Plant-derived lignans as potential antiviral agents: a systematic review

Xin-Ya Xu · Dong-Ying Wang · Yi-Ping Li · Stephen T. Deyrup · Hong-Jie Zhang

Abstract Medicinal plants are one of the most important sources of antiviral agents and lead compounds. Lignans are a large class of natural compounds comprising two phenyl propane units. Many of them have demonstrated biological activities, and some of them have even been developed as therapeutic drugs. In this review, 630 lignans, including those obtained from medicinal plants and their chemical derivatives, were systematically reviewed for their antiviral activity and mechanism of action. The compounds discussed herein were published in articles between 1998 and 2020. The articles were identified using both database searches (e.g., Web of Science, Pub Med and Scifinder) using key words such as: antiviral activity, antiviral effects, lignans, HBV, HCV, HIV, HPV, HSV, JEV, SARS-CoV, RSV and influenza A virus, and directed searches of scholarly publisher's websites including ACS, Elsevier, Springer, Thieme, and Wiley. The compounds were classified on their structural characteristics as 1) arylnaphthalene lignans, 2) aryltetralin lignans, 3) dibenzylbutyrolactone lignans, 4) dibenzylbutane lignans, 5) tetrahydrofuranoid and tetrahydrofurofuranoid lignans, 6) benzofuran lignans, 7) neolignans, 8) dibenzocyclooctadiene lignans and homolignans, and 9) norlignans and other lignoids. Details on isolation and antiviral activities of the most active compounds within each class of lignan are discussed in detail, as are studies of synthetic lignans that provide structure–activity relationship information.

Keywords Lignans · Medicinal plants · Antiviral · HBV · HSV · HIV

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Introduction

A virus is a small infectious agent ranging from $\sim$ 20 nm to 300 nm in diameter and contains mostly bundles of gene strands of either RNA or DNA as its genome. Viruses are not autonomous organisms and require the host cell environment and cellular factors for their propagation (Bekhit and Bekhit 2014). Due to the intracellular properties of viruses, it is often difficult to design a treatment that inhibits viral replication directly without adverse effects on the infected cells. (Zinser et al. 2018; Bar-On et al. 2018).

Viral infections can be categorized as chronic or acute based on the length of time the infections and symptoms last. Some of the viruses causing the most widespread and harmful chronic infections are hepatitis B virus (HBV), hepatitis C viruses (HCV), herpes simplex virus (HSV), human immunodeficiency virus (HIV), and human papilloma virus (HPV). HIV alone has caused approximately 33 million deaths since the virus was first discovered in 1981 (WHO 2021). Acute viral infections cause several of the most common, severe and rapid infections. This was painfully illustrated in the coronavirus disease 2019 (COVID-19) pandemic (Wu and McGoogan 2020). As of Mar 2021, there are over 123 million confirmed SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infected cases worldwide and over 2.7 million COVID-19 deaths (Worldometer 2021). Annually, seasonal influenza epidemics usually cause 250,000–500,000 deaths. However, they could also cause far more severe damage to human lives. For example, the 1918 H1N1 Spanish flu killed an estimated 50 million people, making it one of the worst pandemics in recorded human history (Short et al. 2018). The viral outbreaks like the Ebola virus (EBOV) in West Africa in 2014 received extensive media coverage due to its epidemic potential and high mortality rates of up to 90% (Martinez et al. 2014).

Many compounds have been tested on various viruses for their antivirtal activity in the past few decades, and some novel antiviral compounds are currently in the process of either preclinical or clinical trials (Chaudhuri et al. 2018). Although public health measures and prophylactic vaccines should remain the most effective means for prevetion of virus infection, for many virues vaccines are either not available or are inefficient. In addition, drug resistance is becoming increasingly common due to the expanding numbers of antiviral drugs. Long-term treatment with antiviral nucleoside analogues can cause delayed and, at times, severe mitochondrial toxicity. Kidney injury associated with antiviral drug use involves diverse mechanisms affecting renal transporters and tubule cells (Hussain et al. 2017; Izzedine et al. 2005). Therefore, the ongoing need to fight viral infections requires continued partnerships between medicinal chemists and biomedical researchers to identify and develop novel antiviral agents that are highly efficacious and cost-effective for the management and control of viral infections when vaccines and standard therapies are unavailable or ineffective.

Globally, medicinal plants have been used in traditional health care systems since ancient times and are still the most important source of medicines for the vast majority of the world's population (Pushpa et al. 2013). Many traditionally used medicinal plants display strong antiviral activities, and some of them are used to treat animals and people who suffer from viral infections. In 2006, polyphenon E®, a partially-purified extract of green tea (*Camellia sinensis*) was approved as the first ever botanical drug by the US FDA to treat genital warts caused by HPV. Furthermore, recent studies showing the antiviral potential of plant extracts against viral strains resistant to conventional antiviral agents have contested modern drug discovery practices (Akram et al. 2018). Therefore, exploring the natural antiviral constituents of medicinal plants has garnered widespread and increased interest.

During the last 30 years, numerous broad-based screening programs have been carried out throughout the world to evaluate the inhibitory effects of medicinal plants on several viruses using in vitro and in vivo assays. For example, the Boots drug company (Nottingham, England) screened 288 plants for anti-influenza activity, and 12 of these plants were discovered to be effective against influenza viruses (Mukhtar et al. 2008). In another study, a joint international drug discovery program evaluated the antiviral effects of 3,760 plants extracts in Vietnam and Laos, which led to the identification of more than 90 plant leads that showed anti-HIV and anti-bird flu virus activities (Zhang et al. 2016; Rumschlag-Booms et al. 2011).

Lignans, constituted by the union of two phenylpropane units, are a large class of plant secondary

metabolites with diversified chemical structures with many being biologically active including the US FDA approved anticancer drugs etoposide and teniposide (Newman and Cragg 2020). They have been found rich in fruits, seeds and vegetables, and received widespread interest due to their various biological activities including antioxidant, antitumor, antibacterial, antiviral, insecticidal, fungistatic, estrogenic, and antiestrogenic activities (Teponno et al. 2016). Their activity against the coronavirus SARS 2003 was also reported to be prominent (Wen et al. 2007).

The first antiviral lignan reported is podophyllin, a toxic lignan obtained from *Podophyllum peltatum* with antiviral activity against papilloma virus in 1942 (Kaplan 1942). Charlton had reviewed 49 natural lignans with antiviral activity from 1942 to 1997 (Charlton 1998). In a recent review article, Cui et al. reported about 25 representative lignans that showed antiviral activities (Cui et al. 2020). However, more than 600 lignans have been reported for their antiviral effects since 1998, and many of them showed potent properties. It's therefore necessary to present a systematic review to include these antiviral lignans.

The present review summarizes the natural antiviral lignans or derivatives from 1998 to 2020. The lignans will be classified in 9 categories according to their chemical structure classes. Their antiviral activities against HIV, HBV, HCV, SARS, herpes simplex virus (HSV), HPV, Ebola virus, influenza virus, vesicular stomatitis virus (VSV) and other viruses will be discussed in detail. The antiviral mechanism studies of lignans will also be included when they were reported.

Arylnaphthalene-type lignans
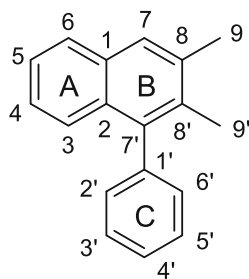
arylnaphthalene lignan

In arylnaphthalene lignans, a naphthalene ring-system is made with carbons 1–8 and 7′ and 8′. There have been numerous arylnaphthalene lignans discovered from natural sources. Among the most common structural motifs found in this class of lignans, as with all classes of lignans, are various substitutions on the aromatic rings, a lactone moiety formed from C-8, C-9, C-8′, and C-9′, and glycosides. Many lignans in this class showed significant and broad antiviral activities, warranting them for further chemical and biological approaches for antiviral drug development.

Between 1998 and 2020, 17 arylnaphthalene lignans were isolated from plants and tested for antiviral activity (**1–13**, **32**, **152** and **153**) (see Table 1 for source plants, antiviral activities, and references). Of particular interest due to their potent antiviral activity (< 1 μM), are **2** and **11**. We found four studies on synthetic arylnaphthalene lignans which displayed significant antiviral activities and provided information about structure–activity relationships.

Globoidnan A (**2**) was considered responsible for the inhibitory activity of HIV integrase of the extract of the buds of *Eucalyptus globoidea* Blakely (Australia). The lignan was found to inhibit the combined 3′-processing and strand transfer activity of HIV integrase with an EC_{50} value of 0.64 μM (Ovenden et al. 2004). Diphyllin (**11**) from *Justicia procumbens* var. *leucantha* was determined to have antiviral activity with an MIC value of 0.66 μM against vesicular stomatitis virus (Asano et al. 1996). It was also identified as a novel v-ATPase blocker against influenza viruses (Chen et al. 2013). It could alter cellular susceptibility to influenza viruses through the inhibition of endosomal acidification, thus interfering with downstream viral replication, including that of known drug-resistant strains. Moreover, the combination treatment of the host-targeting diphyllin with pathogen-targeting therapeutics (oseltamivir and amantadine) has been reported to enhance the antiviral effects and cell protection in vitro (Chen et al. 2013; Shen et al. 2011).

Table 1 Natural lignans from plants and their antiviral activities

Source	Parts	Compounds	Activity	Activity value	References
Daphne acutiloba Rehd. (Thymelaeaceae, Yunnan, China)	Leaves and stems	**1**	HIV-1	EC_{50} 15.6 μM, TI 35.62	Cao et al. (2010)
Eucalyptus globoidea Blakely (Myrtaceae, Australia)	Buds	**2**	HIV integrase	EC_{50} 0.64 μM	Ovenden et al. (2004)
Iryanthera megistophylla A. C. Sm. (Myristicaceae, Colombia)	Bark	**3**	HSV-1	$EC_{50} > 1150$ μM	Ming et al. (2002)
Phyllanthus acutissima Miq. (Euphorbiaceae, Thailand)	Aerial parts	**4,5**	HIV-1	**4** $EC_{50} < 7.4$ μM	Tuchinda et al. (2008)
Phyllanthus flexuosus (Sieb. Et Zucc.) Muell. Arg (Euphorbiaceac, Yunnan, China)	Roots	**6–10**	HSV-1	inactive, EC_{50} value unavailable	Zhao et al. (2014)
Justicia procumbens var. *leucantha* (Acanthaceae, Tokyo, Japan)	Aerial parts	**11**	VSV V-ATPase	VSV MIC 0.66 μM; V-ATPase IC_{50} 0.04–0.49 μM	Asano et al. (1996); Chen et al. (2013)
Phyllanthus myrtifolius Moon. (Euphorbiaceae, Taiwan, China)	Aerial parts	**12–13**	HIV-1	**12** EC_{50} 3.5 μM; **13** EC_{50} 5.5 μM	Chang et al. (1995)
Taiwania cryptomerioides Hayata (Taxodiaceae, Taiwan, China)	aerial parts	**32**	HBV	EC_{50} 1 μM	Yeo et al. (2005)
Justicia gendarussa Burm. f. and *Justicia* cf. *patentiflora* Hemsley (Acanthaceae, Vietnam)	Roots and stems	**151–153**	Drug-resistant HIV-1	**152, 153** EC_{50} 47–495 nM	Zhang et al. (2017a); Zhang et al. (2017b)
Symplocos setchuensis Brand. (Sympocaceae, Sichuan, China)	Stems	**154**	HIV replication	EC_{50} value unavailable	Ishida et al. (2001)
Parakmeria yunnanensis Hu. (Magnoliaceae, Yunnan, China)	Leaves and stems	**154–156**	HIV	**155** EC_{50} 250 μM **156** EC_{50} 240 μM	Shang et al. (2013b)
Streblus asper Lour. (Moraceae, Guangxi, China)	Roots	**157, 158**	HBV	**157** anti-HBsAg EC_{50} 3.67 μM; anti-HBeAg EC_{50} 14.67 μM; **158** anti-HBsAg EC_{50} 6.98 μM, anti-HBeAg EC_{50} 26.74 μM	Li et al. (2013)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Streblus asper Lour. (Moraceae, Guangxi, China)	Stem bark	**158–160**	HBV	**158** HBsAg 6.58 μM, HBeAg 24.86 μM; **159** HBsAg 39.56 μM, HBeAg 61.23 μM	Li et al. (2012a)
Schisandra propinqua (Wall.) Hook. F. et Thoms. var. *sinensis* Oliv. (Schisandreae, Sichuan, China)	Aerial parts	**162–165**	anti-HIV-1	**162** EC_{50} 4.5 μM; **165** EC_{50} 4.5 μM	Li et al. (2012b); Li et al. (2009a); Lei et al. (2007)
Schisandra sphenanthera Rehd. et Wils (Schisandraceae, Shanxi, China)	Fruits	**166–169**	HSV-2 adenovirus	**166–169** HSV-2 EC_{50} 31.6, 65.7, 65.7, 68.4 μM; adenovirus EC_{50} 59.7, 126.8, 131.3, 100.5 μM	Song et al. (2013)
Carissa spinarum L. (Apocynaceae, Thailand)	Stems	**170, 249–250, 337, 342, 343, 389**	HSV-1, HSV-2	EC_{50} values > 100 μg	Wangteeraprasert et al. (2012)
Zanthoxylum ailanthoides Sieb. & Zucc. (Rutaceae, Taiwan, China)	Root bark	**171–172**	HIV	EC_{50} > 238 μM	Cheng et al. (2005b)
Strobilanthes cusia Bremek. (Acanthaceae, Japan)	Roots	**173–174**	HSV-1	**173** EC_{50} > 172 μM; **174** EC_{50} > 141 μM	Tanaka et al. (2004)
Polygonum multiflorum Sieb. Et Zucc. (Polygonaceae, Shanghai, China)	Roots	**175, 176**	HIV-1	**175** EC_{50} 136.1 μM; **176** EC_{50} 162.1 μM	Lin et al. (2010)
Phyllanthus species (Taiwan, China)	-	**177–179**	HBV	**177** HBsAg and HBeAg EC_{50} value unavailable, **178** HBsAg EC_{50} value 36.9 μM, **179** HBsAg EC_{50} value > 50 μM, **178–179** BeAg EC_{50} value > 50 μM	Huang et al. (2003a)
Phyllantthus niruri L. (Euphorbiaceae, Guangxi, China)	Whole plants	**178, 180–181**	HBV	**179–181** HBsAg EC_{50} 97.2, 9.5, 16.7 μM; HBeAg EC_{50} 232.1, 17.4, 69.3 μM	Wei et al. (2012)
Lindera glauca (Siebold & Zucc.) Blume (Lauraceae, Korea)	Twigs	**171, 224–226**	influenza A/PR8	**171** and **225** with 30.1% and 29.3% virus infected Vero cells were survived with the treatment of 10 μM	Park et al. (2018)
Chamaecyparis obtusa (Cupressaceae, Taiwan, China)	Leaves	**227**	HSV-1	EC_{50} 30.6 μM	Kuo et al. (2006)
Styrax japonica (Styracaceae, Korea)	Stem bark	**228–230**	HIV-1 virus cell fusion	**228** fusion index 0.25, fusion inhibition 59.4% **229** fusion index 0.22, fusion inhibition 65.1%	Lee et al. (2010a)
Symplocos setchuensis (Symplocaceae, Sichuan, China)	Stems	**230–232**	HIV	**231** EC_{50} 2.0 μM; **232** EC_{50} 6.9 μM	Ishida et al. (2001)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Bombax ceiba (Bombacaceae, Guangdong, China)	Roots	**231, 233**	HBV	**231**, HBsAg EC$_{50}$ 218.2 μM; **233**, HBsAg EC$_{50}$ 123.7 μM	Wang et al. (2013)
Phenax angustifolius (Urticaceae, USA)	Leaves	**234–238**	HIV	**234–238** EC$_{50}$ 3.0, 5.0, 0.8, 2.8, 5.2 μM	Piccinelli et al. (2005); Rastrelli et al. (2001)
Phyllanthus acutissima (Euphorbiaceae, Thailand)	Whole plants	**239, 240**	HIV	**239** EC$_{50}$ 27.8 μM; **240** EC$_{50}$ 98.3 μM	Tuchinda et al. (2008)
Hernandia ovigera (Hernandiaceae, Taiwan, China)	Seeds	**241, 242**	EBV	470, 480 mol ratio/32 pmol TPA	Ito et al. (2001)
Phyllanthus species	–	**243, 244**	HBV	inhibition of HBsAg and HBeAg 33.9% and 68.3% at concentration of 50 μM	Huang et al. (2003a)
Chamaecyparis obtusa (Cupressaceae, Taiwan, China)	Heartwood	**243, 245**	SARS-CoV replication	**243** EC$_{50}$ > 10 μM, **245** EC$_{50}$ 1.13 μM	Wen et al. (2007)
Zanthoxylum ailanthoides (Rutaceae, Taiwan, China)	Root bark	**243**	HIV-1	**243** EC$_{50}$ < 0.28 μM	Cheng et al. (2005b)
Arctium lappa L.(Asteraceae, Osaka, Japan)	Fruits	**246, 247**	influenza A virus (A/NWS/33, H1N1)	**246** EC$_{50}$ 24 μM, **247** EC$_{50}$ 3.8 μM	Hayashi et al. (2010)
Trachelospermum jasminoides (Lindl.) Lem	Stems, leaves	**248**	HCV	EC$_{50}$ 0.87 μM (HCVcc model), 0.69 μM (HCVpp model)	Qian et al. (2016)
Brucea javanica (Simaroubaceae, Fujian, China)	Seeds	**250**	TMV	EC$_{50}$ > 138 μM	Chen et al. (2009)
Machilus robusta (Lauraceae, Guangxi, China)	Bark	**251–256**	HIV-1 replication	inactive, EC$_{50}$ value unavailable	Li et al. (2011)
Schisandra sphenanthera (Schisandraceae, Shaanxi, China)	Fruits	**257–259**	HSV-2, ADV	**257–259** HSV-2, EC$_{50}$ 34.2, 160.1, 35.4 μM; ADV, EC$_{50}$ 68.4, 142.5, 224.7 μM	Song et al. (2013)
Schisandra sphenanthera (Schisandraceae, Shaanxi, China)	Leaves and stems	**230, 260**	HIV	233 EC$_{50}$ 31.5 μM	Liang et al. (2013)
Saururus chinensis rhizomes (Saururaceae, Korea)	Underground part	**261**	HIV-1	EC$_{50}$ 5.6 μM	Lee et al. (2010b)
Phyllanthus niruri (Euphorbiaceae, Guangxi, China)	Whole plants	**262**	HBV	HBsAg 15.6 μM, HBeAg 25.1 μM	Liu et al. (2014)
Schisandra rubriflora (Yunan, China)	Fruits	**281**	HIV-1	EC$_{50}$ 5.8 μM	Xiao et al. (2010a)
Kadsura angustifolia (Yunnan, China)	Stems	**259, 282, 283**	HIV-1	EC$_{50}$ 15.6, 27.0, 21.5 μM	Gao et al. (2008)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Schisandra propinqua (Sichuan, China)	Aerial parts	**259, 279, 284, 285**	HIV-1	EC_{50} 4.0, 14.8, 9.4, 2.9 μM	Li et al. (2009b)
Schisandra chinensis (Heilongjiang, China)	Leaves and stems	**286, 287**	HIV-1	$EC_{50} > 200$ μM	Shi et al. (2014)
Daphne feddei (Thymelaeaceae, Yunnan, China)	Leaves and stems	**288**	HIV	EC_{50} 23.2 μM	Hu et al. (2011)
Daphne acutiloba (Thymelaeceae, Yunan, China)	Stems	**289, 290**	HIV	**290** EC_{50} 0.64 μM	Huang et al. (2012)
Isatis indigotica (Brassicaceae, Anhui, China)	Roots	**291**	influenza, RSV, ADV, PIV3, EV71, HRV	influenza strains after viral adsorption, 137–1137 μM, RSV, ADV, PIV3, EV71, HRV inactive	Yang et al. (2013a)
Isatis indigotica (Brassicaceae, Anhui, China)	Roots	**292**	influenza A virus A/PR/8/34 (H1N1)	EC_{50} 102 μM	Li et al. (2015)
Schisandra propinqua (Yunnan, China)	Fruits	**293**	HIV-1	EC_{50} 15.9 μM	Fan et al. (2010)
Schisandra propinqua var. sinensis (Sichuan, China)	Aerial parts	**294–297**	HIV-1	**294 + 295** EC_{50} 7.7 μM	Li et al. (2009b)
Schisandra propinqua (Hubei, China)	Leaves and stems	**298–306**	HIV-1 IN DNA binding	$EC_{50} > 25$ μM	Shang et al. (2013a)
Schisandra rubriflora (Yunnan, China)	Fruits	**307**	HIV-1 IIIB induced syncytium formationHIV-1IIIB inducted MT-4 cells lytic effects	HIV-1 IIIB induced syncytium formation EC_{50} 30.0 μM HIV-1IIIB inducted MT-4 cells lytic effects EC_{50} 10.8 μM	Xiao et al. (2010a)
Schisandra chinensis (Heilongjiang, China)	Leaves and stems	**308–309**	HIV-1	**309** EC_{50} 66.1 μM	Shi et al. (2014)
Kadsura longipedunculata (Sichuan, China)	Leaves and stems	**310–311**	HIV-1	**311** EC_{50} 35.9 μM	Pu et al. (2008a)
Schisandra lancifolia (Yunnan, China)		**312–313**	HIV-1	**312** EC_{50} 212 μM, **313** EC_{50} 149 μM	Xiao et al. (2010b)
Peperomia heyneana (Piperaceae, Yunnan, China)	Whole plants	**314**	HIV-1	EC_{50} 50 μM	Zhang et al. (2007)
Saururus chinensis (Saururaceae, Guangxi, China)	Roots	**315–323**	EBV DNA replication	EC_{50} 6.95–69.9 μM	Cui et al. (2014)
Brucea javanica (Simaroubaceae, Fujian, China)	Seeds	**324–326**	TMV replication	**324–326** $EC_{50} > 100$ μM	Chen et al. (2009)
Parakmeria yunnanensis (Magnoliaceae, Yunnan, China)	Leaves and stems	**327–333**	HIV-1	$EC_{50} > 80$ μg/mL	Shang et al. (2013b)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Miliusa fragrans (Annonaceae, Thailand)	Leaves and stems	**334–336**	HSV-1, HSV-2	$EC_{50} > 100$ μg/mL	Sawasdee et al. (2013)
Fraxinus sinboldiana (Oleaceae, Korea)	Stems	**337**	HIV gp41 binding	$EC_{50} > 266$ μM	Kim et al. (2002)
Machilus robusta (Lauraceae, Guangxi, China)	Bark	**326, 338, 339**	HIV-1	inactive, EC_{50} value unavailable	Li et al. (2011)
Phyllanthus virgatus (Taiwan, China)	Whole plants	**340**	HBV	inactive, EC_{50} value unavailable	Huang et al. (2003a)
Phyllanthus flexuosus (Euphorbiaceae, Yunnan, China)	Roots	**341**	HSV-1	inactive, EC_{50} value unavailable	Zhao et al. (2014)
Herpetospermum caudigerum (Cucurbitaceae, Tibet, China)	Seeds	**344, 345**	HBV	HBsAg **344** EC_{50} 317 μM, **345** EC_{50} 629 μM, HBeAg **344** EC_{50} 297 μM, **345** EC_{50} 655 μM	Yuan et al. (2005)
Herpetospermum caudigerum (Sichuan, China)	Seeds	**346–350**	HBV	HBsAg **349** EC_{50} 20.5 μM, **350** EC_{50} 4.89 μM, HBeAg **349** EC_{50} 3.54 μM, **350** EC_{50} 8.02 μM	Yu et al. (2014)
Vitex leptobotrys (Lamiaceae, Vietnam)	Leaves and twigs	**351, 352**	HIV-1, EBV	**351, 352** anti-HIV-1 inactive; **351** anti-EBV EC_{50} 67 μM	Pan et al. (2014)
Litsea verticillata (Lauraceae, Vietnam)	Leaves and twigs	**353, 354**	HIV-1, EBV, HCMV	**353** anti-HIV-1 EC_{50} 42.7 μM; anti-EBV EC_{50} 16.2 μM; **354** anti-EBV EC_{50} 22.0 μM; anti-HCMV EC_{50} 58.3 μM	Hoang et al. (2002); Guan et al. (2016)
Dipsacus asper (Dipsacaceae, Guizhou, China)	Roots	**355–360**	HIV-1	$EC_{50} > 50$ μM	Sun et al. (2015)
Ligularia kanaitizensis (Asteraceae, Yunnan, China)	Roots and rhizomes	**361, 362**	HIV RT	**362** 53.3% inhibition at 439 μM	Li et al. (2005c)
Hernandia ovigera (Hernandiaceae, Taiwan, China)	Seeds	**363**	EBV	590 mol ratio/32 pmol TPA	Ito et al. (2001)
Bombax ceiba (Bombacaceae, Guangdong, China)	Roots	**343, 364**	HBV	HBsAg **343** EC_{50} 18.9 μM; **364** EC_{50} 118.3 μM	Wang et al. (2013)
Citrus hystrix (Rutaceae, Thailand)	Roots	**365**	HIV-1	inactive, EC_{50} value unavailable	Panthong et al. (2013)
Forsythia suspensa (Oleaceae, Heilongjiang, China)	Fruits	**343, 366–369**	influenza A (H1N1)	inactive, EC_{50} value unavailable	Li et al. (2014)
Symplocos setchuensis (Symplocaceae, Sichuan, China)	Stems	**343, 367**	HIV-1	inactive, EC_{50} value unavailable	Ishida et al. (2001)
Calotropis gigantea (Asclepiadaceae, Thailand)	Latex	**367, 370**	influenza A (H1N1)	**370** EC_{50} 24.5 μM	Parhira et al. (2014)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Rhus javanica (Anacardiaceae, Taiwan, China)	Roots	**343, 365, 367, 371–374**	TMV	**372–374** EC_{50} 218, 280, 193 μM	Ouyang et al. (2007)
Swietenia macrophylla (Meliaceae, Taiwan, China)	Stems	**375**	HCV	EC_{50} 10.5 μM	Wu et al. (2012)
Aster flaccidus bge (Asteraceae, Shanxi, China)	Roots	**376**	HIV-1	EC_{50} 670 μM	Liu et al. (2010)
Forsythia suspensa (Oleaceae, Heilongjiang, China)	Fruits	**377, 378**	influenza A (H1N1), RSV	influenza A (H1N1), **378** EC_{50} 41.1 μM, RSV **377** EC_{50} 166.4 μM	Li et al. (2014)
Saururus chinensis (Saururaceae, Korea)	Rhizomes	**379–382**	HIV-1-induced cytopathic effects	**379–381** EC_{100} 1.0, 1.0, 0.2 μM	Lee et al. (2010b)
Saururus chinensis (Saururaceae, Guangxi, China)	Roots	**321, 379–380, 383–388**	EBV	**321, 379–380, 383–388** EC_{50} 6.95, 3.42, 1.72, 14.5, 7.55, 2.69, 3.52, 1.70, 1.09 μM	Cui et al. (2014)
Lindera glauca (Siebold & Zucc.) Blume (Lauraceae, Korea)	Twigs	**365, 390–391**	HRV1B and cvb3	**391** against HRV1B and cvb3 with 75% and 90% virus infected Vero cells were survived with the treatment of 10 μM	Park et al. (2018)
Parakmeria yunnanensis (Magnoliaceae, Yunnan, China)	Leaves and stems	**392**	HIV-1	EC_{50} 79.7 μM	Shang et al. (2013b)
Styrax japonica (Styracaceae, Korea)	Stem bark	**393, 394**	HIV-1 syncytia formation	**393** and **394** percent fusion inhibition of 18.0% and 36.5% at the concentration of 20 μg/mL	Lee et al. (2010a)
Forsythia suspensa (Oleaceae, Heilongjiang, China)	Fruits	**395–398**	influenza A virus (H1N1)	**396** EC_{50} 60.5 μM	Li et al. (2014)
Streblus asper (Moraceae, Guangxi, China)	Roots	**399, 400**	HBV	EC_{50} > 1000 μM	Li et al. (2013)
Streblus asper (Moraceae, Guangxi, China)	Stem bark	**399**	HBV	EC_{50} > 1000 μM	Li et al. (2012a)
Piper regnelli (Piperaceae, Brazil)	Leaves	**392**	BHV-1, poliovirus	EC_{50} > 170 μM	Bertol et al. (2012)
Herpetospermum caudigerum (Cucurbitaceae, Tibet, China)	Seeds	**401, 402**	HBV	HBsAg, HBeAg EC_{50} > 100 μM	Yang et al. (2010a); Yuan et al. (2006)
Schisandra micrantha (Yunnan, China)	Leaves and stems	**403**	HIV-1	EC_{50} 9.75 μM	Li et al. (2005a)
Kadsura angustifolia (Yunnan, China)	Stems	**404, 405**	HIV	EC_{50} 40.86, 13.07 μM	Gao et al. (2008)
Schisandra lancifolia (Yunnan, China)	Leaves and stems	**406**	HIV-1	EC_{50} 8.43 μM	Xiao et al. (2010b)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Schisandra sphenanthera (Shanxi, China)	Leaves and stems	**407**	HIV-1	inactive, EC_{50} value unavailable	Liang et al. (2013)
Illicium henryi (Illiciaceae, Yunnan, China)	Stems and roots	**408–414**	HBV	**409** HBsAg EC_{50} 60 μM	Liu et al. (2011)
Ailanthus altissima (Simaroubaceae, Fujian, China)	Root bark	**415, 416**	TMV	$EC_{50} > 200$ μg/mL	Tan et al. (2012)
Daphne feddei (Thymelaeaceae, Yunan, China)	Leaves and stems	**417**	HIV-1	EC_{50} 27.7 μM	Hu et al. (2011)
Brucea javanica (Simaroubaceae, Fujian, China)	seeds	**416**	TMV	$EC_{50} > 134$ μM	Chen et al. (2009)
Streblus asper (Moraceae, Guangxi, China)	Stem bark	**418–424**	HBV	**424** HBsAg EC_{50} 2.03 μM; HBeAg EC_{50} 3.76 μM	Li et al. (2012a)
Streblus asper (Sichuan, China)	Heartwood	**423, 425–427**	HBV	EC_{50} 131.23–156.75 μM	Li et al. (2012c)
Streblus asper (Guangxi, China)	Roots	**428, 429**	HBV	**429** HBsAg EC_{50} 3.14 μM HBeAg EC_{50} 4.74 μM	Chen et al. (2012)
Streblus asper (Guangxi, China)	Roots	**423, 424, 430–437**	HBV	**423** and **437** EC_{50} 2.03 and 1.58 μM for HBsAg, 3.76 and 3.24 μM for HBeAg, 8.67 and 9.02 μM for DNA replication	Li et al. (2013)
Kadsura interior (Yunnan, China)	Stems	**442–455**	EBV-EA	**446, 447, 452, 453** showed inhibitory effects on relative ratio 7.1, 2.6, 4.7 and 9.4% at the concentration of 1000 mol ratio/TPA of EBV-EA activation	Chen et al. (2002)
Kadsura matsudai	Stems	**456–474**	HBV	**456, 457** HBeAg EC_{50} 90.1 and 94.3 μM	Kuo et al. (1999); Li et al. (2000); Kuo et al. (2001); Wu et al. (2003)
Schizandra arisanensis (Schizandraceous, Taiwan, China)	Stems	**448, 475–477**	HBV	$EC_{50} > 50$ μg/mL	Wu et al. (2003)
Kadsura japonica (Schizandraceous, Taiwan, China)	Stems	**471, 472**	HBV	HBsAg EC_{50} about 50 μM	Kuo et al. (2005)
Schisandra rubriflora (Schizandraceous, Yunnan, China)	Fruits	**443, 444, 476–499**	HIV-1	**478**, EC_{50} 11.3; **480**, $EC_{50} < 0.65$; **481**, EC_{50} 2.4; **477**, EC_{50} 5.7; **499**, EC_{50} 3.9 μM	Chen et al. (2006)

