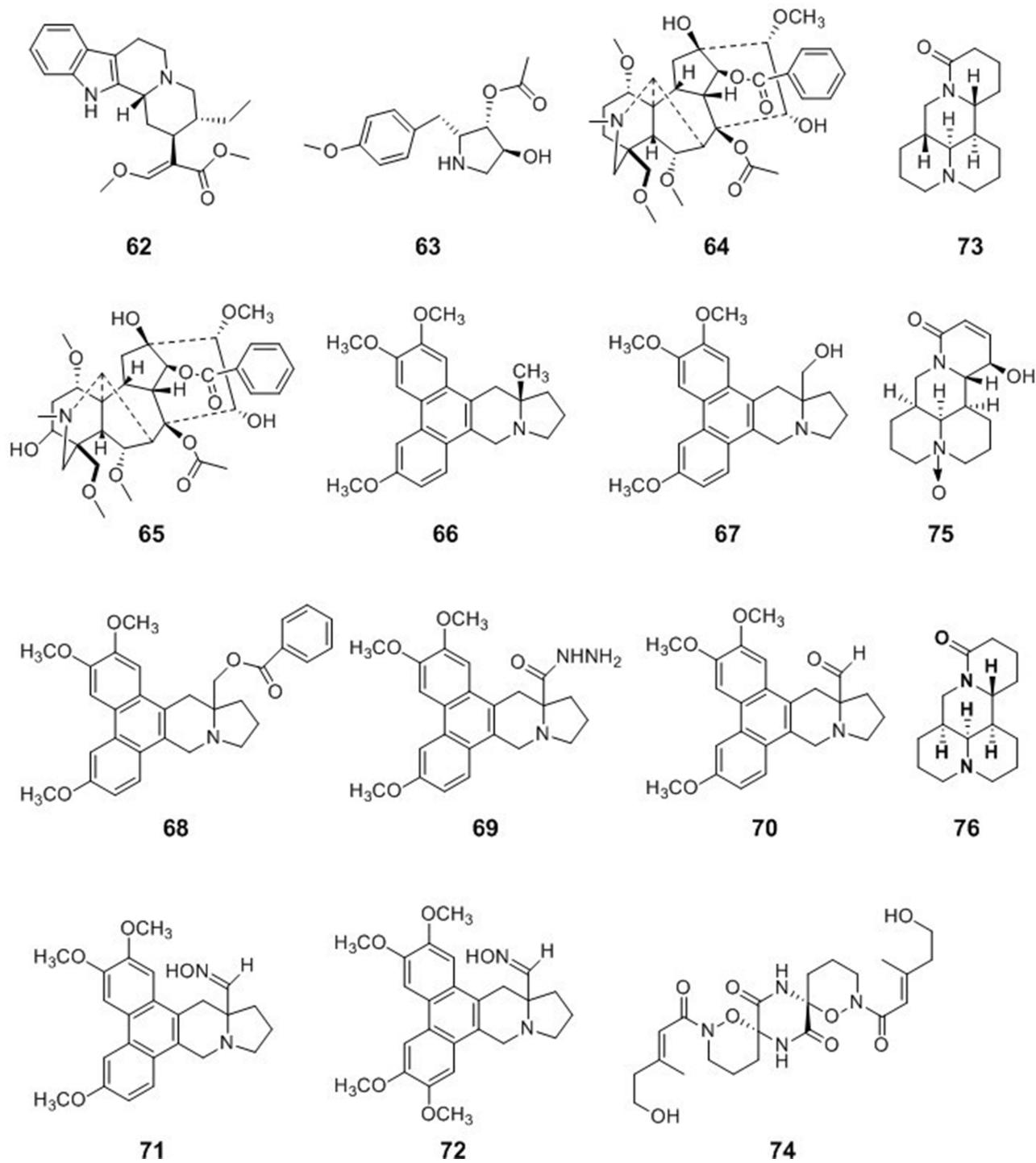
#### Piperazinedione-Type Alkaloids

The alkaloid dimer (+)-pestaloxazine A (74), with an unprecedented symmetric spiro-[oxazinane-piperazinedione] skeleton consisting of 22 carbons and 12 heteroatoms, was isolated from a *Pestalotiopsis* sp. fungus derived from a soft coral. Compound 68 exhibited potent antiviral activity against EV71 with an IC<sub>50</sub> value of 14.2 ± 1.3 µM, which was stronger than that of the positive control ribavirin<sup>81</sup> (Figure 7).