Table 1 continued

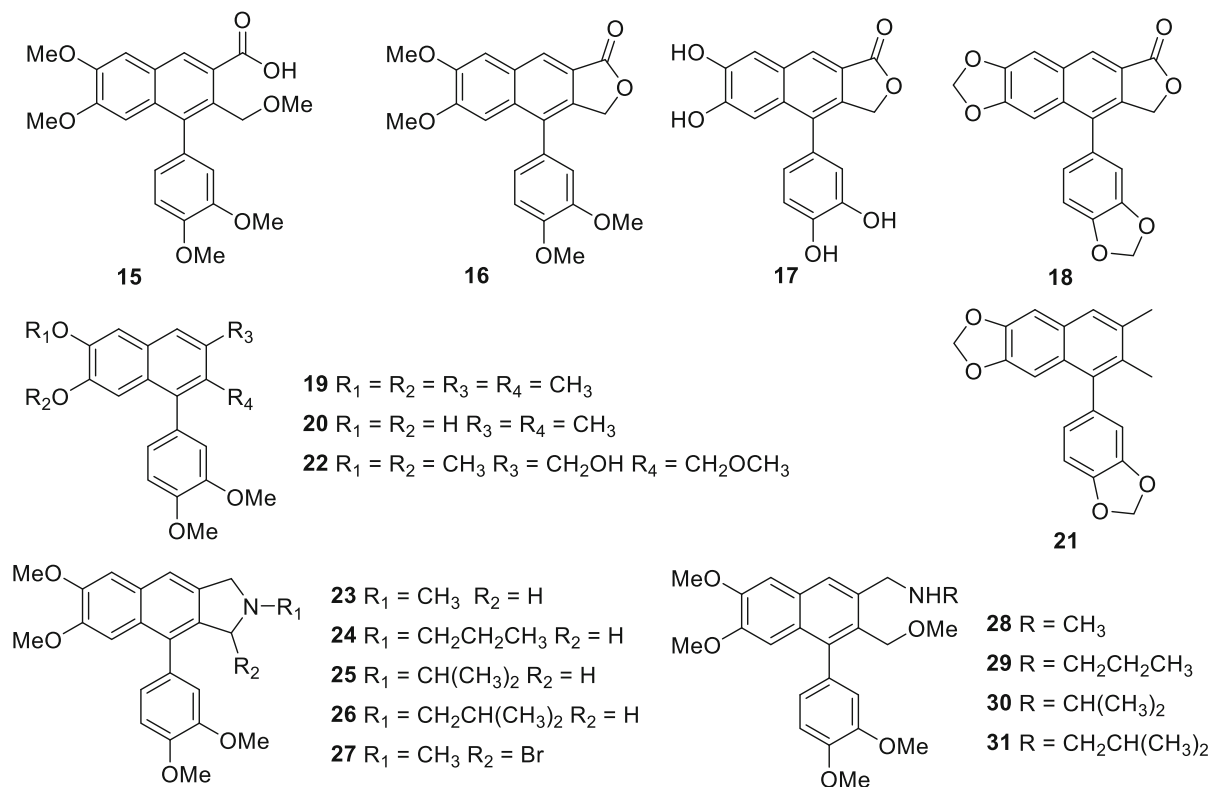| Source	Parts	Compounds	Activity	Activity value	References
Schisandra rubriflora (Schizandraceous, Yunnan, China)	Aerial parts	**443, 444, 477, 480, 488–492, 494, 495, 498**	HIV-1	**488**, EC_{50} 39.4; **489**, EC_{50} 36.9; **491**, EC_{50} 110 μM	Li et al. (2008)
Schisandra rubriflora (Schizandraceous, Yunnan, China)	Fruits	**496, 497**	HIV-1	**496**, EC_{50} 4.77; **497** EC_{50} 3.84 μM	Mu et al. (2011)
Kadsura longipedunculata (Schizandraceous, Yunnan, China)	Roots and stems	**500–504**	HIV-1	**500** EC_{50} 94.0 μM	Sun et al. (2006)
Kadsura induta (Schizandraceous, Yunnan Province, China)	Stems	**452, 505–509**	HBV	$EC_{50} > 100$ μg/mL	Ma et al. (2007)
Kadsura angustifolia (Schisandraceae, Yunnan, China)	Stems	**373, 466, 492, 507–509, 577, 510–522**	HIV-1	**520** EC_{50} 3.86 μM	Gao et al. (2008)
Kadsura heteroclita (Schisandraceae, Yunnan, China)	Stems	**451, 453, 454, 521, 523–527**	HIV-1	**451, 527** EC_{50} 3.3, 2.9 μM	Pu et al. (2008b)
Schisandra sphenanthera Rehd. Et Wils (Schisandraceae, Sichuan, China)	Leaves, stems	**455, 498, 499, 528**	HIV-1	**455, 498, 499, 528** EC_{50} 35.4, 39.4, 41.5, 35.9 μM	Xiao et al. (2008)
Schisandra propinqua vas. *sinensis* (Schisandraceae, Sichuan, China)	Aerial parts	**449, 454, 519, 529–542**	HIV-1	**449** EC_{50} 9.9 μM; **535** EC_{50} 7.9 μM; **538** EC_{50} 9.1 μM; **540** EC_{50} 7.3 μM; **542** EC_{50} 9.1 μM	Li et al. (2009b)
Schisandra lancifolia (Schisandraceae, Sichuan, China)	Leaves and stems	**543–545**	HIV-1	**543–545** EC_{50} 5.40, 9.30, 8.15 μM	Yang et al. (2010b)
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Fruits	**455, 477, 482, 546–557**	HBV	**546** inhibitory effects on HBsAg and HBeAg secretion by 59.7% and 34.7% at a concentration of 97 μM	Ma et al. (2009)
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Fruits	**553–555**	HIV-1	**553–555** EC_{50} 8.1, 15.4, 6.9 μM	Yang et al. (2010d)
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Fruits	**558–576**	HIV-1	**558–576** EC_{50} 6.9, 13.6, 13.4, 6.2, 3.6, 3.3, 4.1, 6.5, 6.1, 4.1, 4.7, 3.5, 3.4, 6.2, 5.8, 3.2, 4.2, 3.9 and 4.1 μM	Yang et al. (2010c); Yang et al. (2013b)
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Fruits	**443, 444, 447, 455, 476, 482–483, 485, 492, 498, 499, 556, 577–587**	HIV-1, HBV	**447, 498** anti-HIV-1 EC_{50} 3.9, 5.5 μM; **556** anti-HBV on HBsAg and HBeAg secrtion by 59.7 and 34.7% at a concentration of 97 μM	Ma et al. (2013)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Schisandra neglecta (Schisandraceae, Yunnan, China)	Fruits	**588, 589**	HIV-1	**588, 589** EC_{50} 4.6, 5.8 μM	Duan et al. (2011)
Schisandra neglecta (Schisandraceae, Sichuan, China)	Fruits	**583, 585, 590–598**	HIV-1	**583, 585, 590–598** EC_{50} 4.7, 9.8, 2.2, 1.4, 5.9, 3.5, 8.2, 8.2, 8.3, 11.5, 8.3 μM	Gao et al. (2013)
Nicotiana tabacum (Solanaceae, Yunnan, China)	Leaves	**599–604**	HIV-1 TMV	**599–604**, anti-HIV-1 EC_{50} 8.8, 4.6, 31.7, 20.4 μM; anti-TMV inhibition rate of 15.2, 58.4, 22.6 and 16.1% at the concentration of 20 μM	Gao et al. (2012)
Nicotiana tabacum (Solanaceae, Yunnan, China)	Roots, stems	**600–604**	TMV	**600–604** anti-TMV inhibition rate of 14.7, 17.6, 21.4, 22.5 and 23.4% at the concentration of 20 μM	Liao et al. (2012)
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Stems	**605–607**	HIV-1	**605–607** anti-HIV-1$_{IIIB}$ induced syncytia formation EC_{50} 1.5, 4.5, 5.4 μM; **605** reduce p24 EC_{50} 9.0 μM; inhibited primary isolate HIV-1TC-2 replication in PBMCs EC_{50} 1.4 μM	Zhang et al. (2010)
Schisandra sphenanthera fruits (Schisandraceae, Shaanxi, China)	Fruits	**608–610**	HSV-2, adenovirus	**608–610** anti-HSV-2 EC_{50} 29.1, 122, 35.2 μM, anti-adenovirus EC_{50} 96, 126, 105 μM	Song et al. (2013)
Schisandra lancifolia (Schisandraceae, Yunnan, China)	Leaves, stems	**611**	HIV-1	EC_{50} 117 μM	Xiao et al. (2010b)
Herpetospermum caudigerum (Cucurbitaceae, Sichuan, China)	Seeds	**612**	HBV	HBsAg EC_{50} 0.34 μM, HBeAg EC_{50} 4.83×10^{-4} μM	Yu et al. (2014)
Parakmeria yunnanensis (Magnoliaceae, Yunnan, China)	Leaves and stems	**613, 614**	HIV-1	**613** EC_{50} 288 μM	Shang et al. (2013b)
Peperomia heyneana (Piperaceae, Yunnan, China)	Whole plants	**615–617**	HIV-1	**615, 616** EC_{50} 5.3, 5.4 μM	Zhang et al. (2007)
Schisandra sphenanthera (Schisandraceae, Shaanxi, China)	Fruits	**618**	HSV-2, adenovirus	HSV-2, EC_{50} 42.7 μM; adenovirus EC_{50} 55.0 μM	Song et al. (2013)
Schisandra lancifolia (Schisandraceae, Yunnan, China)	Fruits	**619**	HIV-1	EC_{50} 1.82 μM	Li et al. (2009a)
Schisandra lancifolia (Schisandraceae, Yunnan, China)	Leaves and stems	**620**	HIV-1	EC_{50} 30.3 μM	Xiao et al. (2010b)
Schisandra lancifolia (Schisandraceae, Yunnan, China)	Leaves and stems	**621, 622**	HIV-1	**621, 622** EC_{50} 8.6, 7.2 μM	Xue et al. (2011)

Table 1 continued

Source	Parts	Compounds	Activity	Activity value	References
Schisandra wilsoniana (Schisandraceae, Yunnan, China)	Fruits	**623–626**	HIV-1	**623–626** EC_{50} 10.5, 9.8, 8.9, 7.6 µM	Yang et al. (2013b)
Kadsura angustifolia (Schisandraceae, Yunnan, China)	Stems	**627, 628**	HIV	**627** EC_{50} 44.68 µM	Gao et al. (2008)
Daphne feddei (Thymelaeaceae, Yunan, China)	Leaves and stems	**627, 629–630**	HIV	**627, 629–630** EC_{50} 104, 10.0, 8.3 µM	Hu et al. (2011)

15 16 17 18

19 $R_1 = R_2 = R_3 = R_4 = CH_3$
20 $R_1 = R_2 = H$ $R_3 = R_4 = CH_3$
22 $R_1 = R_2 = CH_3$ $R_3 = CH_2OH$ $R_4 = CH_2OCH_3$