### Extracts and Alkaloids from Plants with Anti-Coxsackievirus B<sub>3</sub> (CVB<sub>3</sub>) Infection Activity

#### Extracts

The antiviral effect of an ethanol extract of the roots and rhizomes of *Rheum palmatum* (Polygonaceae family) against coxsackievirus B<sub>3</sub> (CVB<sub>3</sub>) was evaluated in tissue culture cells and a mouse model. The ethanol extract from *R. palmatum* showed significant inhibitory activity against CVB<sub>3</sub>-infected HEP-2 cells when added after infection. The serum of mice still contained the pharmaceutical compound 24 h after intraperitoneal injection, and the extract exhibited an antiviral effect on CVB<sub>3</sub>-infected cells. The ethanol extract-treated mice showed alleviated clinical signs, a better survival rate, and a higher maximum tolerated dose along with decreased viral titers compared with the virus control group. These results indicated that the ethanol extract from *R. palmatum* had anti-CVB<sub>3</sub> activity in vitro and in vivo<sup>82</sup> (Table 1).



**Figure 7** Chemical structures of natural plant alkaloids with other antiviral properties.

### Indole-Type Alkaloids

Isatibisindosulfonic acid B (37) and isatindosulfonic acid B (38) showed antiviral activities against coxsackievirus B3 [50]. Isatindigobisindoloside B (39), isatindigobisindoloside E (40), and isatindigobisindoloside F (41) also showed antiviral activities against coxsackievirus B3 [51].

### Matrine-Type Alkaloids

The matrine-type alkaloid (-)-12 $\beta$ -hydroxyoxysophocarpine (75) was isolated from the rhizomes of *Sophora tonkinensis*. Alkaloid 75 exhibited antiviral activity against coxsackievirus B3 with an IC<sub>50</sub> value of 26.62  $\mu\text{M}$ <sup>83</sup> (Figure 7).

## Extracts and Alkaloids from Plants with Anti-Measles Virus Infection Activity

*Cajanus cajan* (Leguminosae family), a tropical shrub, is a source of food and traditional medicines, and aqueous and ethanol extracts of *Cajanus cajan* have been evaluated for activity against the measles virus. An antivirus assay showed that a hot-water extract of *Cajanus cajan* had high activity against the measles virus<sup>84</sup> (Figure 7).

## Extracts and Alkaloids from Plants with Anti-Porcine Reproductive Respiratory Syndrome Virus and Porcine Circovirus Type 2 Infection Activity

Matrine (76) is an alkaloid extracted from *Sophora flavescens* Ait. Matrine exhibited antiviral activity against PRRSV/PCV2 co-infection in PAM cells in vitro. The underlying antiviral mechanism of matrine may be mediated through its ability to partly regulate the TLR3,4/NF-κB/TNF-α pathway<sup>85</sup> (Figure 7).

## Extracts and Alkaloids from Plants with Anti-Chikungunya Virus Activity

BBR (32) ( $EC_{50} = 1.8 \mu M$ ) is a plant-derived isoquinoline alkaloid that inhibited CHIKV replication in a dose-dependent manner and had broad antiviral activity against two other alphaviruses, Semliki Forest virus and Sindbis virus.<sup>86</sup>

## Extracts and Alkaloids from Plants with Anti-Inflammatory Effects

Many viral infections, such as influenza virus infections, are characterized by an excessive inflammatory response, and the viral load does not correlate with the worsening of symptoms. Much research on infectious diseases has focused on removing the pathogens using antimicrobial drugs. Immunological complications, such as a cytokine storm can occur, and thus antiviral treatment alone is not enough and should be combined with appropriate anti-inflammatory agents.

Inflammation is a defense system that removes deleterious stimuli or microbial infections. When the inflammatory responses are initiated, damaged tissue is rapidly repaired by eliciting the appropriate signals.<sup>87</sup> Inflammation has relevance to numerous diseases, including viral diseases, rheumatoid arthritis, chronic bronchitis, asthma, and cancer.<sup>88,89</sup> Many members of the TLR family

are involved in controlling the inflammatory response. After TLR activation, they are dimerized or collaborate with other receptors at the cell surface.<sup>90</sup> The myeloid differentiation primary response 88 (MyD88) gene is the most generally used TLR adaptor. The MyD88-dependent pathway initiates the formation of a cytoplasmic Toll-interleukin-1 receptor (TIR) domain. MyD88 is recruited through TIR domain interaction, promoting the recruitment of IL-1 receptor-associated kinase 4 (IRAK-4) (the death domain of IRAK-4 interacts with the death domain of MyD88) and the phosphorylation of IRAK-1. These enzymes induce the activation of the inhibitory κB (IkB) kinase complex. Phosphorylated IkB undergoes proteasomal degradation, which in turn activates NF-κB. The released NF-κB translocates to the nucleus and binds DNA, regulating the expression of a wide range of genes encoding inflammatory cytokines, such as TNFα and interleukin-6 (IL-6)<sup>91</sup> (Figure 9). Many natural alkaloids have been shown to regulate the NF-κB signaling pathway. Inflammation alters the expression of several cellular genes and a cellular signaling network, including MAPK and JAK-STAT signaling pathways, occurs during inflammation.

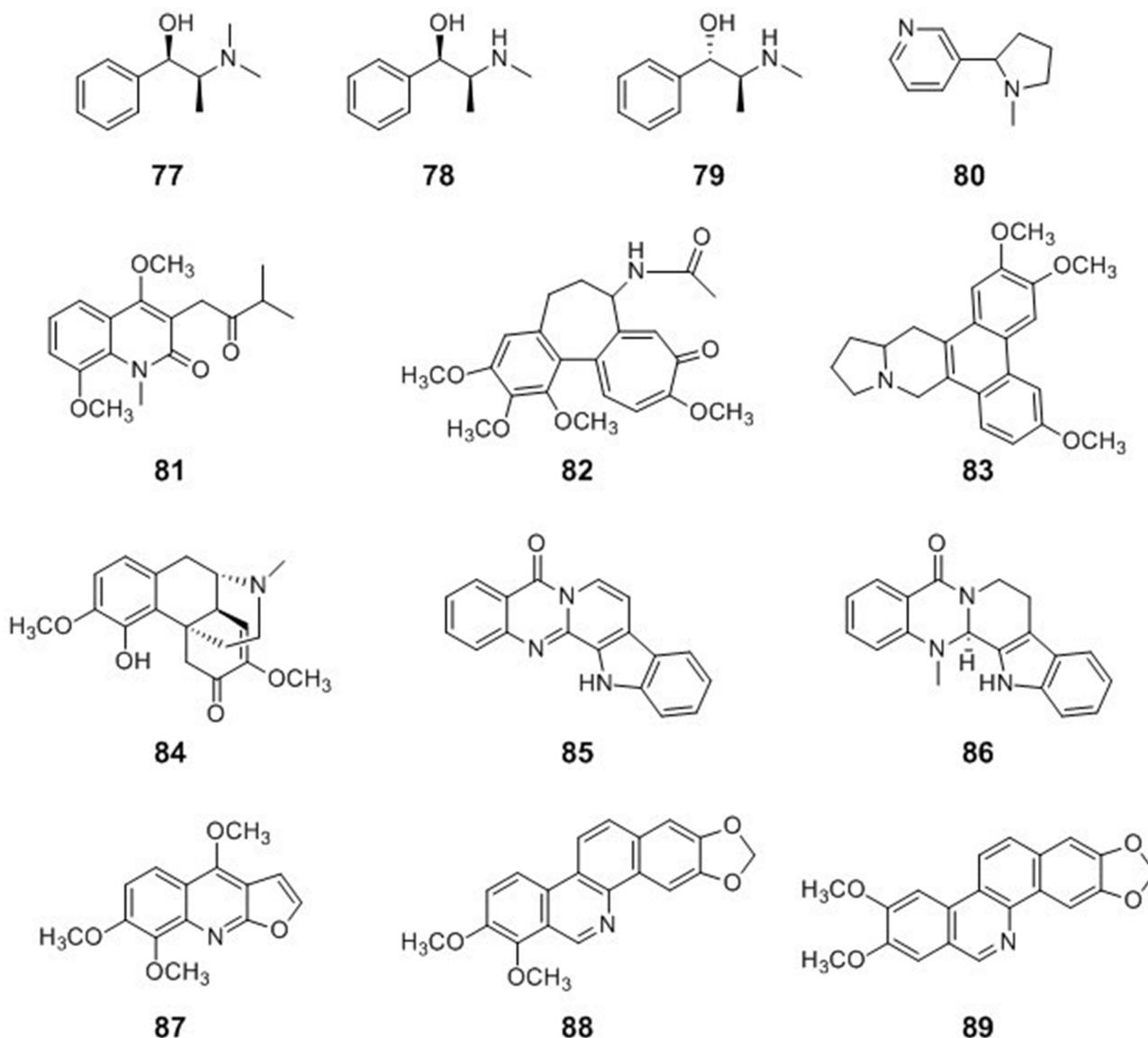
In particular, the influenza viruses initiate host cellular and molecular immune mechanisms. Th1/Th2 cells are usually considered to start the cell immune response. It has been demonstrated that the secretion of inflammatory cytokines, type I interferon (IFN), chemokines, and antimicrobial peptides are intimately involved in the Th1/Th2 balance and immune response.<sup>92</sup> Here, we summarize recent findings of the use of alkaloids to treat lung infections involving anti-inflammatory or innate immune responses (Figure 8).