21

23 $R_1 = CH_3$ $R_2 = H$
24 $R_1 = CH_2CH_2CH_3$ $R_2 = H$
25 $R_1 = CH(CH_3)_2$ $R_2 = H$
26 $R_1 = CH_2CH(CH_3)_2$ $R_2 = H$
27 $R_1 = CH_3$ $R_2 = Br$

28 R = CH_3
29 R = $CH_2CH_2CH_3$
30 R = $CH(CH_3)_2$
31 R = $CH_2CH(CH_3)_2$
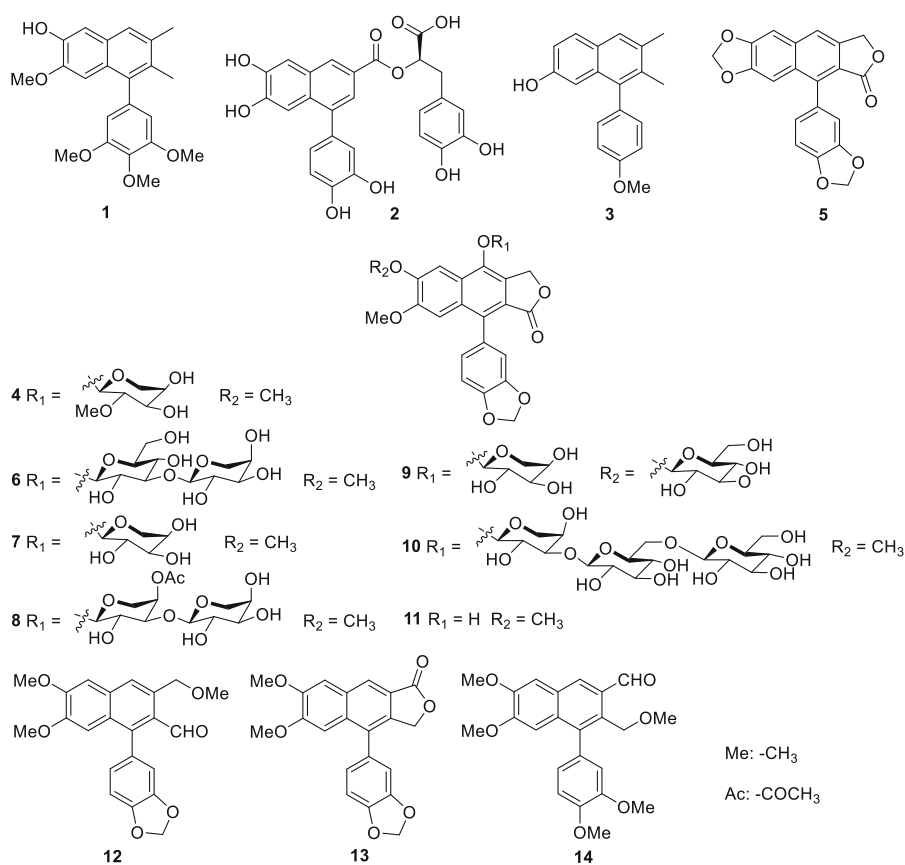
Phyllamycin B (**12**) and retrojusticidin B (**13**), obtained from *Phyllanthus myrtifolius* Moon (Euphorbiaceae, Taiwan, China), exhibited inhibitory effects on HIV-1 RT with EC_{50} values 3.5 and 5.5 μM. They showed less inhibition activities on human DNA polymerase-α (HDNAP-α) with EC_{50} values more than 200 μM (Chang et al. 1995). Interest in the antiviral activities of 12 and 13 led to the synthesis and bioassay of 18 derivatives (**14–31**) including a range of nitrogen containing azalignans including 1-aryl-pyrronaphthalenes **23–27** and 3-*N*-alkylaminomethyl-1-arylnaphthalenes **28–31**. The results indicated that compounds **17**, **25**, **26**, and **31** have good activity against HIV, with EC_{50} values of 0.77, 2.63, 0.02, 0.71 μM, respectively. It was noted that in the 9, 9'-γ-lactone series (**16–18**), the dicatechol **17** that contains four hydroxyl groups are much more active than the tetramethoxy (**16**) and dimethylenedioxy (**18**) derivatives. In addition, the *N*-isobutyl azalignans **26** and **31** were the most active among the series of compounds **23–31**. Interestingly, *N*-isobutyl-pyrro[4,3-*b*]naphthalene (**26**) possessed the highest activity (EC_{50} = 0.024 μM) with an excellent therapeutic index (TI) (6,000). Therefore, this compound could act as a lead compound for further anti-HIV drug development (Sagar et al. 2004).

32 **33**

34 R_1 = ONa R_2 = OH
35 R_1 = R_2 = $OCH_2C_6H_5$
36 R_1 = OH R_2 = $OCH_2C_6H_5$
37 R_1 = $O(CH_2)_3OCH_2C_6H_5$ R_2 = $OCH_2C_6H_5$
38 R_1 = $O(CH_2)_3OH$ R_2 = H
39 R_1 = $NH(CH_2)_2OCH_2C_6H_5$

40 R = H
41 R = $(CH_2)_3OCH_2C_6H_5$

42

43 R_1 = R_2 = H
44 R_1 = H R_2 = CH_3
45 R_1 = R_2 = CH_3

46

47 R = H
48 R = CH_3
58 R = NHAc

49 R = H
50 R = CH_3
51 R = $(CH_2)_3OCH_2C_6H_5$
52 R= $(CH_2)_3OH$
57 R = NHAc
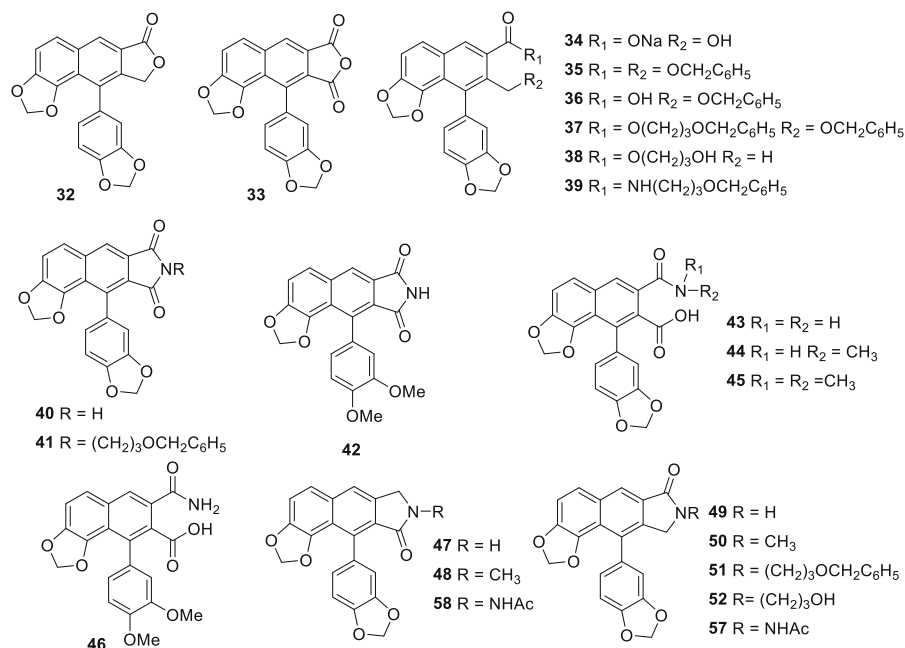
Helioxanthin (**32**) was used as a scaffold to create 45 analogues (**33–77**) with particular attention paid to the lactone ring and methylenedioxy group, these synthetic analogs were evaluated for their antiviral activities against HBV, HCV, HSV-1, HSV-2, Epstein-Barr virus (EBV), cytomegalovirus (CMV) and HIV (Yeo et al. 2005). Of these analogues, the lactam **49** and the cyclic hydrazide derivative of helioxanthin (**59**) exhibited significant in vitro anti-HBV activity with EC_{50} values of 0.08 and 0.03 μM, respectively, and compound **49** was also found to be the most potent HCV inhibitor (55% inhibition at the concentration of 1.0 μM). Compound **43**, the acid-hydrolyzed product of the cyclic amide **40**, displayed more potent activity than **32** against HBV with an EC_{50} value of 0.8 μM. In addition, compounds **46** and **53**, containing dimethoxy moieties instead of methylenedioxy groups in the C ring of compounds **43** and **49**, displayed potent antiviral activities against HCV (64% and 80% inhibition at 3.0 μM, respectively) as well as HBV (EC_{50} = 0.8 and 0.9 μM, respectively). Compounds **43** and **49** were found to be the strongest HSV inhibitors. They showed inhibitory activity against HSV-1 with EC_{50} values of 0.15 and 0.29 μM, respectively, and against HSV-2 with EC_{50} values of < 0.1 and 0.16 μM, respectively. Compound **43** was further determined to have broad-spectrum antiviral activity against HSV-1 (EC_{50} = 0.15 μM), HSV-2 (EC_{50} < 0.1 μM), EBV (EC_{50} = 9.0 μM) and CMV (EC_{50} = 0.45 μM). This compound was approximately 140 and 210 times more potent than the reference drug acylovir (EC_{50} = 21 μM) against HSV-1 and HSV-2, respectively. The cyclic hydrazide **59** and its brominated product **73** showed anti-HIV activities with EC_{50} values of 2.7 and 2.5 μM, respectively (Yeo et al. 2005). Moreover, as established by quantification of viral DNA, RNA, covalently closed circular DNA, and protein synthesis, compound **59** inhibited duck HBV (DHBV) activity without affecting the stability of cellular macro-molecules, and it had a sustained antiviral effect even after drug removal. When DHBV replication was induced, virus-harbouring cells were more susceptible to the cytotoxicity of the compound than the non-induced cells (Ying et al. 2010).

In a study of inhibitors of HBV gene expression and replication, compound **32** and its lactam analogue **49** demonstrated strong anti-HBV activity by markedly decreasing HBV DNA, 3.5-kb and 2.4/2.1-kb RNA, and the core protein in HepG2.2.15 cells. Compounds **32** and **49** revealed EC_{50} values of 1.0 and 0.08 μM against HBV DNA, and 1.0 and 0.09 μM against HBV RNA (3.5 kb), respectively. In addition, western blot analysis of the cell lysate from HepG2.2.15 cells

confirmed that the core protein expression decreased in a dose-dependent manner after drug treatment. Moreover, the EC$_{50}$ values for compounds **32** and **49** as inhibitors of HBV DNA production were determined to be 0.4 μM and 0.004 μM against the drug-resistant mutant W10, and 0.1 μM and 0.0003 μM against the drug-resistant mutant DM2, respectively (Li et al. 2005b; Cheng et al. 2005a; Tseng et al. 2008).

In a study of the anti-HBV mechanism, compound **59** was found to suppress HBV RNA and protein expression as well as DNA replication of both the wild-type and 3TC-resistant virus. In addition, the time-course analyses revealed that RNA expression was inhibited first after treatment with compound **59**, followed by viral proteins, and then DNA. This compound inhibited the activity of all HBV promoters by decreasing the binding of hepatocyte nuclear factor (HNF)-4, HNF-3, and fetoprotein factor to the pre-core/core promoter enhancer II region. Therefore, compound **59** suppressed HBV replication by post-transcriptional downregulation of critical transcription factors in HBV-producing cells, thus reducing HBV promoter activity and blocking viral gene expression and replication (Ying et al. 2007; Quasdorff & Protzer 2010).
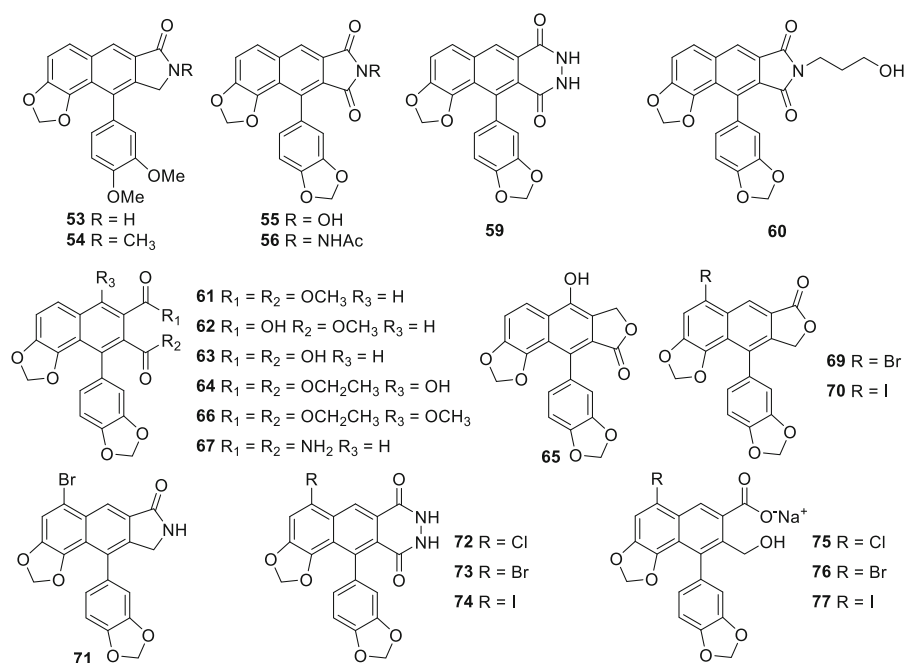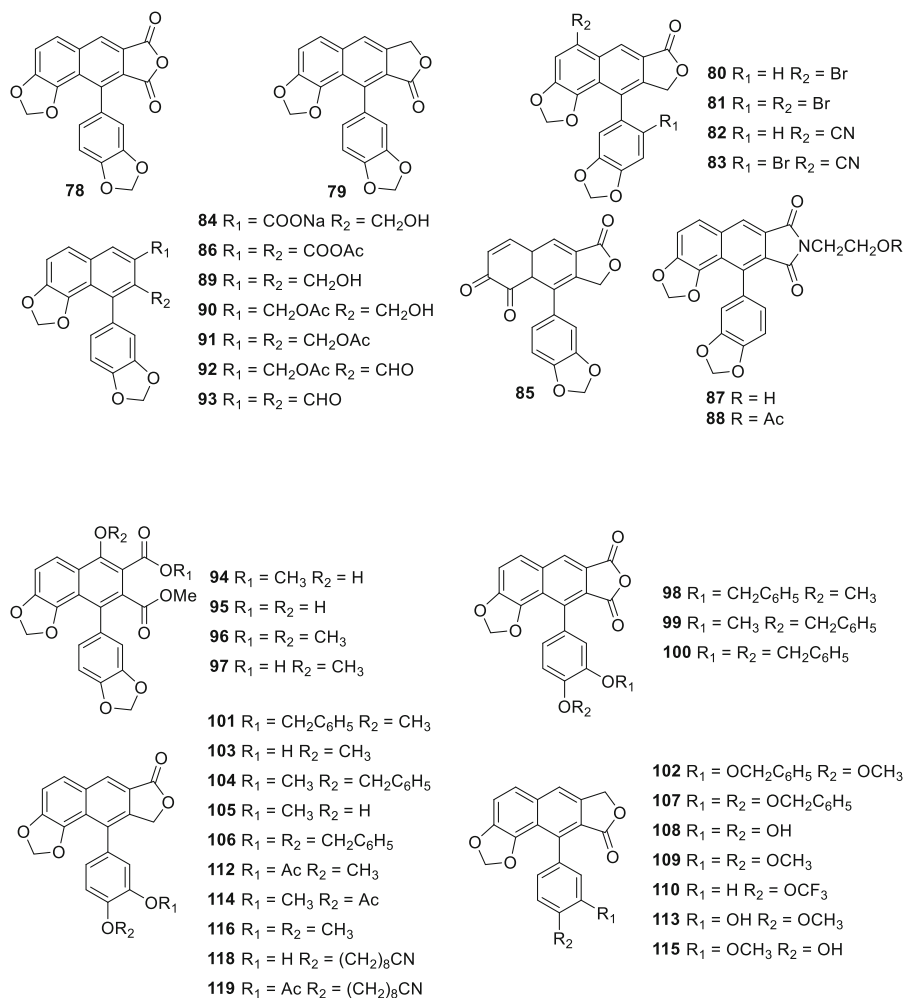
Yeh et al. also synthesized series of helioxanthin analogues (**78–110**) by modification at the lactone rings. These compounds were evaluated for their anti-HBV activity in HepA2. Among them, helioxanthin (**32**) and the derivative **103** were found to possess the best activity (EC$_{50}$ = 0.16 μM and 0.14 μM, respectively), whereas the retro-isomer **79** (EC$_{50}$ = 2.18 μM) is less active. Interestingly, compound **105** differs from **103** only by switching the locations of the hydroxyl (OH) and the methoxy (OCH$_3$) groups, yet its anti-HBV activity was markedly reduced to an EC$_{50}$ value of 1.89 *μM*. The γ-lactam ring opening analogues **84**, **89, 90** and **91** exhibited antiviral activity against HBV with EC$_{50}$ values of 0.89, 1.41, 0.42 and 1.22 μM, respectively. Analogues **93**, **108** and **109** exhibited moderate to low anti-HBV effects (EC$_{50}$ = 2.39, 3.06 and 7.64 μM, respectively), while all other compounds did not display detectable anti-HBV effects within the same range of concentrations. Compound **103** potently suppressed both endogenously expressed HBsAg and HBeAg production with EC$_{50}$ values of 0.06 and 0.14 μM, respectively. It not only inhibited HBV DNA with wild-type (stably transfected with 1.3-fold wild-type HBV ayw strain genome in HepG2 cells) and lamivudine-resistant (HepG2 cell line [HBV] containing the lamivudine-resistant HBV with L515M/M539V double mutation in the DNA polymerase region) strains, but also suppressed all HBV transcripts and HBV core protein in 1.3 ES2 cells. Additionally, it could selectively suppress viral promoter activity for HBV surface antigen, core antigen and enhancer I in HepA2 cells (Janmanchi et al. 2010).
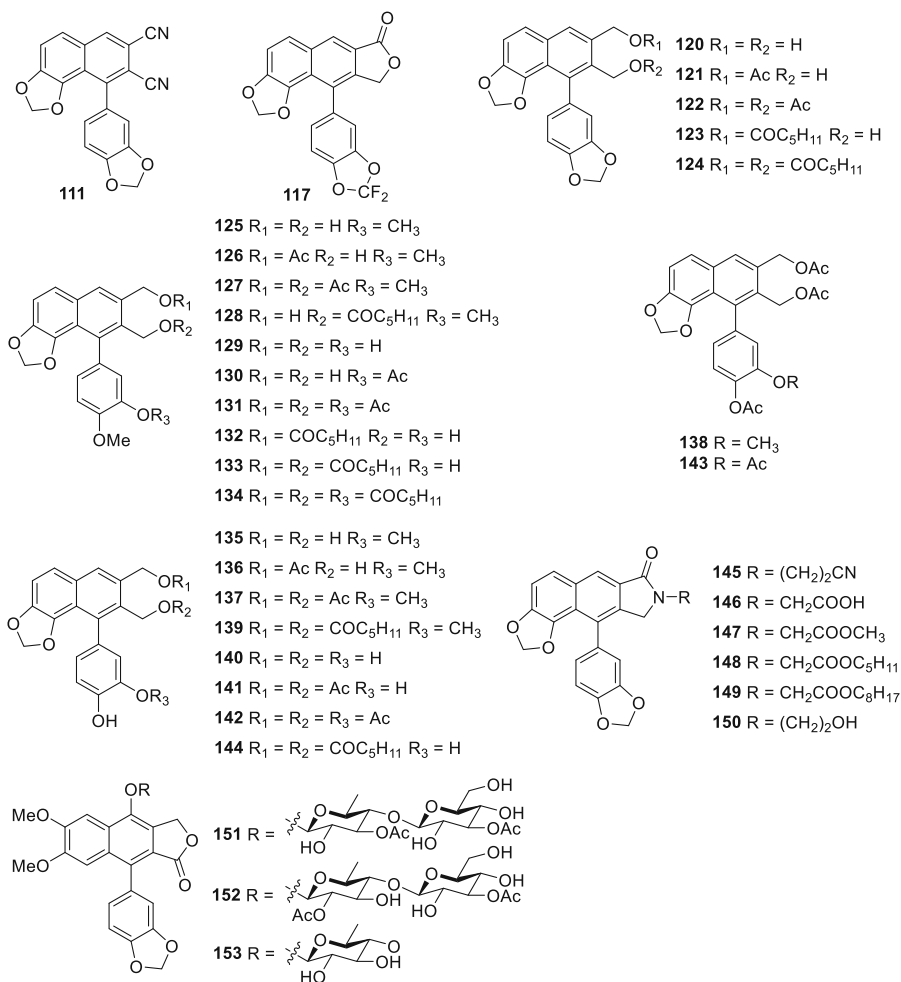
Helioxanthin analogues 103, 105, 108, 111–150) were also synthesized and evaluated for their anti-hepatitis B virus activity. Among them, 112 exhibited the strongest inhibition (EC_{50} value 0.06 μM), which was about three times more active than its parent compound (32). Potent activities were also found for the fluorine containing 117, the γ-lactone ring opening 129–131 and the lactone group containing 147 with EC_{50} values of 0.38, 0.67, 0.49, 0.65 and 0.86 μM, respectively. From these synthesized arylnaphthalene lignans, no distinguished structure–activity relationship could be concluded. However, it is obvious that the retro-lactonization and the ring opening of the lactone group do not lower the anti-HBV activity. The most effective compound, 112, not only suppressed HBsAg production in HepA2 cells and viral replication of HBV (stably transfected with 1.3-fold wild-

type HBV ayw strain genome in HepG2 cells), but also inhibited all HBV transcripts in 1.3ES2 cells and viral core promoter activity in HepA2 cells (Janmanchi et al. 2013).