## A Pyridine Alkaloid

Nicotine (80) reduced NF-κB-mediated transcription as measured by IL-2 and IkB transcription.<sup>93</sup> The α7nAChR plays a major role in the anti-inflammatory effects of nicotine, and nicotine attenuates inflammation in both obesity and ulcerative colitis. The anti-inflammatory effects of nicotine may be mediated via the expression of several nAChRs on a particular target cell. Selective α7nAChR agonists may be a potential new class of anti-inflammatory drugs.<sup>94</sup>

## A Quinolone Alkaloid

The quinolone alkaloid orixalone A (81) from *Orixa japonica* strongly inhibited NO production in murine



**Figure 8** Chemical structures of natural plant alkaloids with anti-inflammatory activities.

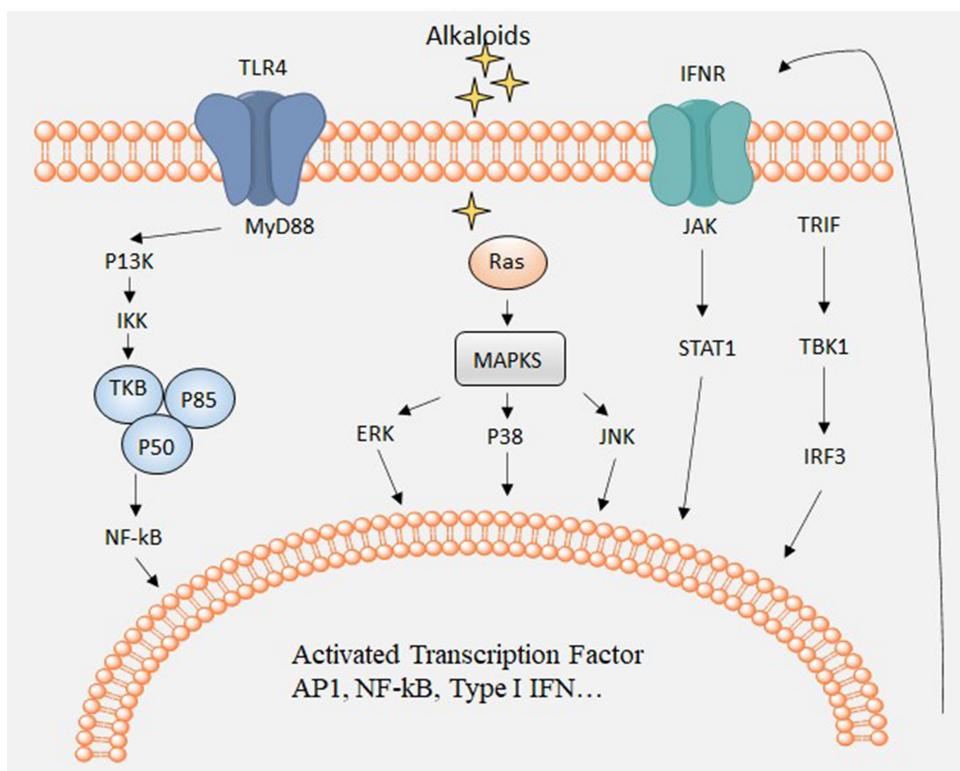
macrophage RAW 264.7 cells stimulated with interferon- $\gamma$  and LPS at micromolar concentrations and, thus, might be used as an anti-inflammatory or cancer-preventive agent to suppress the excessive synthesis of NO.<sup>95</sup>

## An Isoquinoline-Type Alkaloid

Anti-inflammatory activity of BBR (32) has been indicated by the reduction of proinflammatory cytokines, including TNF- $\alpha$ , IL-13, IL-6, IL-8, and IFN- $\gamma$ . In cell models, BBR was able to completely antagonize the TNF- $\alpha$ -mediated barrier defects, which are related to tyrosine kinase, and the pAkt and NF- $\kappa$ B pathways.<sup>11</sup> BBR significantly inhibited the binding of NF- $\kappa$ B and AP-1 at concentrations of 4–10 M or higher. BBR also inhibited LPS-induced MCP-

1/CCL2 production in vitro via AP-1 and NF- $\kappa$ B-dependent pathways.<sup>61,96–99</sup> It has been reported that BBR repressed proinflammatory responses through AMP-activated protein kinase activation in macrophages, significantly down-regulating the expression of proinflammatory genes, such as TNF- $\alpha$ , IL-1 $\beta$ , IL-6, monocyte chemoattractant protein-1 (MCP-1), inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2).

BBR (32), a natural isoquinoline alkaloid isolated from the *berberis* species, has a wide array of biological properties, such as anti-inflammatory, antibacterial, antifungal, and antihelminthic effects. BBR relieved pulmonary inflammation, and reduced necrosis, inflammatory cell infiltration, and pulmonary edema, induced by a viral



**Figure 9** Major cell signaling pathways related to inflammation.

infection in mice when compared with vehicle-treated mice. BBR suppressed the viral infection-induced up-regulation of components of the TLR7 signaling pathway, such as TLR7, MyD88, and NF- $\kappa$ B (p65), at both the mRNA and protein levels. Furthermore, BBR significantly inhibited the viral infection-induced increases in the Th1/Th2 and Th17/Treg ratios, as well as the production of inflammatory cytokines.<sup>49</sup>

BBR inhibited EV71 replication by downregulating autophagy and the MEK/ERK signaling pathway. These findings suggested that BBR may be a potential agent or supplement against EV71 infection.<sup>100</sup>

BBR reduces virus replication and targets specific interactions between the virus and its host. BBR inhibits the replication of HSV, human cytomegalovirus, human papillomavirus, and HIV. This alkaloid has the ability to regulate the MEK-ERK, AMP-activated protein kinase/mTOR, and NF- $\kappa$ B signaling pathways, which are necessary for viral replication. Furthermore, it has been reported that BBR can support the host immune response leading to viral clearance.<sup>100</sup>

## Amine Alkaloids

Colchicine (**82**) is a widely available, inexpensive drug with a range of anti-inflammatory properties. Colchicine affects

the assembly of the NLRP3 inflammasome, thereby reducing the release of IL-1 $\beta$  and other interleukins, including IL-6, that are formed in response to danger signals. In endothelial cells, colchicine inhibits the production of IL-1 $\beta$  and the expression of E-selectin required for neutrophil adhesion.<sup>101</sup> Colchicine can limit the extent of inflammatory injury by promoting anti-inflammatory macrophages to release IL-10, TGF- $\beta$ , and other anti-inflammatory cytokines that act to suppress proinflammatory signaling and promote favorable healing by dampening the growth of vascular smooth muscle cells.<sup>9</sup>

The potential antiviral mechanisms of compounds from *Ephedra sinica* Stapf have been investigated. L-Methylephedrin (LMEP, **77**), L-ephedrine (LEP, **78**), and D-pseudo-ephedrine (DPEP, **79**) significantly inhibited the proliferation of influenza A virus in vitro. These compounds also significantly inhibited the mRNA expression levels of related genes in the TLR3, TLR4, and TLR7 signaling pathways, which was accompanied by the down-regulation of TNF- $\alpha$  levels and the up-regulation of IFN- $\beta$  levels in the cell supernatant. Animal research further indicated, at the 3rd and 7th days after infection, that LEP and DPEP significantly attenuated lung injury, decreased the lung index, the

virus load in the lung, and the level of IL-1 $\beta$  in serum, inhibited the mRNA expression levels of TNF- $\alpha$ , TLR3, TLR4, TLR7, MyD88, NF- $\kappa$ B p65, and RIG-1, as well as the protein expression levels of TLR4, TLR7, MyD88, and NF- $\kappa$ B p65, and markedly increased the thymus index, the level of IL-10 in serum, and the mRNA expression level of IFN- $\gamma$ .<sup>10</sup>

### An Indolizidine Alkaloid

Antofine (83) is a phenanthroindolizidine alkaloid isolated from the root of *Cynanchum paniculatum* Kitagawa (Asclepiadaceae) that is used as a herbal remedy.<sup>102</sup> Chou et al recently reported that antofine may not only inhibit endotoxin-stimulated inflammation but also modulate cellular metabolism via an AMP-activated protein kinase.<sup>103</sup>

### A Isoquinoline Alkaloid

Sinomenine (84) is a morphine-type alkaloid isolated from the Chinese herb *Caulis Sinomenii*. Sinomenine is one of the most widely known alkaloids owing to its various therapeutic properties, including anti-inflammatory and immunosuppressive activities.<sup>104</sup>

### Indolopyridoquinazolinone Alkaloids

Two indolopyridoquinazolinone alkaloids, rutaecarpine (85) and evodiamine (86), as well as the structurally related quinazoline-2,4-dione, goshuyuamide II, were evaluated for their anti-inflammatory activities. These compounds strongly inhibited PGE2 synthesis in LPS-treated RAW 264.7 cells at 1–10  $\mu$ M, and evodiamine also inhibited cyclooxygenase-2 (COX-2) induction and NF- $\kappa$ B activation.<sup>105</sup>

### A Quinolinone Alkaloid

*Ruta graveolens* L. (Rutaceae), commonly known as rue, has been reported to have medicinal properties against aching pain, eye problems, rheumatism, and dermatitis.<sup>106</sup> Skimmianine (87), isolated from *R. graveolens* L., was injected into mice (5.0 mg/kg) and found to alleviate carrageenan-induced acute inflammation, decrease the mRNA levels of TNF- $\alpha$  and IL-6, and reduce PGE2 and NO levels, COX-2 and 5-lipoxygenase activities, neutrophil infiltration, lipid peroxidation, and associated oxidative stress in the paw tissue.<sup>71</sup>