Justiprocumins A (151) and B (152), patentiflorin A (153) were obtained from Justicia gendarussa Burm. f. and Justicia cf. patentiflora Hemsley (Vietnam). Compounds 152 and 153 displayed potent activity against a broad spectrum of HIV strains with EC_{50} values in the ranges of 15–37 nM (AZT, EC_{50} 77–95 nM). They also showed potent inhibitory effects against drug-resistant HIV-1 isolates (HIV-1_{1617-1}/HIV-1_{N119}) of both the nucleotide analogue (AZT) and non-nucleotide analogue (nevaripine) with EC_{50} values in the ranges of 47–495 nM (Zhang et al. 2017a, 2017b). In this study, the C-7 sugar unit-containing compounds (151, 153) display better anti-
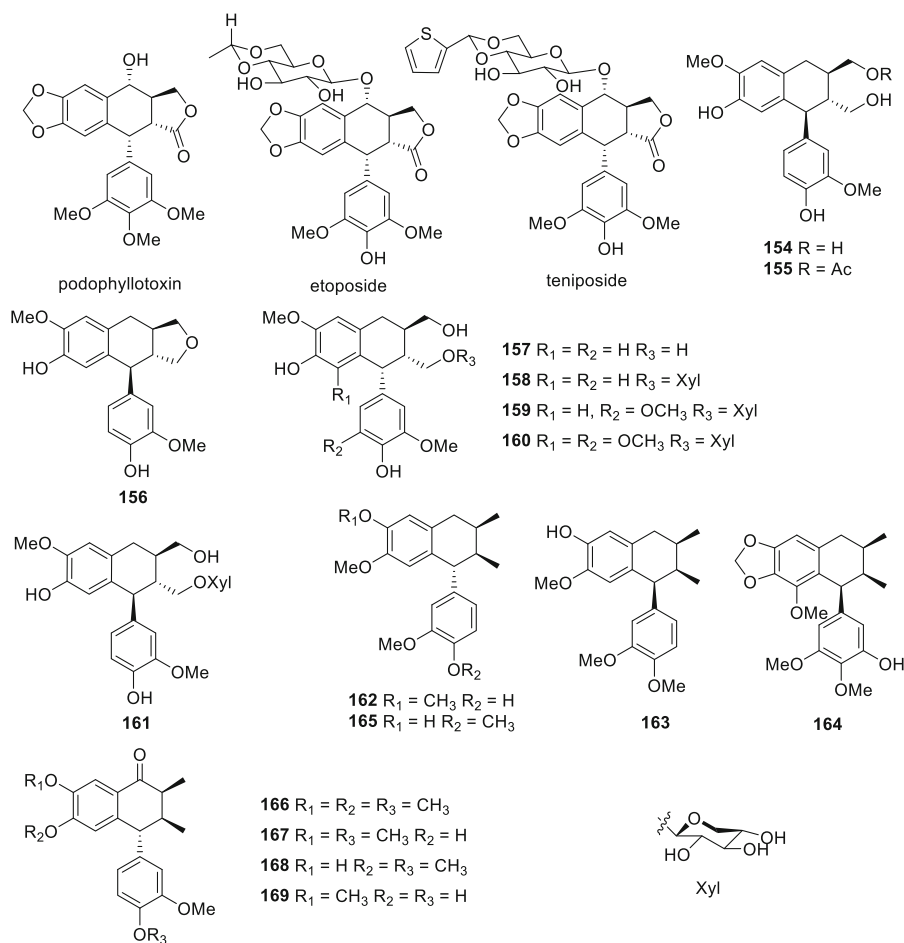
HIV activity than their aglycone diphylin (**11**). Compound **153** also exhibited potent inhibitory activity against Zika virus (ZIKV) infection in vitro and in vivo, a mosquito-borne *flavivirus* that causes microcephaly and severe brain malformations in fetus. It blocked ZIKV infection in African greenmonkey kidney epithelial cells (VERO), human fibroblast cells (HT1080), and human microglial cells (CHME3) with EC_{50} values between 0.01–0.03 μM. The result was confirmed in vivo by using type I interferon receptor knockout mouse model C57BL/6 *Ifnar1*$^{-/-}$. Compound **153** also showed a broad spectrum inhibition against other Flaviviridae viruses including DENV1, tick-borne encephalitis virus (TBEV), West Nile virus (WNV), JEV and EBV with the EC_{50} values ranged between 0.12–1.0 μM (Martinez-Lopez et al. 2019).

Aryltetralin-type lignans
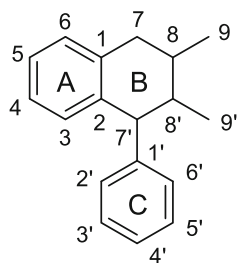
Aryltetralin lignans have a 10-membered bicyclic core, with two aromatic ring systems. Unlike aryl-naphthalene lignans, which involve all three rings being aromatized, aryltetralin lignans have a variety of configurations possible in the non-aromatic ring (ring B) formed by fusion of the two phenylpropanoid units. This leads to a greater diversity of possible isomers and stereochemical outcomes in aryltetralin lignans. We have included lignans bearing a dialin ring-system in this section, since they also contain stereocenters in the core of the molecule and are not typically recognized as a separate class of lignans. The most well-known lignan of this type of compounds may be podophyllotoxin. The compound was discovered from *Podophyllum peltatum* L. in 1880 (Cragg et al. 2011). Two of its derivatives, etopside and teniposide, were granted as anticancer medications by the US FDA in 1983 and 1992, respectively (Hande 1998; Cragg and Newman 2005).
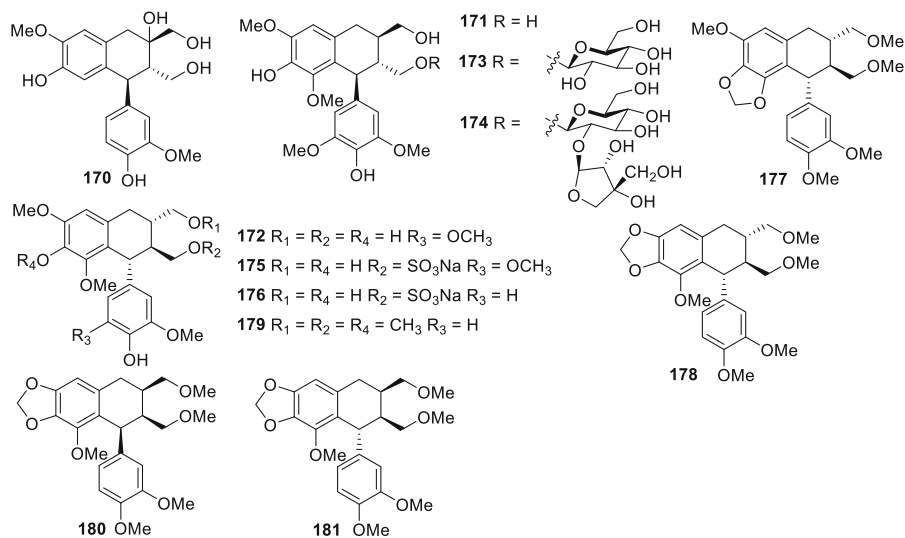
During the time covered by this review, 31 aryltetralin lignans isolated from plants were tested for antiviral activity (**154–181**, **224–226**) (see Table 1 for source plants, antiviral activities, and references). Of the plant-derived aryltetralin lignans, only compounds **157**, **162**, and **165** displayed antiviral activity at concentrations below 5 μM. There were three studies on synthetic podophyllotoxin analogues which displayed significant antiviral activities and provided information about structure–activity relationships.

podophyllotoxin

etoposide

teniposide

154 R = H
155 R = Ac

156

157 $R_1 = R_2 = H$ $R_3 = H$
158 $R_1 = R_2 = H$ $R_3 = Xyl$
159 $R_1 = H$, $R_2 = OCH_3$ $R_3 = Xyl$
160 $R_1 = R_2 = OCH_3$ $R_3 = Xyl$

161

162 $R_1 = CH_3$ $R_2 = H$
165 $R_1 = H$ $R_2 = CH_3$

163

164

166 $R_1 = R_2 = R_3 = CH_3$
167 $R_1 = R_3 = CH_3$ $R_2 = H$
168 $R_1 = H$ $R_2 = R_3 = CH_3$
169 $R_1 = CH_3$ $R_2 = R_3 = H$

Xyl

In an ongoing study of the chemical composition of *Streblus asper* Lour. (Moraceae, Guangxi, China), Li et al. isolated (-)-isolariciresinol (**157**) and 9-β-xylopyranosyl-(-)-isolariciresinol (**158**) from the plant's roots. In tests for potential inhibition of the secretion of HBV s antigen (HBsAg) and HBV e antigen (HBeAg), and the replication of HBV DNA in HBV-infected HepG2.2.15 cells, compounds **157** and **158** displayed anti-HBV activity of EC_{50} values of 3.67 and 6.98 μM for HBsAg with TI values 35.28 and 30.15, and EC_{50} values of 14.67 and 26.74 μM for HBeAg with TI values 8.82 and 7.87, respectively. In addition, the compounds showed inhibitory activity on the replication of HBV DNA with EC_{50} values of 12.72 and 17.68 μM and TI of 10.18 and 11.90, respectively (Li et al. 2013). Compounds **158**, 5-methoxy-9-β-xylopyranosyl-(-)-isolariciresinol (**159**) and 9-β-xylopyranosyl-lyoniresinol (**160**) were obtained from the stem bark. The only difference of

160 from **158** is that it contains an extra methoxyl group in ring C, and its difference from **159** is that it is lacking an methoxyl group in ring A. Compounds **158** and **159** inhibited the expression of HBsAg and HBeAg with EC_{50} values of 6.58 and 39.56 μM for HBsAg (TI > 2), and 24.86 μM (TI = 8.06) and 61.23 μM (TI = 1.75) for HBeAg, respectively, while **160** showed no activity against HBV at the concentration of 1000 μM (Li et al. 2012a).

Three new aryltetralin lignans, sinensisins A-C (**162–164**) and the known (8R,7'R,8R)-5-hydroxy-4,3',4'-trimethoxy-2,7'-cyclolignan (**165**) were isolated from the aerial parts of *Schisandra propinqua* (Wall.) Hook. F. et Thoms. var. *sinensis* Oliv. (Sichuan, China) and tested for HIV-1 inhibitory effects in a microtiter syncytium formation infectivity assay. Among them, both **162** and **165** displayed anti-HIV-1 activity with EC_{50} values of 4.5 μM and TI values of 6.7 (Li et al. 2012b, 2009a; Lei et al. 2007).

170 · **171** R = H · **173** R = · **174** R = · **177** · **172** R$_1$ = R$_2$ = R$_4$ = H R$_3$ = OCH$_3$ · **175** R$_1$ = R$_4$ = H R$_2$ = SO$_3$Na R$_3$ = OCH$_3$ · **176** R$_1$ = R$_4$ = H R$_2$ = SO$_3$Na R$_3$ = H · **179** R$_1$ = R$_2$ = R$_4$ = CH$_3$ R$_3$ = H · **178** · **180** · **181**
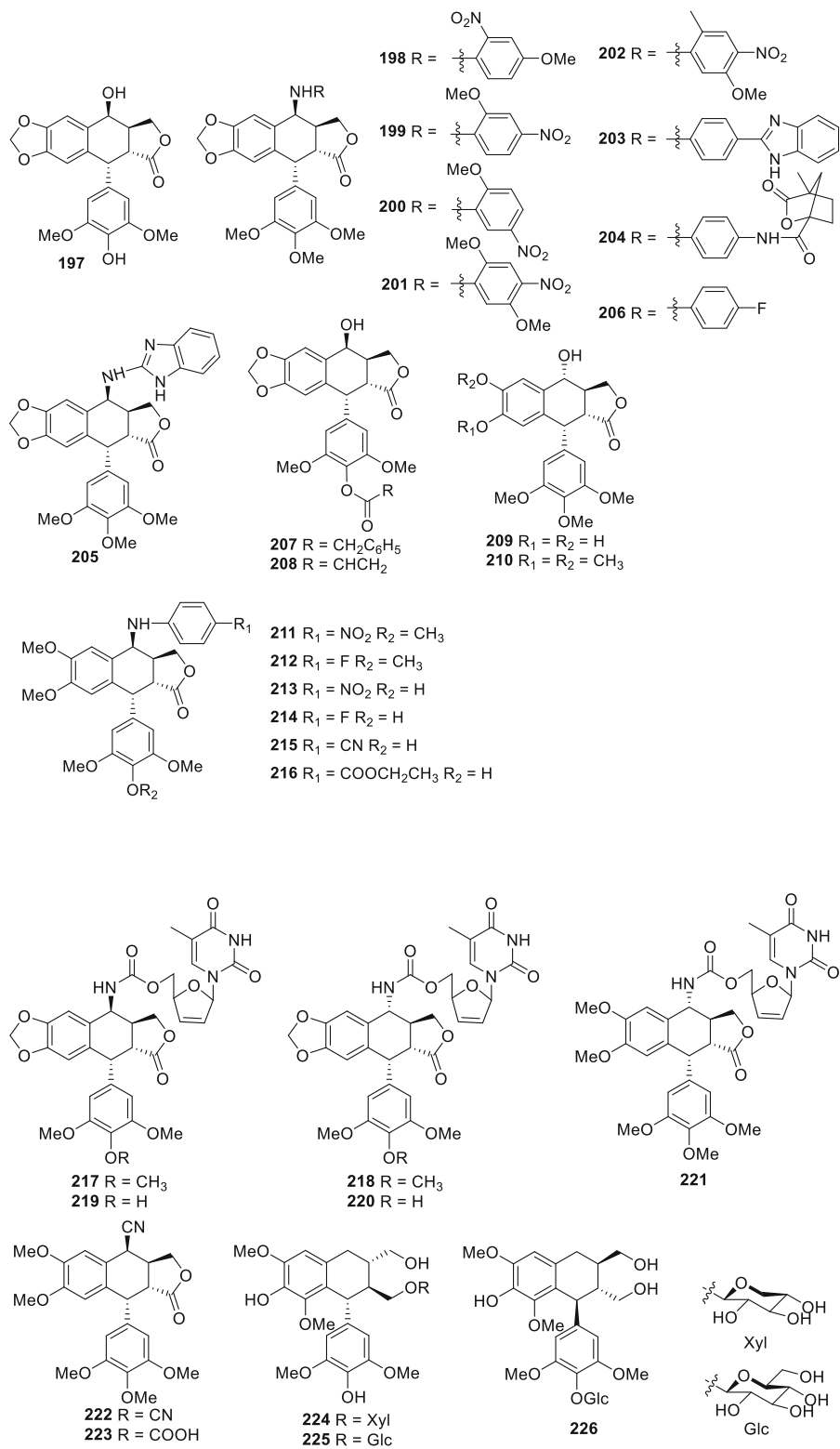
Thirteen podophyllotoxin derivatives (**182–194**) containing modifications in the phenyl C-ring or the lactone ring were prepared and evaluated for their antiherpetic activity against HSV-2 on Vero cells. Among them, phenazines **192** and **193** showed the highest antiviral potency against HSV-2 (Castro et al. 2003).
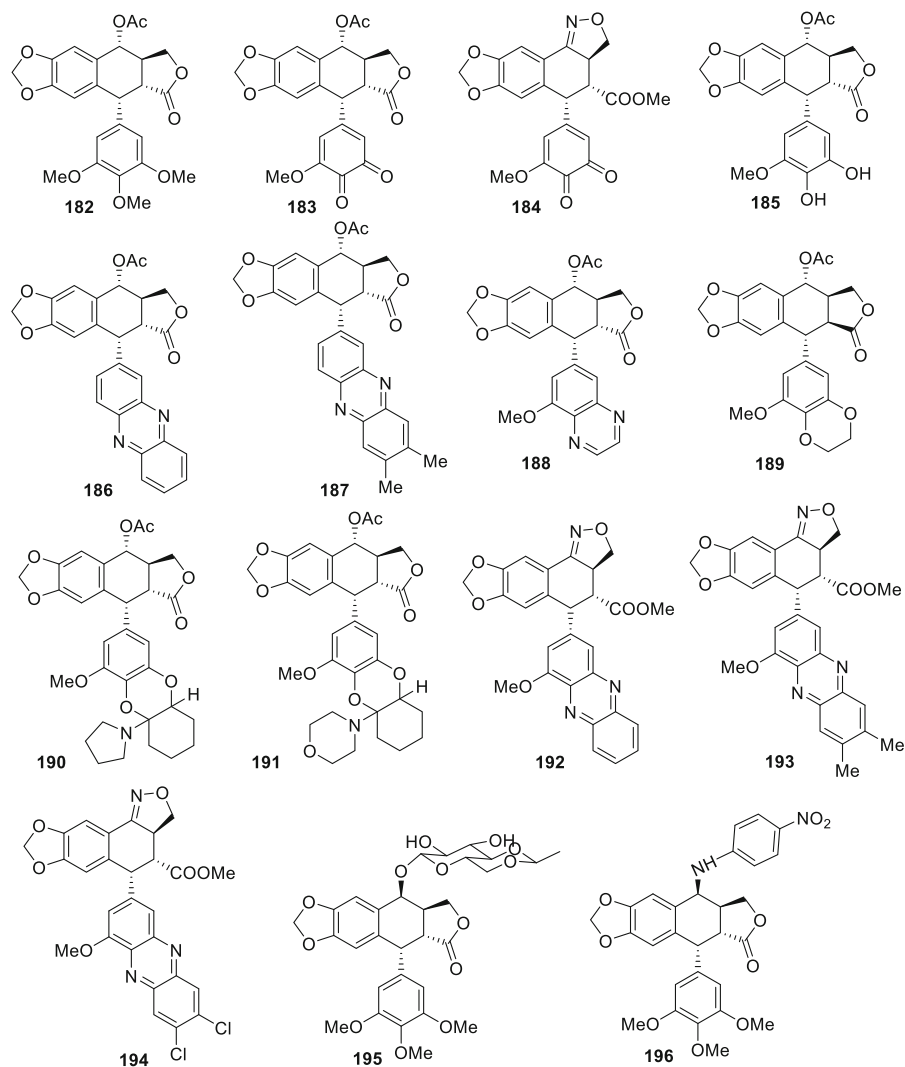
A series of derivatives (195–216) of podophyllo-toxin with structural modifications mostly at C-7 were synthesized and tested for their inhibitory effects of HIV-1 replication in acutely infected H9 cells. Among the derivatives, the 4-amino derivatives 213–216 were the strongest HIV inhibitors exhibiting EC$_{50}$ values of < 0.002 μM and TI values > 120. The 4-amino substituted compounds 199 and 203 also displayed strong HIV activity with EC$_{50}$ values of 0.021 and < 0.002 μM and TI values of 19.1 and > 16, respectively. The 4β-hydroxyl containing compound

197 and its corresponding vinyl carbamate 208 were the strongest HIV inhibitors among the non-nitrogen containing derivatives with EC$_{50}$ values of 0.14 and 0.072 μM, respectively. However, compound 210, which contains a 4α-hydroxyl group showed less inhibitory activity with an EC$_{50}$ value of 0.90 μM and a TI value of 19.4. Comparison of the anti-HIV activity of these derivatives suggested that the methylenedioxy group of C-4 and C-5 being substituted by two methoxy groups enhanced the anti-HIV activity (Zhu et al. 2004).

198 R =

199 R =

200 R =

201 R =

202 R =

203 R =

204 R =

206 R =

197

205

207 R = CH₂C₆H₅
208 R = CHCH₂

209 R₁ = R₂ = H
210 R₁ = R₂ = CH₃

211 R₁ = NO₂ R₂ = CH₃
212 R₁ = F R₂ = CH₃
213 R₁ = NO₂ R₂ = H
214 R₁ = F R₂ = H
215 R₁ = CN R₂ = H
216 R₁ = COOCH₂CH₃ R₂ = H

217 R = CH₃
219 R = H

218 R = CH₃
220 R = H

221

222 R = CN
223 R = COOH

224 R = Xyl
225 R = Glc

Xyl

Glc

226

In 2007, a new series of podophyllotoxin derivatives (**217–223**) some of which contained the antiviral drug molecule stavudine and different structural podophyllotoxin analogues were designed, synthesized, and tested for their inhibitory activity against HIV-1 replication in acutely infected C8166 cells by Tu et al. Among these compounds, **219** and **220** showed the highest anti-HIV-1 activities with EC_{50} values of 0.29 and 0.17 μM and TI values of 354.5 and 466.9, respectively. Moreover, the 7β–cyano-substituted 4,5–dimethoxy compound **222** also showed promising anti-HIV activity (EC_{50} = 1.05 μM and TI = 131.28). However, compound **223**, which is a carboxylic acid derivative of podophyllotoxin obtained by hydrolyzation of **222**, was significantly less active than **222** with an EC_{50} value of 46.90 μM and a TI value > 9.31 (Chen et al. 2007).

Dibenzylbutyrolactone-type lignans
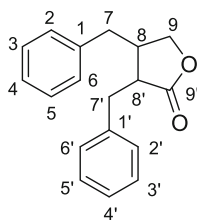
dibenzylbutyrolactone lignans

Dibenzylbutyrolactone lignans are defined by the presence of a five-membered lactone ring formed by the cyclization of oxidized C-9 and C-9′ carbons. Similar to the aryltetralin lignans, this type of lignan may possess a wide variety of relative and absolute configurations, leading to a large number of isomers. The lactone ring in dibenzylbutyrolactone lignans is reminiscent of the lactones frequently observed in the structures of the previously discussed arylnaphthalene and aryltetralin lignans. Most of this type of lignan showed insignificant antiviral activity, although a few of them were studied in mice for their antiinfluenza activity.

From 1998 to 2019, 22 dibenzylbutyrolactone lignans were isolated from plants and tested for antiviral activity (**227–248**) (see Table 1 for source plants, antiviral activities, and references). Compounds **236**, **243**, **245**, and **248** are worthy of additional discussion due to their potent antiviral activity ($\leq$ 1 μM). Interestingly, considering the potent activity of the four aforementioned potently active compounds, we could find no studies on antiviral activities of synthetic dibenzylbutyrolactone lignans.
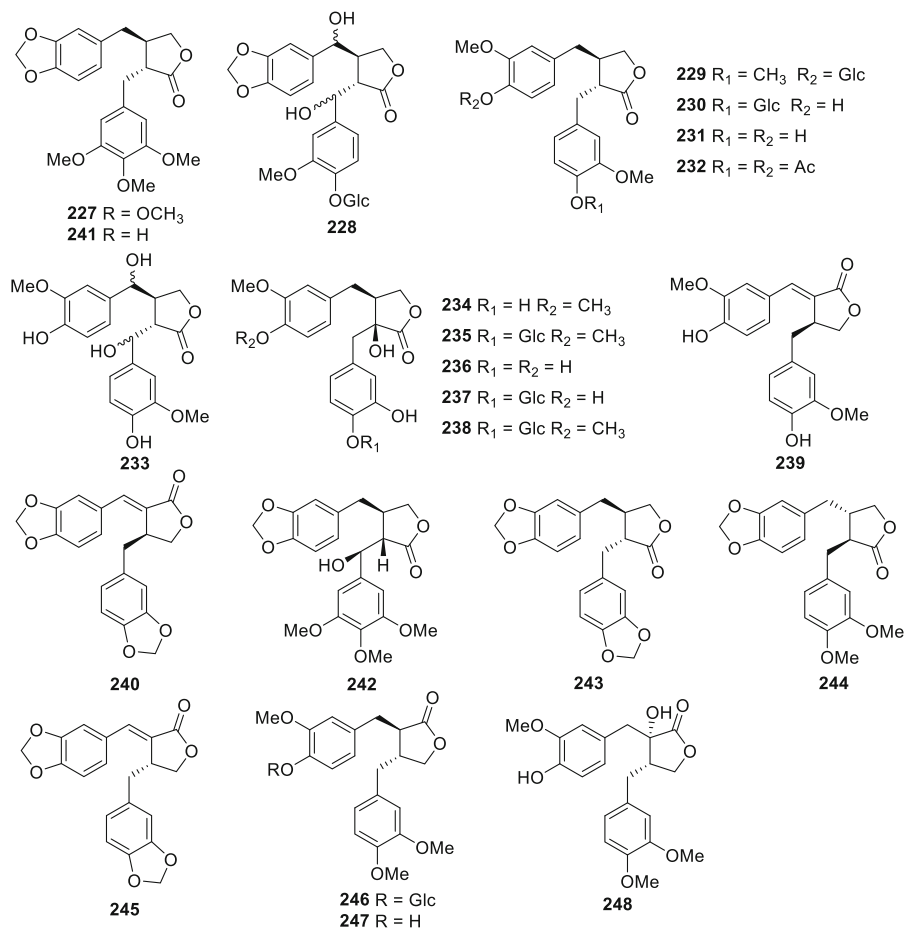
Phenaxolactones 1–5 (**234–238**) were isolated from the leaves of *Phenax* spp. (Urticaceae, USA). Compound **234** showed anti-HIV activity with an EC_{50} value of 3.0 μM and TI value of 37.3. Compound **236** exhibited increased anti-HIV activity with an EC_{50} value of 0.8 μM but lower TI value of 12.5, while **237**, the glycosylated derivative of **236,** showed less activity with an EC_{50} of 2.8 μM and TI of 6.4. Moderate antiviral activity was observed for **235** (EC_{50} of 5.0 μM and TI of 15.0) and **238** (EC_{50} of 5.2 μM and TI of 14.4) (Piccinelli et al. 2005; Rastrelli et al. 2001).

Hinokinin (**243**), isolated from a *Phyllanthus* species, significantly inhibited both HBsAg and HBeAg production with inhibitions of 33.9% and 68.3% at a concentration of 50 μM, respectively. (+)–*trans*–8-(3,4-(Methylenedioxybenzyl)-8′-(3′,4′-dimethoxybenzyl)-butyrolactone (**244**), and a tannin virgatyne were found to have no antiviral activity

(Huang et al. 2003a). Purified from the heartwood of *Chamaecyparis obtusa* (Cupressaceae, Taiwan, China), **243** and savinin [**245**, the enantiomer of isogadian (**240**)] showed high inhibitory activity in the cell-based assay utilizing CPE on Vero E6 cells via SARS-CoV infection at the concentration of 20 μM. In the evaluation for inhibition of SARS-CoV replication using ELISA, **243** had an EC_{50} value higher than 10 μM, but the EC_{50} value of **245** was determined to be much more potent with a value of 1.13 μM (TI > 667). In the test for inhibitory effect of SARS-CoV 3CL protease activity, **243** and **245** displayed EC_{50} values of > 100 and 25 μM, respectively, and a *Ki* value for **245** was determined to be 9.1 μM in the study of the inhibitory mechanism (Wen et al. 2007). Isolated from the root bark of *Zanthoxylum ailanthoides* (Rutaceae, Taiwan, China) as well, hinokinin (**243**) displayed significant anti-HIV-1 activity with an EC_{50} value of < 0.28 μM and a TI value of > 18.7 in

the test for inhibition of HIV replication (Cheng et al. 2005b).

Trachelogenin (**248**), obtained from the stems and leaves of *Trachelospermum jasminoides* (Lindl.) Lem., exhibited anti-HCV potential with EC_{50} values of 0.87 μM (in HCVcc model) and 0.69 μM (in HCVpp model). Compound **248** was a HCV entry inhibitor by interfering with the interactions between HCV glycoprotein E2 and the host entry factor CD81 (Qian et al. 2016).
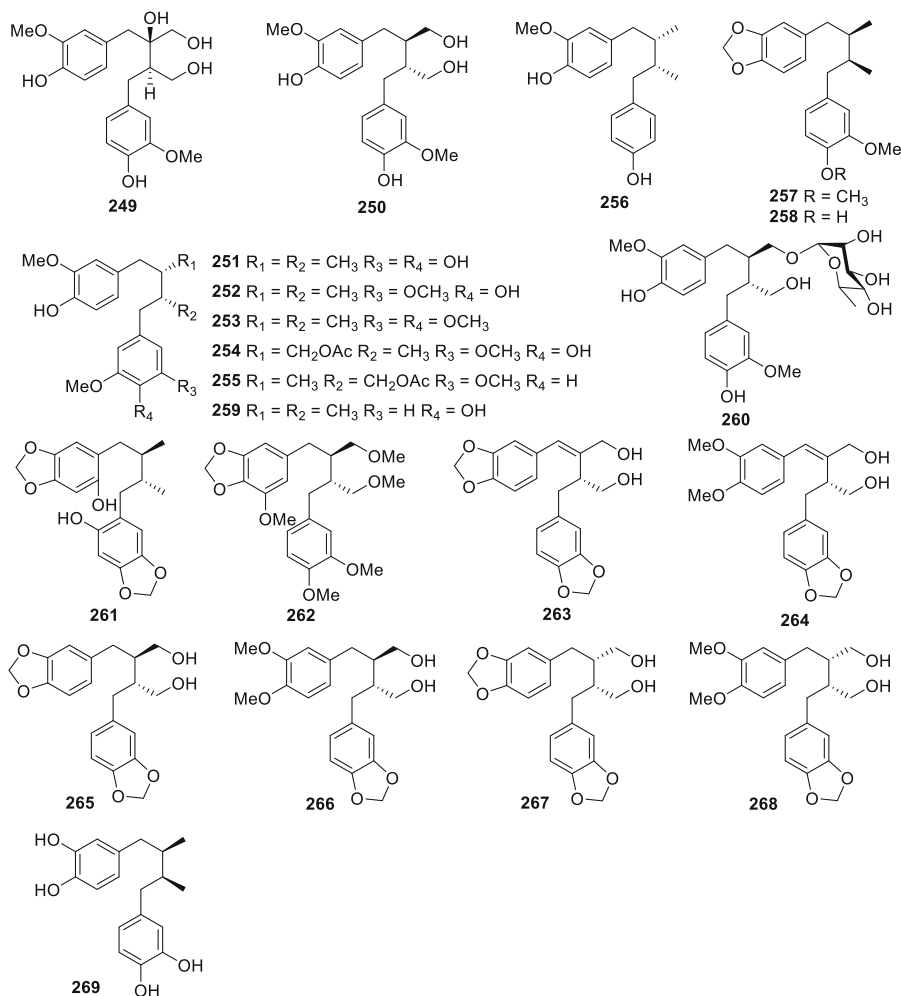
Dibenzylbutane-type lignans
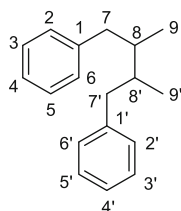
dibenzylbutane lignans

Dibenzylbutane lignans bear the least modified connections between the 8 and 8′ carbons of the phenylpropanoid precursors. This class also contains a large number of stereoisomers due to the chiral carbons created by linking C-8 to C-8′. The carbons derived from C-9 and C-9′ are found in a variety of oxidation states varying from methyl groups to carboxylic acid functionalities. As with benzylbutyrolactones, this type of lignans is also lacking lead molecules that show attractive antiviral activities.

We found records of 29 dibenzylbutyrolactone lignans isolated from plants and tested for antiviral activity (**249–262**, **269**, **280–287**) (see Table 1 for source plants, antiviral activities, and references). Compounds **259** and **285** displayed the most activity in antiviral assays (< 5 μM). There were 10 synthetic dibenzylbutryolactones published between 1998 and 2020, most of which were modeled off of nordihydroguaiaretic acid (NDGA) (**269**).

249 **250** **256** **257** R = CH$_3$ **258** R = H

251 R$_1$ = R$_2$ = CH$_3$ R$_3$ = R$_4$ = OH
252 R$_1$ = R$_2$ = CH$_3$ R$_3$ = OCH$_3$ R$_4$ = OH
253 R$_1$ = R$_2$ = CH$_3$ R$_3$ = R$_4$ = OCH$_3$
254 R$_1$ = CH$_2$OAc R$_2$ = CH$_3$ R$_3$ = OCH$_3$ R$_4$ = OH
255 R$_1$ = CH$_3$ R$_2$ = CH$_2$OAc R$_3$ = OCH$_3$ R$_4$ = H
259 R$_1$ = R$_2$ = CH$_3$ R$_3$ = H R$_4$ = OH

260 **261** **262** **263** **264**

265 **266** **267** **268**

269

Nordihydroguaiaretic acid (NDGA) (**269**), a lignan obtained from the leaves and twigs of *Larrea tridentate*, was evaluated for its anti-dengue virus (DENV) effects. It displayed a dose-dependent inhibitory effects on the viral yield and nonstructural protein-1 secretion in the supernatants of infected cells treated for 24 and 48 h. In DENV4 replicon-transfected Vero cells, treatment with **269** at 50 and 100 µM significantly reduced DENV replication. Furthermore, treatment with this compound not only led to the reduction in the number of lipid droplets (LDs), the neutral lipid storage organelles involved in DENV morphogenesis that are known to proliferate during DENV infection, but also resulted in dissociation of the C protein from LDs (Soto-Acosta et al. 2014). Compound **269** was assessed for its ability to elicit HIV replication. It was demonstrated to increase the HIV-1 p24 antigen two

fold at the concentration of 15 µM. In addition, the treatment of **269** at 15 µM also increased reactive oxygen species production in U1 cells up to 140% compared with control cells (Barquero et al. 2014). Compound **269** was tested as an HPV16 E6 gene inhibitor. This compound was shown to inhibit HPV16 E6 mRNA expression, influence E6 gene transcription, and induce decreased protein expression levels of E6 and p53 (Chen et al. 2008). In an investigation on host lipid/fatty acid synthesis and the HCV life cycle, **269** canceled the HCV-induced alteration of host lipid homeostasis. This compound not only reduced sterol regulatory element-binding protein activation and increased the expression of the genes involved in β-oxidation, but it also inhibited very-low-density lipoprotein (VLDL) secretion by affecting mediators of VLDL biosynthesis. Whereas HCV induced the

accumulation and perinuclear distribution of LDs, **269** decreased the overall number and increased the average size of the LDs (Syed and Siddiqui 2011). Furthermore, when **269** was added simultaneously with the virus, it could inhibit Junin viral replication (Konigheim et al. 2005).

concentration of 5.0 μM. Furthermore, at 100 μM, **270** was harmless towards 174 × CEM cells and H9 cells (Huang et al. 2003b).

Nine synthesised NDGA derivatives **271–277**, Mal.4 (**278**), and M₄N (**279**) inhibited Tat transactivation in a dose-dependent manner. At 80 μM, these compounds
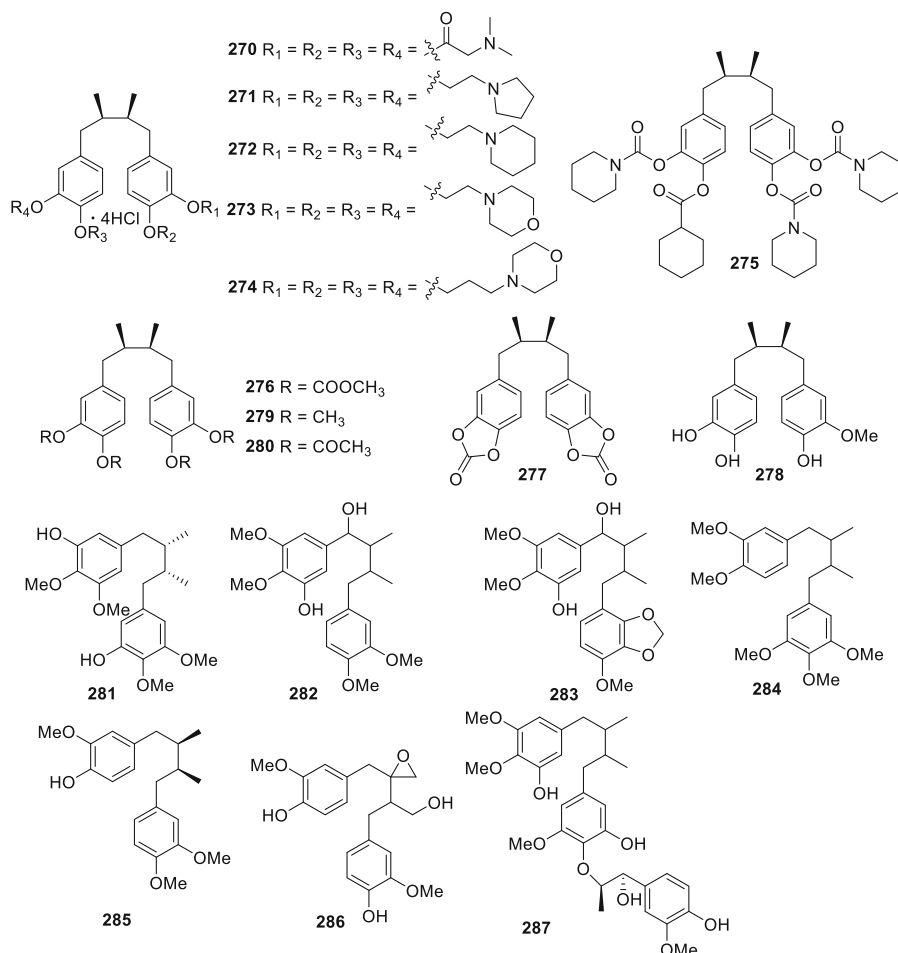
Tetra-*O*-glycyl-*NDGA* (**270**), a water-soluble derivative of **269**, competed effectively with the DNA binding domain of recombinant Sp1 protein to bind to the HIV long terminal repeat, as determined by an electrophoretic mobility-shift assay. By inhibiting Sp1 binding to the HIV long terminal repeat, **270** repressed Sp1-regulated HIV Tat transactivation and replication in cultured cells, with an EC_{50} of 12 μM. Moreover, replication of simian immunodeficiency virus was completely blocked by **270** at a

blocked Tat-regulated secreted alkaline phosphatase production by > 90%; and at 20 μM, the inhibition was still > 50%. All of these newly synthesized derivatives showed a greater inhibitory activity than the parent NDGA **269** (EC_{50} = 20 μM) and Mal.4 (**278**, EC_{50} = 25 μM). Except for compounds **271** (EC_{50} = 17.2 μM) and **273** (EC_{50} = 17.3 μM), all other NDGA derivatives demonstrated greater potency than M₄N (**279**, EC_{50} = 11.1 μM). Compound **272** (EC_{50} = 0.88 μM) was determined to be the strongest inhibitor

of HIV Tat-regulated transactivation among all of the new NDGA derivatives (Hwu et al. 2008). Furthermore, three synthesized NDGA derivatives, tetra-acetyl NDGA (**280**), **278** and **279**, were all demonstrated to inhibit gene expression from the early promoter P_{97} of HPV16. Using luciferase activity as the indicator of gene expression, compounds **278** and **279** were shown to be active in a dose-dependent manner. However, **280** ($EC_{50} = 11$ μM) was shown to be a better inhibitor of the HPV P_{97} promoter activity than **278** ($EC_{50} = 37$ μM) and **279** ($EC_{50} = 28$ μM). These compounds demonstrated very little effect on the gene expression guided by the ADV major late promoter and the CMV promoter (Craigo et al. 2000; Halim et al. 2013). Compound **279** inhibited 10 passages of HSV-1 and 4 passages of HSV-2 with the EC_{50} values ranges 4–11.7 μM, while the EC_{50} ranges of ACV increased from 7 μM to 444 μM. The results indicated that **279** had less drug resistance than ACV. Compound **279** inhibited HSV by decreasing the expression of the HSV immediate early gene α-ICP4 with an EC_{50} value of 43.5 μM, which was essential for HSV replication (Chen et al. 1998).
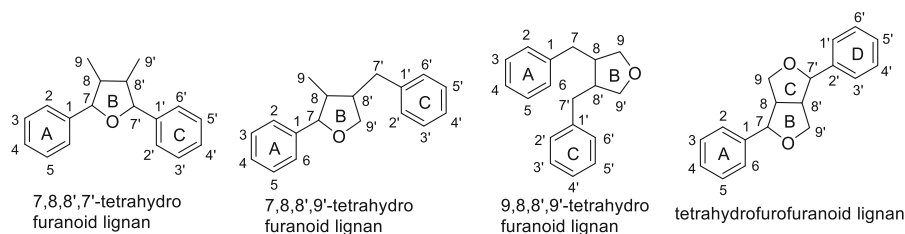
Compound **281**, 3,3′-Dihydroxy-4,4′,5,5′-tetramethoxylignan, was isolated from the fruits of *Schisandra rubriflora* (Yunan, China). It showed inhibitory activity on HIV-1$_{IIIB}$ induced syncytium formation with an EC_{50} value of 5.8 μM and a TI value of 4.46 (Xiao et al. 2010a). Kadangustins H (**282**) and I (**283**), *meso*-dihydroguaiaretic acid (**259**), tiegusanin N (**284**), *meso*-monomethyldihydroguaiareticacid (**285**) and **279** were isolated from the stems of *Kadsura angustifolia* (Yunnan, China). The compounds showed anti-HIV activity with EC_{50} values of 27.0, 21.5, 15.6/4.0, 2.9 and 14.8 μM, and TI values of 2.8, 1.1, 3.2/6.2, 5.8 and 2.0, respectively (Gao et al. 2008; Li et al. 2009b).
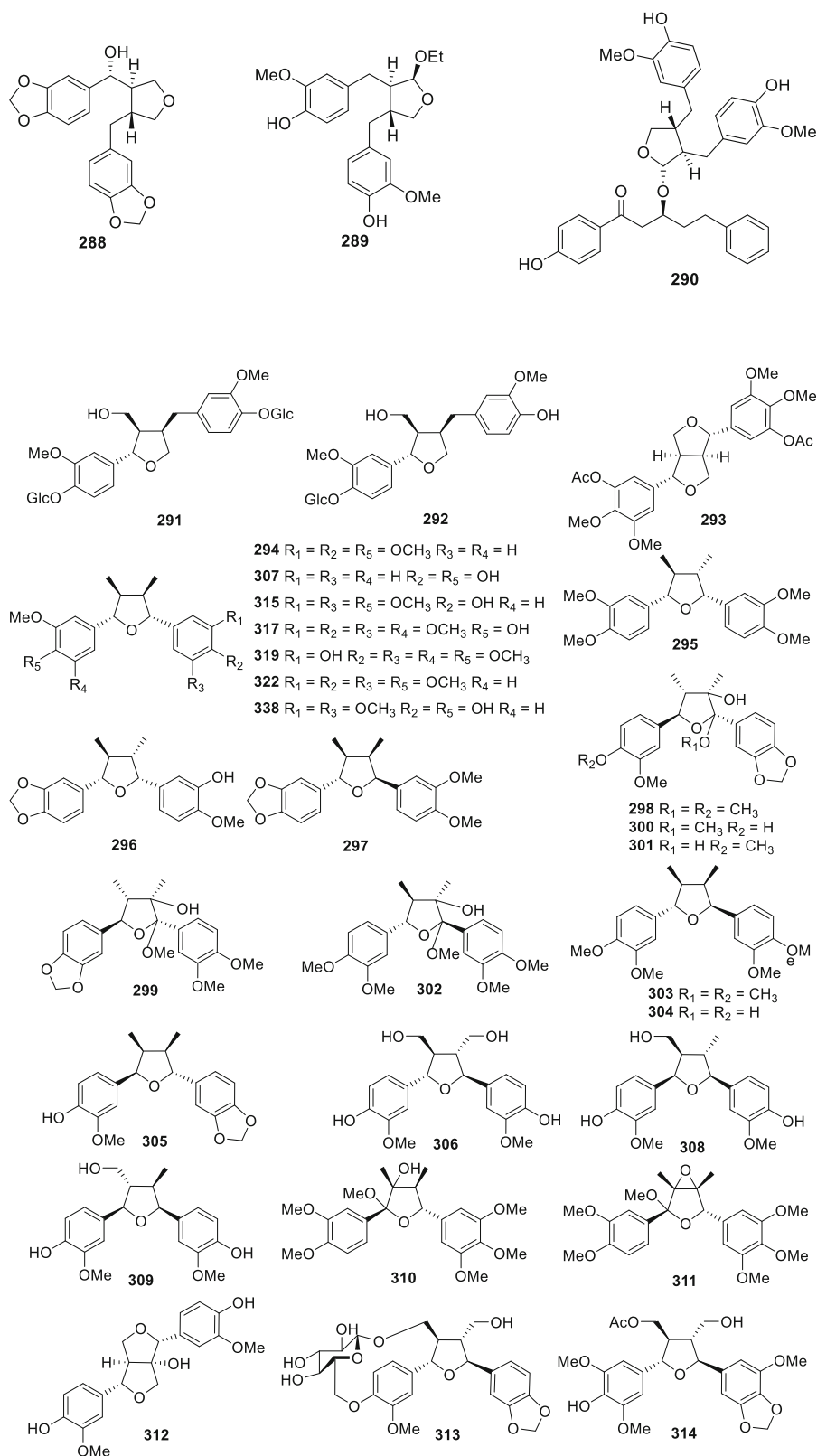
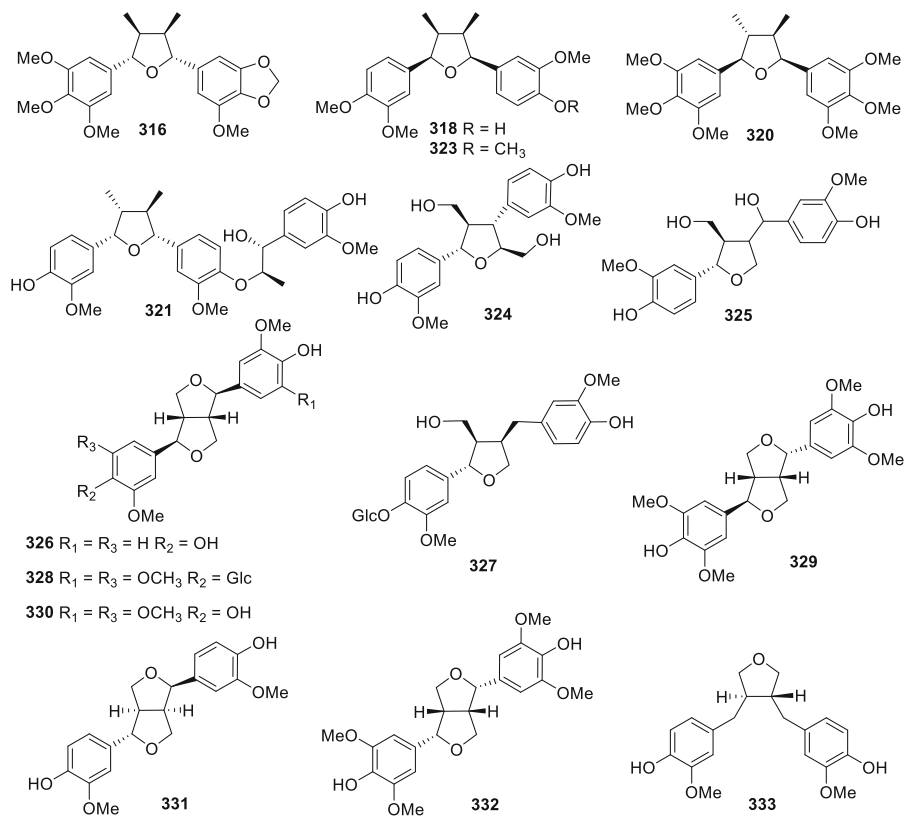## Tetrahydrofuranoid and tetrahydrofurofuranoid-lignans