### A Phenanthridine Alkaloid

*Zanthoxylum schinifolium* is an aromatic shrub, the pericarp and leaves of which are widely used in culinary

applications in East Asian countries. Norchelerythrine (88) and nornitidine (89) from *Zanthoxylum schinifolium* exhibited significant inhibition of NF- $\kappa$ B activation in a dose-dependent manner. Furthermore, these compounds inhibited TNF- $\alpha$ -induced expression of inducible nitric oxide synthase (iNOS) and intercellular adhesion molecule-1 mRNA, and dose-dependent inhibition of iNOS promoter activity.<sup>107</sup>

### A Matrine-Type Alkaloid

Oxymatrine (15) is a major active compound of *Sophora* root.<sup>108</sup> Oxymatrine had excellent anti-influenza A virus activity against eight strains in vitro. Oxymatrine significantly decreased the promoter activities of the TLR3, TLR4, TLR7, MyD88, and TRAF6 genes, inhibited virus-induced activation of the Akt, ERK1/2, p38 MAPK, and NF- $\kappa$ B pathways, and suppressed the expression of inflammatory cytokines and MMP-2/9. Activators of the TLR4, p38 MAPK, and NF- $\kappa$ B pathways significantly antagonized the anti-influenza activity of oxymatrine in vitro, including virus replication and virus-induced cytopathogenic effects.<sup>109</sup>

### A Pyrrole-Type Alkaloid

Epigoitrin (46), a natural alkaloid from *Isatis indigotica*, provides protection against influenza infection by reducing the host's susceptibility to the influenza virus under stress. Epigoitrin significantly decreased the susceptibility of mice to an influenza virus as evidenced by lower mortality, attenuated inflammation, and decreased viral replication in the lungs. In addition, epigoitrin reduced the protein expression of mitofusin-2, which elevated mitochondria antiviral signaling protein expression and subsequently increased the production of IFN- $\beta$  and interferon-inducible transmembrane 3, thereby helping to fight viral infections. This study indicated that epigoitrin reduced the susceptibility to the influenza virus via mitochondrial antiviral signaling.<sup>57</sup>

### Conclusions and Perspectives

Alkaloids have attracted considerable attention from researchers worldwide since the study of alkaloids began in 1803 when nicotine was discovered. Alkaloids represent a promising and expanding platform for the development of active natural compounds as new pharmaceuticals. The molecular structures of alkaloids provide valuable leads for antiviral drug design. Isoquinoline (BBR, 32) alkaloids exhibit broad-spectrum antiviral activity, including activity against HIV, HCV, IFV, HSV and may also reduce related anti-inflammatory activities. Quinoline alkaloid

compounds have provided a new route for drug development via the treatment of both HIV and HCV infections. The discovery of aloperine (1), a quinolizidine-type lead compound, which functions by virus-induced cell-cell fusion, has provided a route to develop drugs that target both HIV and HCV infections. In addition to the activities mentioned herein, alkaloids exhibit other important bioactivities, including antifungal, antiparasitic, insecticidal, and antiplatelet activities. We hope that such alkaloids will provide more avenues for the development of new drugs in the future through targeted pharmacological viral infected host modeling and the resulting synthetic modifications.

Viral infections are a worldwide public health problem that affects a large proportion of the world's population. Medicinal plants or herbs have been widely used to treat various infectious diseases for thousands of years. Literature reviews have demonstrated that plants are therapeutically effective for treating viral diseases. Medicinal plants and herbs are recognized as a rich source of therapeutic agents for the management of viral disorders. The active constituents of plants, such as alkaloids, have been reported to have antiviral activity. Such compounds can function by interacting with different viral protein receptors and have been shown to play an important role in the management of viruses and the inflammatory response in host models. Although the contribution of modern synthetic medicine for elevating human suffering cannot be underestimated, the fact that synthetic drugs exert serious side effects cannot be ignored. In the future, more scientific studies are needed to develop alkaloidal compounds as antiviral therapeutic agents and potential regulators of the host immune response.

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## Disclosure

The authors report no conflicts of interest for this work.

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