Tetrahydrofuranoid lignans have a characteristic five-membered oxygen-containing ring connecting the two phenylpropanoid precursor units. This ring can be derived from a C-7 and C-8 to C-7′ and C-8′ linkage (7,8,8′,7′-tetrahydrofuranoid lignans, compounds **294–311, 313–323, 334–336, 338, 340, 379–388**), a C-7 and C-8 to C-8′ and C-9′ linkage (7,8,8′,9′-tetrahydrofuranoid lignans, compounds **291, 292, 324, 325, 327, 337, 339, 344, 346, 347, 376–378, 390** and **391**), or a C-8 and C-9 to C-8′ and C-9′ linkage (9,8,8′,9′-tetrahydrofuranoid lignans, compounds **288–290, 333** and **389**). This diversity of precursor orientations, combined with the possibility of stereoisomers leads to a large diversity of possible isomers being isolated. Tetrahydrofurofuranoid lignans are defined by the presence of a bicyclic furofuran ring-system formed by the connection of C-7 to C-9′ through an oxygen atom, and a connection between C-9 and C-7′ through an oxygen atom (tetrahydrofurofuranoid lignans, compounds **293, 312, 326, 328–332, 341–343, 345, 348–375**).
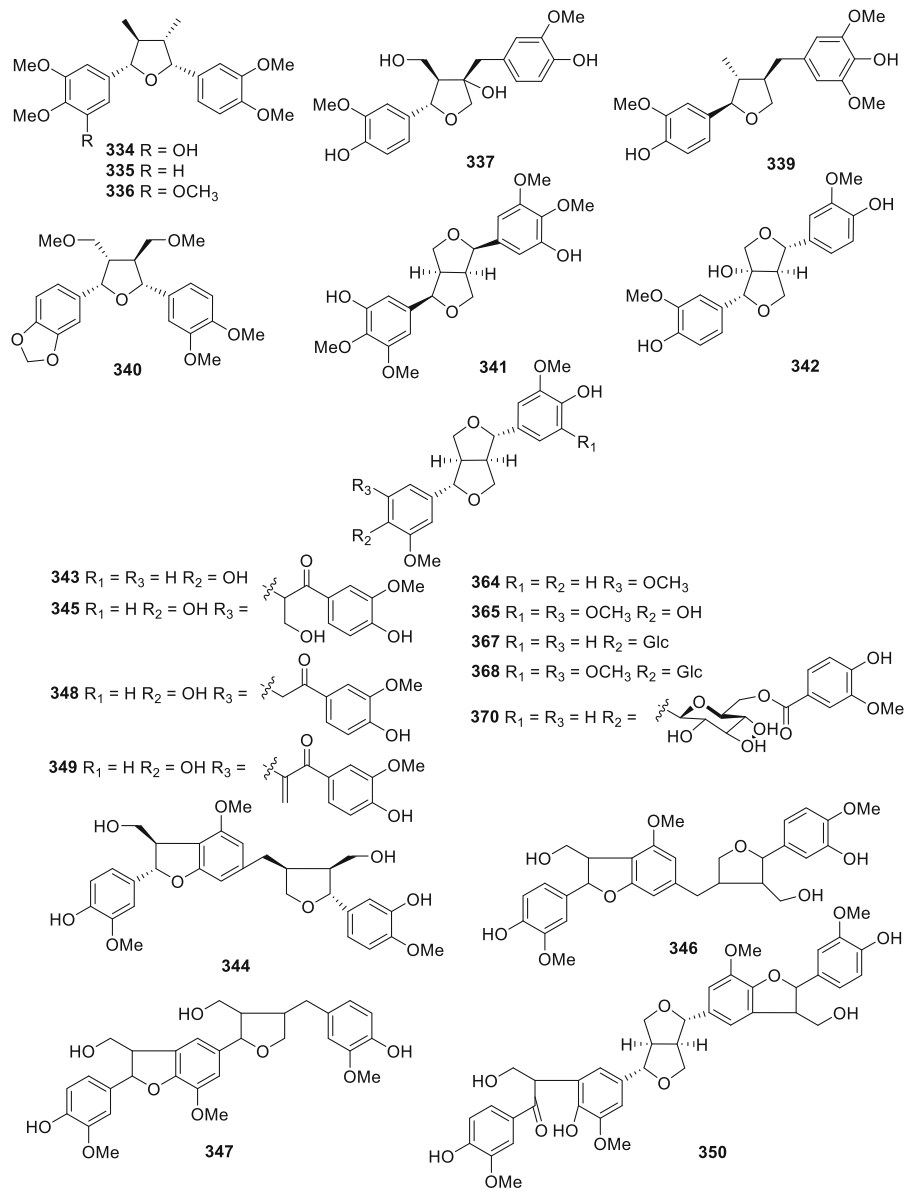
The antiviral activity of 104 plant-derived tetrahydrofuranoid and tetrahydrofurofuranoid lignans were reported between 1998 and 2020 (**288–391**) (see Table 1 for source plants, antiviral activities, and references). Five compounds in this class (**290, 379–381, 388**) displayed antiviral activity at concentrations of 1 μM or less. We did not find any antiviral studies on synthetic tetrahydrofuranoid or tetrahydrofurofuranoid lignans during the time period covered in this review.
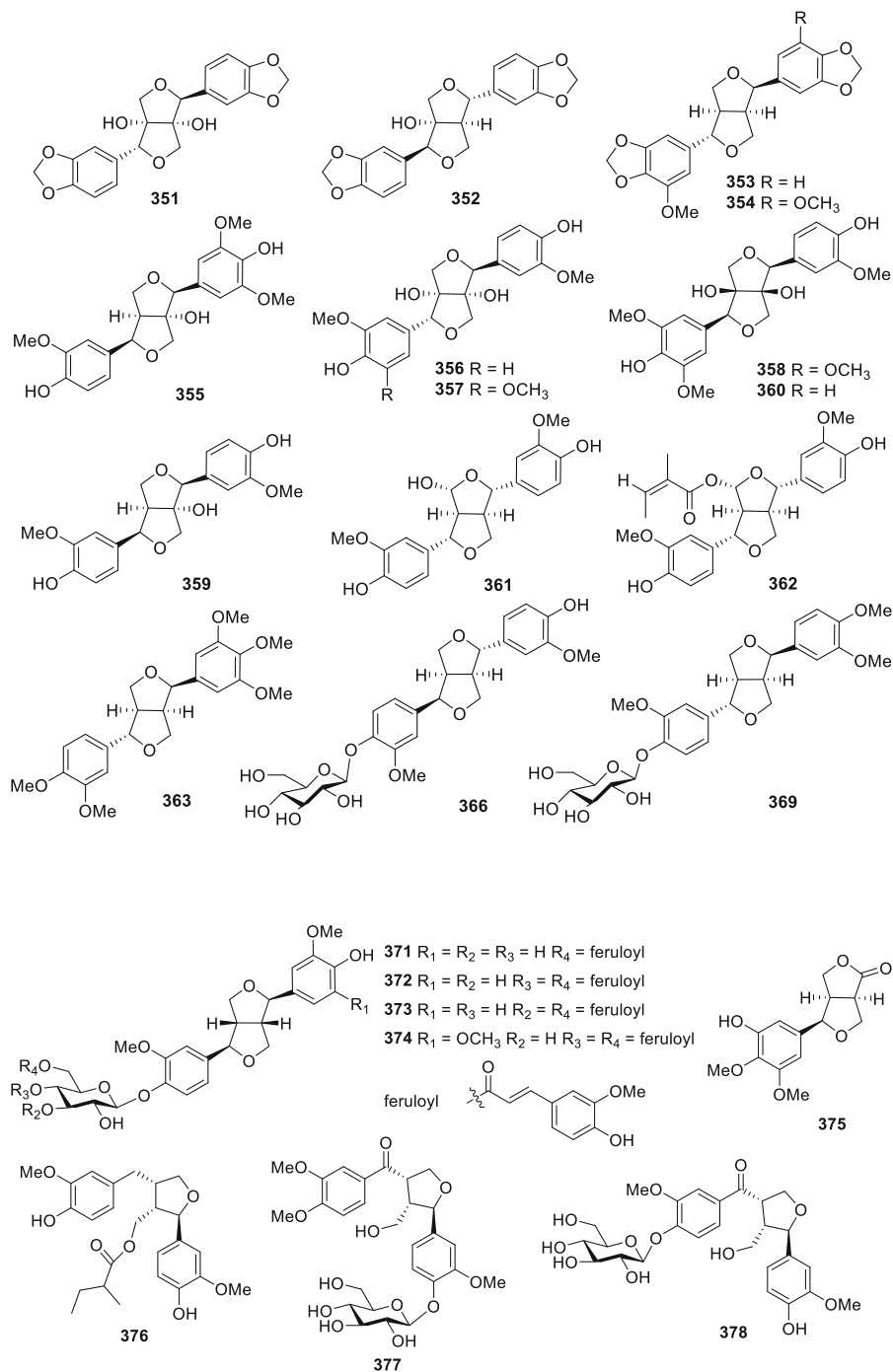
4,4′-Dihydroxy-3,3′-dimethoxy-9-ethoxy-9,9′-epoxylignan (**289**) and daphnenin (**290**), are two lignans that were isolated from the stems of *Daphne acutiloba* (Thymelaeceae, Yunan, China). Compound **290** showed anti-HIV activity with an EC_{50} value of 0.64 μM (Huang et al. 2012).
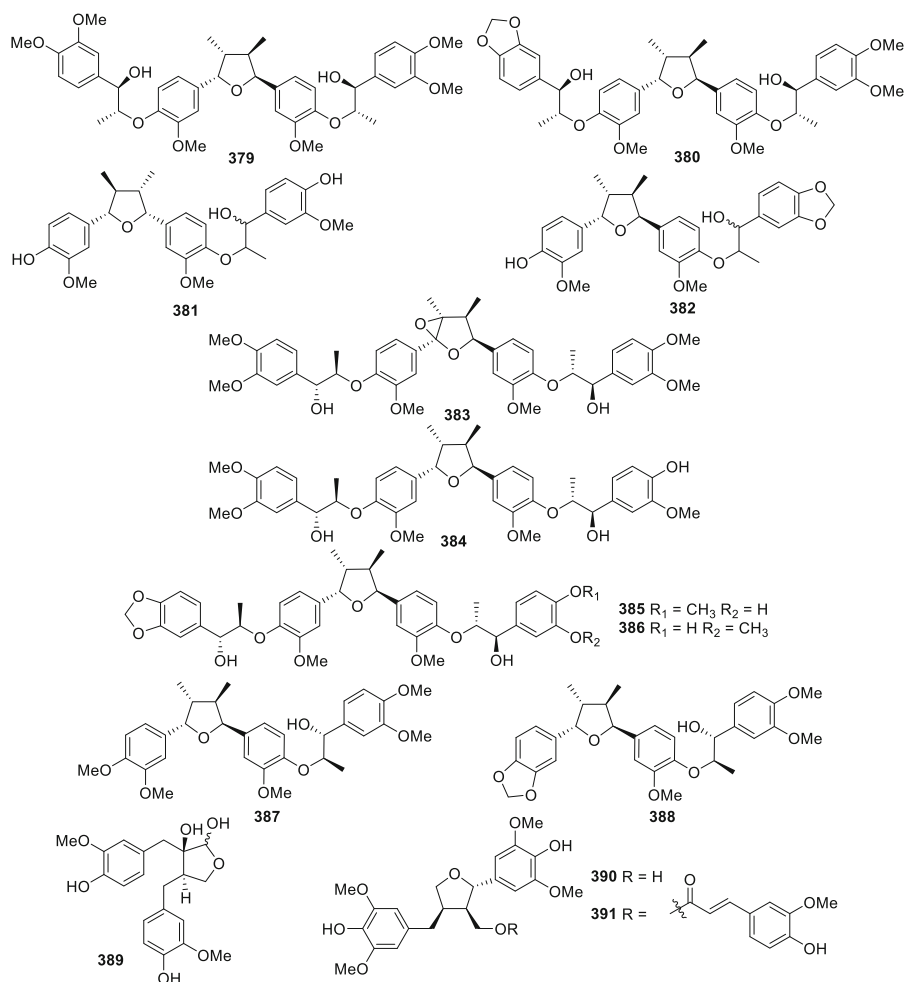

7,8,8′,7′-tetrahydro furanoid lignan

7,8,8′,9′-tetrahydro furanoid lignan

9,8,8′,9′-tetrahydro furanoid lignan

tetrahydrofurofuranoid lignan

The structures of compounds **288** through **314** are shown, each labeled with its compound number.

294 $R_1 = R_2 = R_5 = OCH_3$ $R_3 = R_4 = H$
307 $R_1 = R_3 = R_4 = H$ $R_2 = R_5 = OH$
315 $R_1 = R_3 = R_5 = OCH_3$ $R_2 = OH$ $R_4 = H$
317 $R_1 = R_2 = R_3 = R_4 = OCH_3$ $R_5 = OH$
319 $R_1 = OH$ $R_2 = R_3 = R_4 = R_5 = OCH_3$
322 $R_1 = R_2 = R_3 = R_5 = OCH_3$ $R_4 = H$
338 $R_1 = R_3 = OCH_3$ $R_2 = R_5 = OH$ $R_4 = H$

298 $R_1 = R_2 = CH_3$
300 $R_1 = CH_3$ $R_2 = H$
301 $R_1 = H$ $R_2 = CH_3$

303 $R_1 = R_2 = CH_3$
304 $R_1 = R_2 = H$

316

318 R = H
323 R = CH$_3$

320

321

324

325

326 R$_1$ = R$_3$ = H R$_2$ = OH

328 R$_1$ = R$_3$ = OCH$_3$ R$_2$ = Glc

330 R$_1$ = R$_3$ = OCH$_3$ R$_2$ = OH

327

329

331

332

333

334 R = OH
335 R = H
336 R = OCH₃

337

339

340

341

342

343 R₁ = R₃ = H R₂ = OH
345 R₁ = H R₂ = OH R₃ =

348 R₁ = H R₂ = OH R₃ =

349 R₁ = H R₂ = OH R₃ =

364 R₁ = R₂ = H R₃ = OCH₃
365 R₁ = R₃ = OCH₃ R₂ = OH
367 R₁ = R₃ = H R₂ = Glc
368 R₁ = R₃ = OCH₃ R₂ = Glc

370 R₁ = R₃ = H R₂ =

344

346

347

350

351

352

353 R = H
354 R = OCH₃

355

356 R = H
357 R = OCH₃

358 R = OCH₃
360 R = H

359

361

362

363

366

369

371 R₁ = R₂ = R₃ = H R₄ = feruloyl
372 R₁ = R₂ = H R₃ = R₄ = feruloyl
373 R₁ = R₃ = H R₂ = R₄ = feruloyl
374 R₁ = OCH₃ R₂ = H R₃ = R₄ = feruloyl

feruloyl

375

376

377

378

379

380

381

382

383

384

385 R$_1$ = CH$_3$ R$_2$ = H
386 R$_1$ = H R$_2$ = CH$_3$

387

388

389

390 R = H
391 R =

Manassantins A–B (**379–380**) and saucerneols B–C (**381–382**) were isolated from *Saururus chinensis* (Saururaceae, Korea) rhizomes and evaluated for their anti-HIV-1 activities. Compound **379** showed dose-dependent inhibitory activities on HIV-1 protease with an EC$_{50}$ value of 38.9 μM. Compounds **379–381** inhibited HIV-1-induced cytopathic effects in a human T lymphoblastoid cell line with EC$_{100}$ values of 1.0, 1.0 and 0.2 μM, respectively. Compound **381** showed the most potent and selective anti-HIV-1 activity with an EC$_{100}$ value of 0.2 μM, a CC$_0$ value of > 125.0 μM, and a TI value of > 520.8 (Lee et al. 2010b). Nine tetrahydrofuran lignans, (–)–(7"R,8"R)–

saucerneol J (**321**), manassantins A–B (**379–380**), saurucinol B (**383**), 4″-*O*-demethylmanassantin A (**384**), 3″-*O*-demethylmanassantin B (**385**), 4–*O*–demethylmanassantin B (**386**), saucerneol methyl ether (**387**) and saucerneol D (**388**) were isolated from the roots of *S. chinensis* (Saururaceae, Guangxi, China). In the examination for their abilities to inhibit EBV lytic DNA replication in P3HR-1 cells, these compounds showed strong to moderate activities with EC$_{50}$ values of 6.95, 3.42, 1.72, 14.5, 7.55, 2.69, 3.52, 1.70 and 1.09 μM, and TI values of 3.3, 58.5, 116.4, 4.4, 9.2, 20.2, 20.2, 65.0 and 41.1, respectively (Cui et al. 2014).
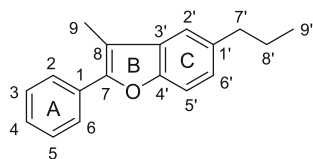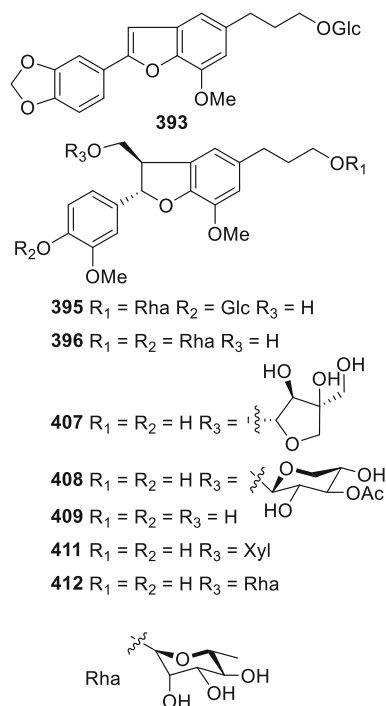
Benzofuran lignans
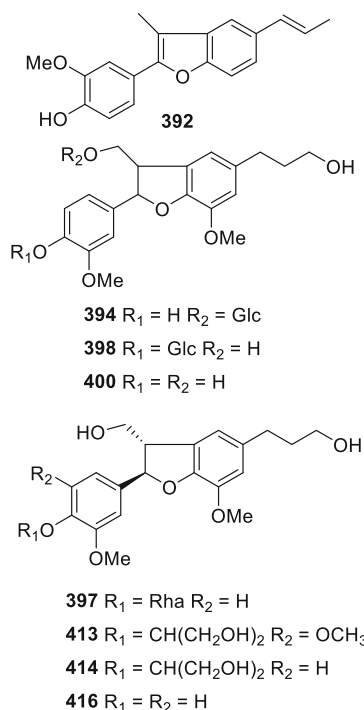
There were 26 benzofuran-type lignans isolated from plants and tested for antiviral activity (**392–417**) in the time period covered by this review (see Table 1 for source plants, antiviral activities, and references). The benzofuran lignans tested between 1998 and 2020 displayed the least antiviral activity of all of the classes of lignans. The most active benzofuran lignans were **403** and **406**, however, there were none with EC_{50} values ≤ 5 μM. There were no antiviral studies on synthetic lignans of this class.

benzofuran lignans

392

393

394 R_1 = H R_2 = Glc
398 R_1 = Glc R_2 = H
400 R_1 = R_2 = H

395 R_1 = Rha R_2 = Glc R_3 = H
396 R_1 = R_2 = Rha R_3 = H
407 R_1 = R_2 = H R_3 =
408 R_1 = R_2 = H R_3 =
409 R_1 = R_2 = R_3 = H
411 R_1 = R_2 = H R_3 = Xyl
412 R_1 = R_2 = H R_3 = Rha

397 R_1 = Rha R_2 = H
413 R_1 = CH(CH$_2$OH)$_2$ R_2 = OCH$_3$
414 R_1 = CH(CH$_2$OH)$_2$ R_2 = H
416 R_1 = R_2 = H

Benzofuran lignans are determined by the presence of a furan juncture created from the linkage of C-7 to C-4′ through an oxygen atom and the direct linkage of C-8–C-3′. Due to the phenylpropanoid precursor units being connected at carbons other than C-8 to C-8′, these compounds are sometimes classified as 8,3′–neolignans. In addition to the isomeric possibilities caused by the stereogenic center in the 7, 8–dihydrofuran ring, there are also many possible modifications of the propyl chain of this class of molecules.

Vladinol F (**403**), a lignan isolated from the leaves and stems of *Schisandra micrantha* (Yunnan, China), displayed anti-HIV-1 activity with an EC_{50} value of 9.75 μM and a TI value of 27.45 (Li et al. 2005a). Balaphonin (**406**) was obtained from the leaves and stems of *S. lancifolia* (Yunnan, China). It showed anti-HIV-1 effects with an EC_{50} value of 8.43 μM and a TI value of 4.3, respectively (Xiao et al. 2010b).

399

401

OMe **402**

403

404 R = H
410 R = OH

405

406

GlcO OMe **415**

417
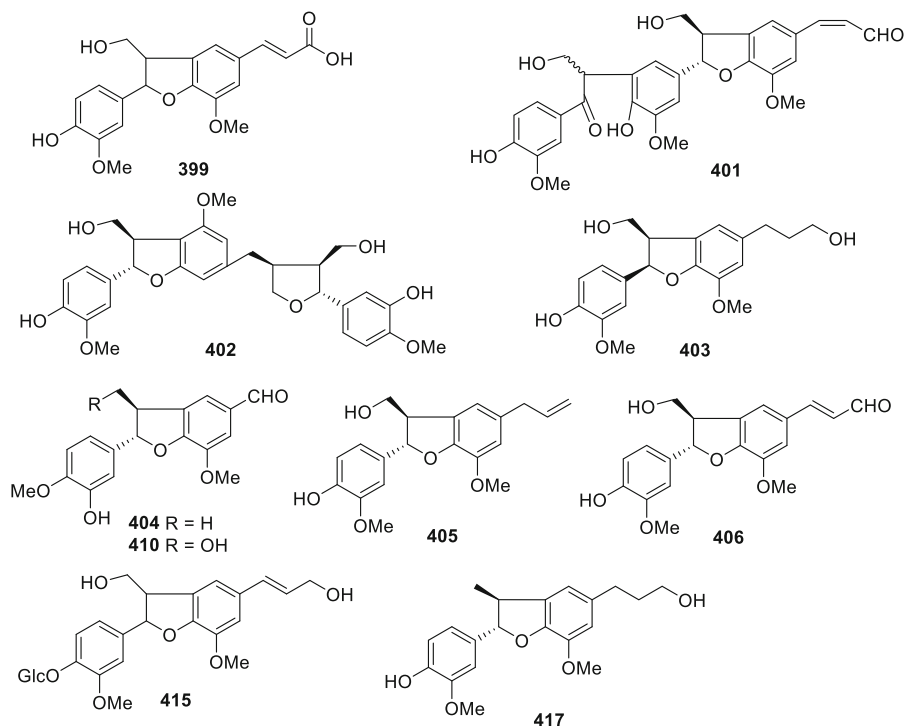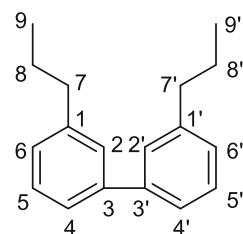
Neolignans

neolignans

Neolignans are phenylpropanoid dimers connected at positions other than C-8/C-8′. Here, we are focusing on neolignans biosynthesized by connection of the C-3/C-3′ carbons in the phenylpropanoid precursors, or via an ether linkage.

Compounds **418–436** represent the 19 neolignans isolated from plants and tested for antiviral activity between 1998 and 2020 (see Table 1 for source plants, antiviral activities, and references). There were three plant-derived neolignans that exhibited EC_{50} values ≤ 5 μM (**424**, **429**, **436**). Among this type of

compounds, **424** may be considered as a lead molecule against HBV infection with a high TI value. There were 5 synthetic neolignans (**437–441**) made and assayed for antiviral activity.

Seven neolignans, (7′S,8′S)–trans–streblusol A (**418**), (7′R,8′S)–erythro–streblusol B (**419**), (7′S,8′S)–threo–streblusol B (**420**), 8′R-streblusol C (**421**), (8R,8′R)-streblusol D (**422**), threo-strebluslignanol (**423**) and magnolol (**424**) were isolated from the stem bark of *Streblus asper* (Moraceae, Guangxi, China). Magnolol (**424**) showed anti-HBV activities against HBsAg antigen with an EC_{50} value of 2.03 μM and a TI value of 31.37, and HBeAg antigen with an EC_{50} value of 3.76 μM and a TI value of 316.94 (Li et al. 2012a). (7R,8S,7′R,8′S)–erythro–Strebluslignanol H (**428**), -and honokiol (**429**) were isolated from the roots of the same plant. Among them, **429** exhibited anti-HBV activities with EC_{50} values of 3.14 μM (TI = 21.5) on HBsAg and 4.74 μM (TI = 14.2) against HBeAg (Chen et al. 2012). Compound **429** also displayed an antiviral effect against HCVcc infection at non-toxic concentrations. It inhibited the cell entry of lentiviral particles pseudo-typed with glycoproteins from HCV genotypes 1a, 1b, and 2a, but not the VSV. The expression levels of the components

of replication complex, NS3, NS5A and NS5B, were down-regulated by **429** in a dose-dependent manner in the concentration range of 10–30 μM. The compound inhibited HCV replication dose dependently in both genotypes 1b and 2a sub-genomic replicons in the concentration of 10 and 20 μM. Therefore, it was determined that **429** inhibited HCV infection by targeting cell entry and replication with an EC_{50} value of 1.2 μM, an EC_{90} value of 6.5 μM, and a TI (LD_{50}/EC_{90}) value of 5.4 (Lan et al. 2012). Furthermore, during the evaluation for activity against anti-SARS-CoV using a cell-based assay measuring SARS-CoV-induced cytopathogenic effects on Vero E6 cells, **424** and **429** showed inhibitory activity at the concentrations between 10 and 20 μM by cell-based CPE assay, and they displayed appreciable levels of anti-SARS virus bioactivity with EC_{50} values ranging from 3.8 to 7.5 μM and the CC_{50} values of > 65 μM (Wen et al. 2007).
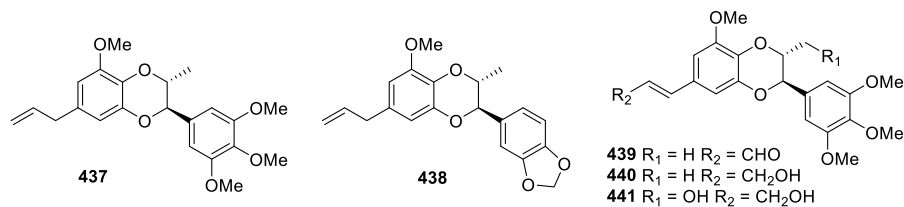
glucopyranoside (**431**), isostrebluslignanaldehyde (**432**), isomagnolol (**433**), obovatol (**434**), strebluslignanol F (**435**) and (7′R,8′S,7″R,8″S)-*erythro*-streblus-lignanol G (**436**) were isolated from the roots of *S. asper* (Guangxi, China) and evaluated for their anti-HBV activities using the HBV transfected HepG2.2.15 cells. The neolignan **424** and the dimeric neolignan **436** displayed activities against anti-HBV with EC_{50} values of 2.03 (TI = 31.37) and 1.58 μM (TI = 74.90) for HBsAg, and with EC_{50} values of 3.76 (TI = 16.94) and 3.24 μM (TI = 36.52) for HBeAg. They also showed HBV DNA replication with EC_{50} values of 8.67 (TI = 7.34) and 9.02 μM (TI = 13.12), respectively (Li et al. 2013).

Five 1,4–benzodioxane neolignans eusiderin A (**437**), eusiderin B (**438**), eusiderin G (**39**), eusiderin M (**440**) and nitidanin (**441**) were synthesized and screened for their anti-HCV activity. They displayed inhibitory effects with the EC_{50} values of 30, 20, 25,
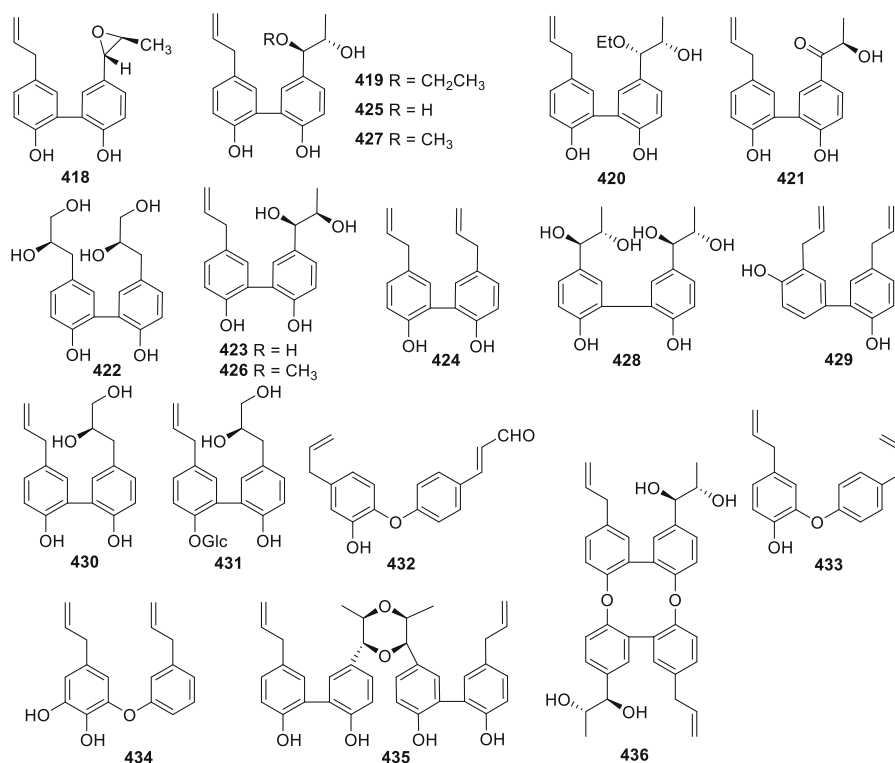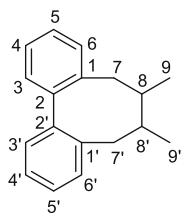

In a separate study, 12 neolignans including **423**, **424**, magnolignan A (**430**), magnolignan A-2-*O*-β-D-

50 and 200 μM and the TI values of 1.21, > 6.25, 1.91, 2.57 and 2.32, respectively (Pilkington et al. 2018).

437   **438**

439 R$_1$ = H R$_2$ = CHO
440 R$_1$ = H R$_2$ = CH$_2$OH
441 R$_1$ = OH R$_2$ = CH$_2$OH

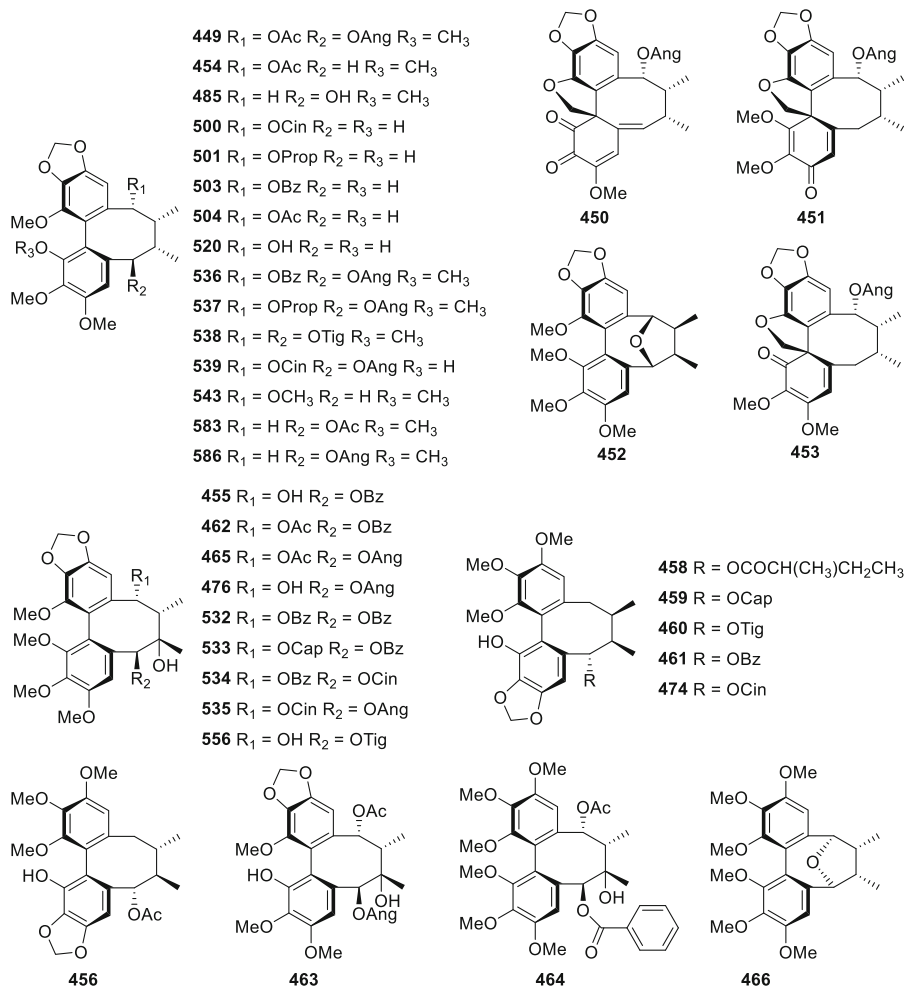## Dibenzocyclooctadiene lignans and homolignans

dibenzocyclooctadiene lignans, which have both aromatic rings intact, homolignans lack one of the 6-carbon aromatic ring moieties. In some cases, homolignans possess a cyclohexadienone moiety, and in some instances, the cyclohexadienone moiety has been cleaved.
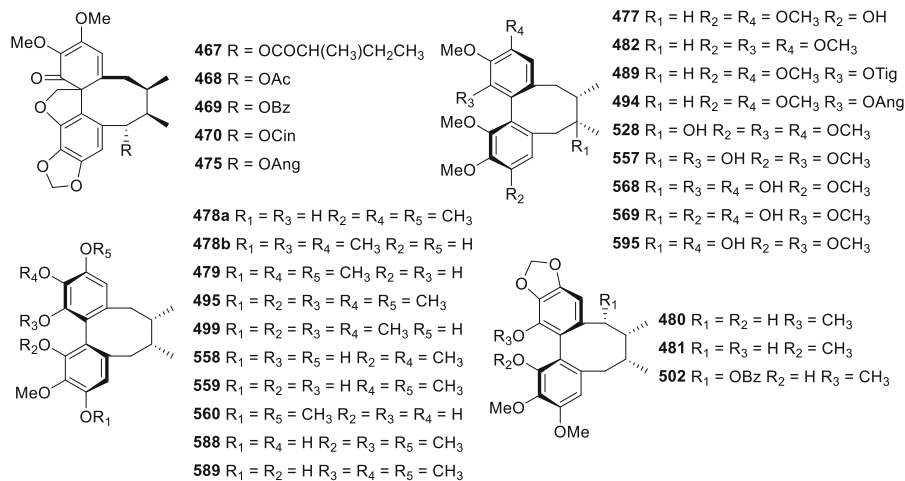
Between 1998 and 2020, 157 dibenzyocyclooctadiene lignans and homolignans (**442–598**) were isolated from plants and tested for antiviral activity, by far the most of any class of lignan over this time period (see Table 1 for source plants, antiviral activities, and references). This class of lignan had 20 compounds with antiviral activity (≤ 5 μM), but the most interesting, due to their potent activities (EC$_{50}$ ≤ 1 μM), are **480** and **591**. There were no studies on synthetic dibenzyocyclooctadiene lignans or homolignans.

dibenzocyclooctadiene lignans

Dibenzocyclooctadiene lignans are defined by having a C-2/C-2′ linkage as well as the usual C-8/C-8′ juncture of the phenylpropanoid precursor units. This endows them with a cyclooctadiene ring. Unlike

442 R$_1$ = H R$_2$ = OBz
444 R$_1$ = H R$_2$ = OAng
447 R$_1$ = R$_2$ = H
488 R$_1$ = H R$_2$ = OCH$_3$
492 R$_1$ = H R$_2$ = OH
507 R$_1$ = OH R$_2$ = OAng
508 R$_1$ = R$_2$ = OH
511 R$_1$ = OAc R$_2$ = OH
578 R$_1$ = H R$_2$ = OCH$_2$CH$_3$
582 R$_1$ = H R$_2$ = OAc

443 R$_1$ = H R$_2$ = OAng
498 R$_1$ = H R$_2$ = OBz
505 R$_1$ = OAc R$_2$ = OAng
506 R$_1$ = OH R$_2$ = OAng

445 R = OAng
457 R = OCap
471 R = OCOCH(CH$_3$)CH$_2$CH$_3$
472 R = OProp
473 R = OBz

446   **448**

Ang   Tig   Bz   Cin   Cap   Prop

The lignans interiotherin B (**443**), angeloylgomisin R (**444**), schisantherin B (**476**), (+)-gomisin K_3 (**477**), rubrisandrins A and B (**478–479**), (±)-gomisin M_1 (**480**), (+)-gomisin M_2 (**481**), deoxyschisandrin (**482**), schisandrin (**483**), tigloylgomisin P (**484**), gomisin O (**485**), angeloylgomisin P (**486**), epigomisin O (**487**), methylgomisin R (**488**), (+)-14-tigloylgomisin K_3 (**489**), 12-demethylwuweilignan I (**490**), schisandrene A (**491**), gomisin R (**492**), (*R*)-(+)-gomisin M_1 (**493**), (+)-angeloylgomisin K_3 (**494**), dimethylgomisin J (**495**), rubrilignans A-B (**496–497**), schisantherin D (**498**), and gomisin J (**499**) were obtained from the extract of *Schisandra rubriflora* and their anti-HIV effects were evaluated (Chen et al. 2006; Li et al. 2008; Mu et al. 2011). Among them, rubrisandrin A (**478**), gomisin J (**499**), (±)-gomisin M_1 (**480**), (+)-gomisin M_2 (**481**) and (+)-gomisin K_3 (**477**) were active in the HIV growth inhibition
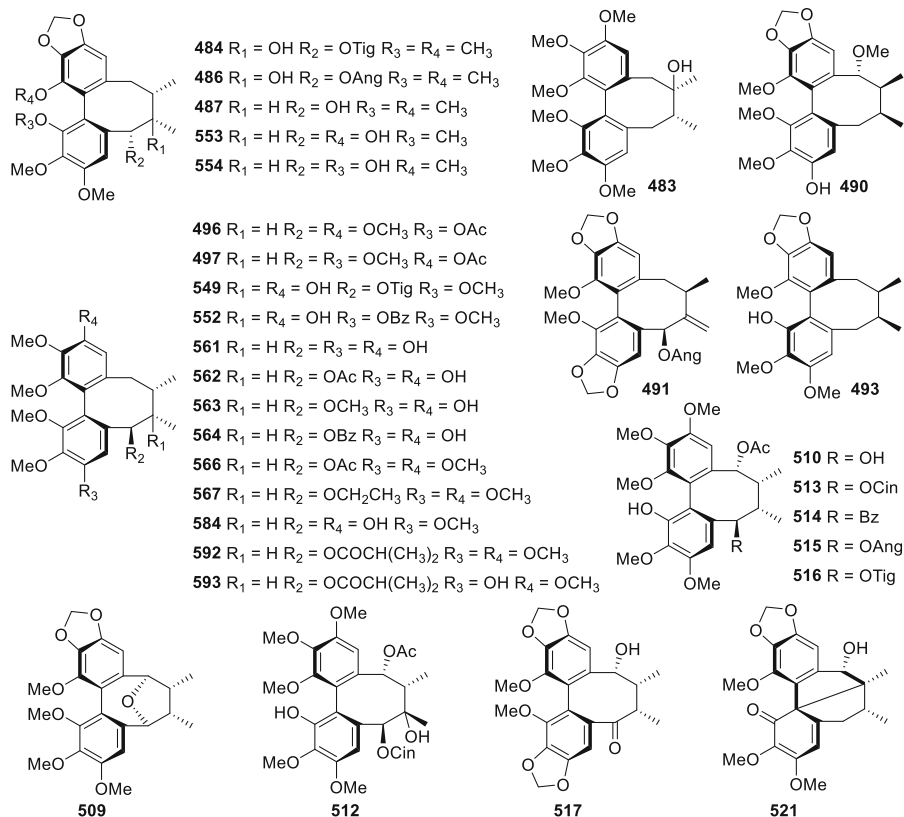
assay with EC_{50} values 11.3, 3.9, < 0.65, 2.4 and 5.7 µM, and TI values of > 5.7, 6.0, > 68, 19.4 and 7.4, respectively (Chen et al. 2006). Compound **480** possessed anti-HIV activity against a wide variety of HIV-1 and HIV-2 viral strains such as NL 4–3 (X4), Bal (R5), (B) BK132 (X4), (AE) 92TH001 (R5) and CBL-23 with EC_{50} values in the range of 1–3 µM. Further investigation indicated that **480** was a nonnucleoside reverse transcriptase inhibitor (NNRTI). The studies in TZM-bl indicator cells showed **480** exerted inhibitory activity against both NL 4–3 and BaL, suggesting that it targets an early step in the HIV life cycle. Quantitative real-time PCR demonstrated that **480** blocked both early and late HIV-1 reverse transcription products (Han et al. 2015). Compounds **496** and **497** showed anti-HIV-1 activities with EC_{50} values of 4.77 and 3.84 µM, and TI of 35.5 and 18.6, respectively (Mu et al. 2011).
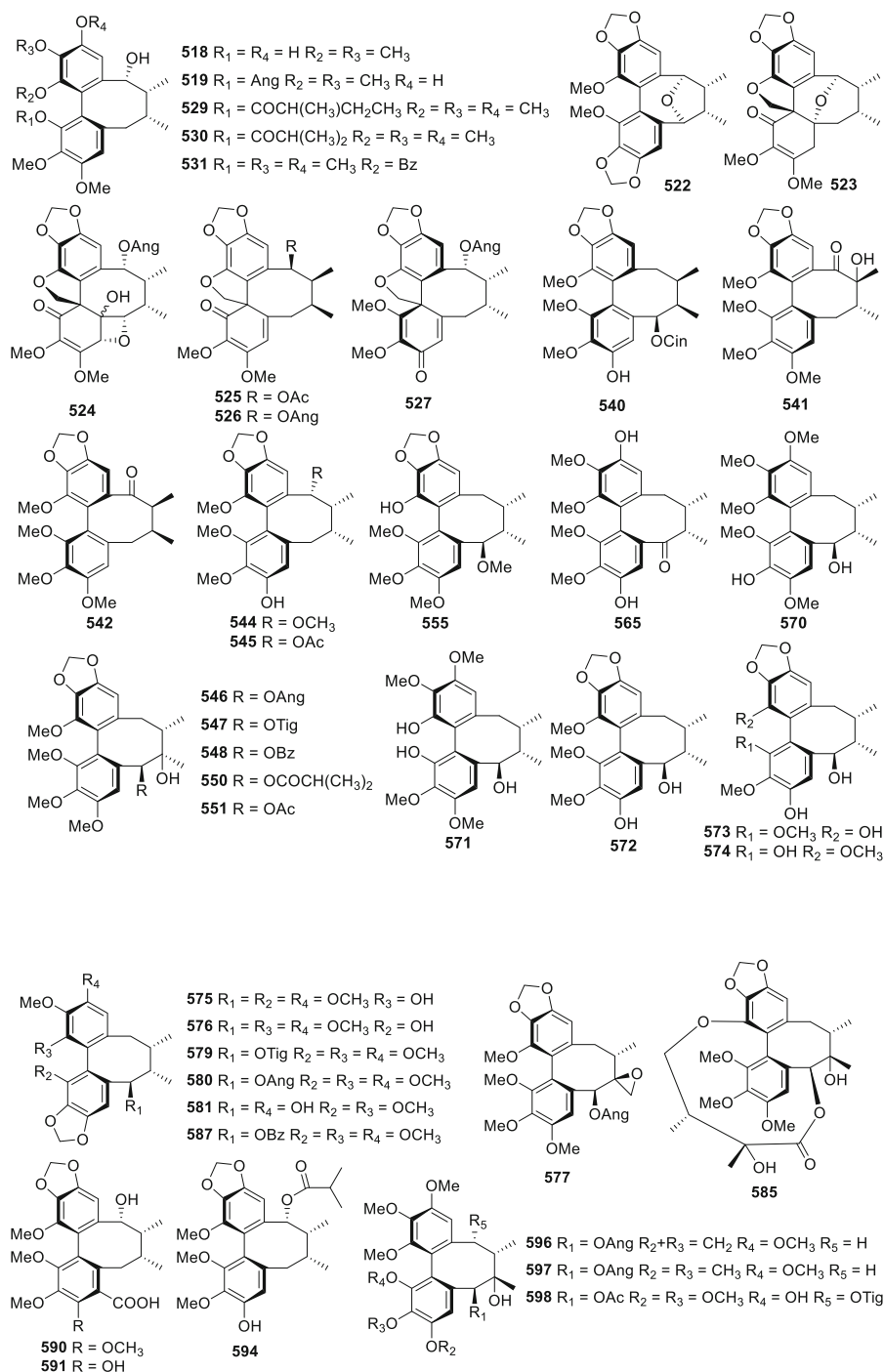

449 R_1 = OAc R_2 = OAng R_3 = CH_3
454 R_1 = OAc R_2 = H R_3 = CH_3
485 R_1 = H R_2 = OH R_3 = CH_3
500 R_1 = OCin R_2 = R_3 = H
501 R_1 = OProp R_2 = R_3 = H
503 R_1 = OBz R_2 = R_3 = H
504 R_1 = OAc R_2 = R_3 = H
520 R_1 = OH R_2 = R_3 = H
536 R_1 = OBz R_2 = OAng R_3 = CH_3
537 R_1 = OProp R_2 = OAng R_3 = CH_3
538 R_1 = R_2 = OTig R_3 = CH_3
539 R_1 = OCin R_2 = OAng R_3 = H
543 R_1 = OCH_3 R_2 = H R_3 = CH_3
583 R_1 = H R_2 = OAc R_3 = CH_3
586 R_1 = H R_2 = OAng R_3 = CH_3

455 R_1 = OH R_2 = OBz
462 R_1 = OAc R_2 = OBz
465 R_1 = OAc R_2 = OAng
476 R_1 = OH R_2 = OAng
532 R_1 = OBz R_2 = OBz
533 R_1 = OCap R_2 = OBz
534 R_1 = OBz R_2 = OCin
535 R_1 = OCin R_2 = OAng
556 R_1 = OH R_2 = OTig

450

451

452

453

458 R = $OCOCH(CH_3)CH_2CH_3$
459 R = OCap
460 R = OTig
461 R = OBz
474 R = OCin

456

463

464

466

467 R = OCOCH(CH₃)CH₂CH₃
468 R = OAc
469 R = OBz
470 R = OCin
475 R = OAng

477 R₁ = H R₂ = R₄ = OCH₃ R₂ = OH
482 R₁ = H R₂ = R₃ = R₄ = OCH₃
489 R₁ = H R₂ = R₄ = OCH₃ R₃ = OTig
494 R₁ = H R₂ = R₄ = OCH₃ R₃ = OAng
528 R₁ = OH R₂ = R₃ = R₄ = OCH₃
557 R₁ = R₃ = OH R₂ = R₃ = OCH₃
568 R₁ = R₃ = R₄ = OH R₂ = OCH₃
569 R₁ = R₂ = R₄ = OH R₃ = OCH₃
595 R₁ = R₄ = OH R₂ = R₃ = OCH₃

478a R₁ = R₃ = H R₂ = R₄ = R₅ = CH₃
478b R₁ = R₃ = R₄ = CH₃ R₂ = R₅ = H
479 R₁ = R₄ = R₅ = CH₃ R₂ = R₃ = H
495 R₁ = R₂ = R₃ = R₄ = R₅ = CH₃
499 R₁ = R₂ = R₃ = R₄ = CH₃ R₅ = H
558 R₁ = R₃ = R₅ = H R₂ = R₄ = CH₃
559 R₁ = R₂ = R₃ = H R₄ = R₅ = CH₃
560 R₁ = R₅ = CH₃ R₂ = R₃ = R₄ = H
588 R₁ = R₄ = H R₂ = R₃ = R₅ = CH₃
589 R₁ = R₂ = H R₃ = R₄ = R₅ = CH₃

480 R₁ = R₂ = H R₃ = CH₃
481 R₁ = R₃ = H R₂ = CH₃
502 R₁ = OBz R₂ = H R₃ = CH₃

Phytochemical investigation of *Kadsura angustifolia* (Schisandraceae, Yunnan, China) led to 19 dibenzocyclooctadiene lignans kadangustins A-G (**510–516**), schisantherins Q (**517)** and L (**507**), gomisin R (**492**), deangeloylschisantherin F (**518**), schisantherin F (**519**), binankadsurin A (**520**), kadsulignan K (**521**), epoxideschisandrin C (**522**), kadsurarin (**373**), kadsulignan N (**466**), schisantherin P (**508**) and kadsulignan L (**509**). Compound **520** showed anti-HIV activity with an EC₅₀ value of 3.86 μM (Gao et al. 2008).

From the stems of *Kadsura heteroclita* (Schisandraceae, Yunnan, China), dibenzocyclooctadiene lignans were obtained, including kadsulignan K (**521**), heteroclitins I (**523**) and J (**524**), acetoxyl oxokadsurane (**525**), benzoyl oxokadsurane (**526**), interiorin B (**527**), interiorin (**451**), heteroclitin D (**453**) and kadsurin (**454**). Compounds **451** and **527** exhibited anti-HIV-1 activity with EC₅₀ values of 3.3 and 2.9 μM, and therapeutic index values of 52.9 and 65.9, respectively (Pu et al. 2008b).

484 R$_1$ = OH R$_2$ = OTig R$_3$ = R$_4$ = CH$_3$
486 R$_1$ = OH R$_2$ = OAng R$_3$ = R$_4$ = CH$_3$
487 R$_1$ = H R$_2$ = OH R$_3$ = R$_4$ = CH$_3$
553 R$_1$ = H R$_2$ = R$_4$ = OH R$_3$ = CH$_3$
554 R$_1$ = H R$_2$ = R$_3$ = OH R$_4$ = CH$_3$

496 R$_1$ = H R$_2$ = R$_4$ = OCH$_3$ R$_3$ = OAc
497 R$_1$ = H R$_2$ = R$_3$ = OCH$_3$ R$_4$ = OAc
549 R$_1$ = R$_4$ = OH R$_2$ = OTig R$_3$ = OCH$_3$
552 R$_1$ = R$_4$ = OH R$_3$ = OBz R$_3$ = OCH$_3$
561 R$_1$ = H R$_2$ = R$_3$ = R$_4$ = OH
562 R$_1$ = H R$_2$ = OAc R$_3$ = R$_4$ = OH
563 R$_1$ = H R$_2$ = OCH$_3$ R$_3$ = R$_4$ = OH
564 R$_1$ = H R$_2$ = OBz R$_3$ = R$_4$ = OH
566 R$_1$ = H R$_2$ = OAc R$_3$ = R$_4$ = OCH$_3$
567 R$_1$ = H R$_2$ = OCH$_2$CH$_3$ R$_3$ = R$_4$ = OCH$_3$
584 R$_1$ = H R$_2$ = R$_4$ = OH R$_3$ = OCH$_3$
592 R$_1$ = H R$_2$ = OCOCH(CH$_3$)$_2$ R$_3$ = R$_4$ = OCH$_3$
593 R$_1$ = H R$_2$ = OCOCH(CH$_3$)$_2$ R$_3$ = OH R$_4$ = OCH$_3$

483

490

491

493

510 R = OH
513 R = OCin
514 R = Bz
515 R = OAng
516 R = OTig

509

512

517

521

Twelve new dibenzocyclooctadiene lignans, marlignans A-L (558–573), were obtained from the leaves and stems of *Schisandra wilsoniana* (Yunnan, China). Compounds 562–564, 567–569 showed anti-HIV-1 activities with EC$_{50}$ values of 3.6, 3.3, 4.1, 4.1, 4.7, and 3.5 μM and the TI values of 8.7, 15.6, 6.7, 9.3, 7.7, and 16.4, respectively (Yang et al. 2010c). Two new dibenzocyclooctadiene ligans, schinegllignans A and B (613, 614), were isolated from the fruits of *Schisandra neglecta* (Schisandraceae, Yunnan, China). Compounds 613 showed anti-HIV-1 activities in C8166 cells with a EC$_{50}$ value of 4.6 and TI value of 18.5 (Duan et al. 2011).

518 $R_1 = R_4 = H \ R_2 = R_3 = CH_3$
519 $R_1 = Ang \ R_2 = R_3 = CH_3 \ R_4 = H$
529 $R_1 = COCH(CH_3)CH_2CH_3 \ R_2 = R_3 = R_4 = CH_3$
530 $R_1 = COCH(CH_3)_2 \ R_2 = R_3 = R_4 = CH_3$
531 $R_1 = R_3 = R_4 = CH_3 \ R_2 = Bz$

525 R = OAc
526 R = OAng

544 R = OCH$_3$
545 R = OAc

546 R = OAng
547 R = OTig
548 R = OBz
550 R = OCOCH(CH$_3$)$_2$
551 R = OAc

573 $R_1 = OCH_3 \ R_2 = OH$
574 $R_1 = OH \ R_2 = OCH_3$

575 $R_1 = R_2 = R_4 = OCH_3 \ R_3 = OH$
576 $R_1 = R_3 = R_4 = OCH_3 \ R_2 = OH$
579 $R_1 = OTig \ R_2 = R_3 = R_4 = OCH_3$
580 $R_1 = OAng \ R_2 = R_3 = R_4 = OCH_3$
581 $R_1 = R_4 = OH \ R_2 = R_3 = OCH_3$
587 $R_1 = OBz \ R_2 = R_3 = R_4 = OCH_3$

590 R = OCH$_3$
591 R = OH

596 $R_1 = OAng \ R_2 + R_3 = CH_2 \ R_4 = OCH_3 \ R_5 = H$
597 $R_1 = OAng \ R_2 = R_3 = CH_3 \ R_4 = OCH_3 \ R_5 = H$
598 $R_1 = OAc \ R_2 = R_3 = OCH_3 \ R_4 = OH \ R_5 = OTig$

From the stems of *Schisandra neglecta* (Schisandraceae, Sichuan, China), the new lignans neglignans A-B (**590, 591**) and E–G (**592–594**) and the known compounds rubschisantherin (**583**), gomisins D (**585**), T (**595**), F (**596**), angeloylgomisin Q (**597**) and schisphenin F (**598**) were obtained. Copmounds **583**, **585**, and **590–598** showed anti-HIV-1 activities with EC_{50} values of 4.7, 9.8, 2.2, 1.4, 5.9, 3.5, 8.2, 8.2, 8.3, 11.5 and 8.3 μM, and TI values of 18.2, 18.9, 40.3,

55.3, > 33.7, > 58.0, 18.1, 15.1, 7.5, 7.4 and 17.8, respectively (Gao et al. 2013).

Norlignans and other lignoids

Norlignans are structures formed by the conjunction of two phenylpropanoid units followed by loss of one carbon from the skeleton. This section covers these compounds, as well as those formed from two phenylpropanoid units, but have undergone skeletal rearrangements or cleavages, termed lignoids. This includes secolignans as well as structures that have seemingly had one of the propyl side-chains completely removed.

During the time covered by this review, 32 norlignans and lignoids isolated from plants were tested for antiviral activity (599–630) (see Table 1 for source plants, antiviral activities, and references). Of the plant-derived norlignans and lignoids, only compounds 605 and 612 displayed antiviral activity at concentrations at or below 1 μM. We found no evidence of synthetic norlignans or lignoids bioassayed for antiviral activity.

Three 7,8-secolignans, marphenols A and B (605–606) together with 7,8-secoholostylone B (607), were isolated from the stems of *Schisandra wilsoniana* (Schisandraceae, Yunnan, China). Compounds 605–607 inhibited HIV-1$_{IIIB}$-induced syncytia formation with EC$_{50}$ values of 1.5, 4.5, 5.4 μM and TI values of 18.27, 4.33 and 9.19, respectively. In a further study of the anti-HIV-1 activity, 605 reduced p24 production in acute HIV-1$_{IIIB}$-infected C8166 cells with an EC$_{50}$ value of 9.0 μM, and inhibited primary isolate HIV-1TC-2 replication in PBMCs with an EC$_{50}$ value of 1.4 μM. However, the compound did not inhibit p24 expression and had no effects on cell to cell fusion in chronically infected H9 cells (Zhang et al. 2010).
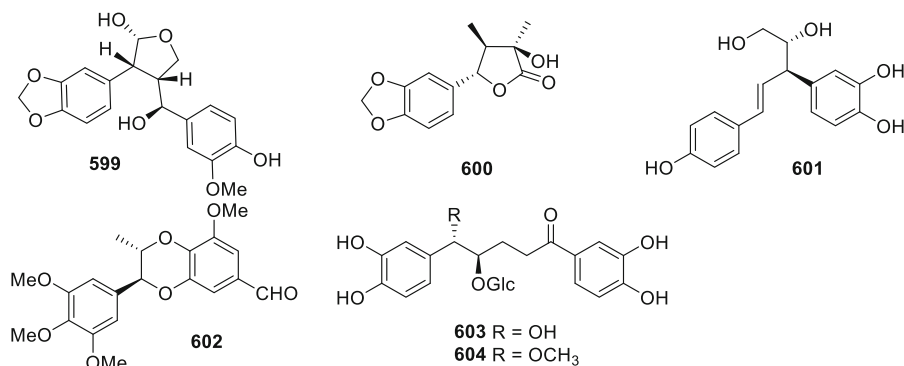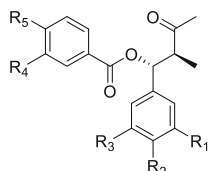
605 R$_1$ + R$_2$ = OCH$_2$O R$_3$ = H R$_4$ = OCH$_3$ R$_5$ = OH
606 R$_1$ = R$_2$ = OCH$_3$ R$_3$ = OH R$_4$ + R$_5$ = OCH$_2$O
607 R$_1$ + R$_2$ = OCH$_2$O R$_3$ = H R$_4$ = R$_5$ = OCH$_3$
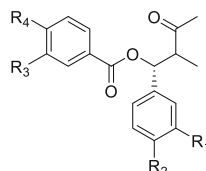
608 R$_1$ = R$_2$ = R$_3$ = R$_4$ = OCH$_3$
609 R$_1$ = R$_2$ = OCH$_3$ R$_3$ + R$_4$ = OCH$_2$O
610 R$_1$ + R$_2$ = R$_3$ + R$_4$ = OCH$_2$O

611 **612** **613** **614**

615 **616** **617**
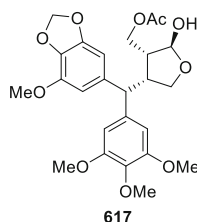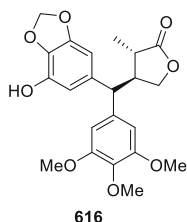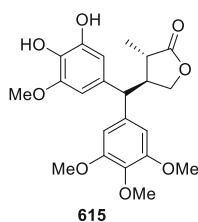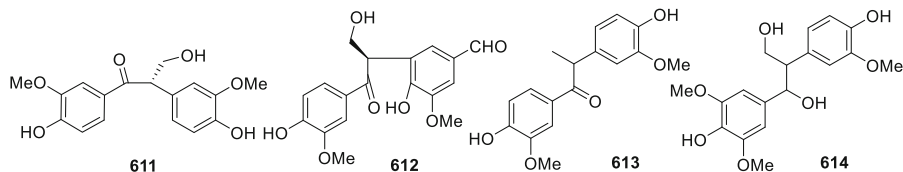
(1S)–4–Hydroxy–3–[2–(4–hydroxyl–3–methoxy–phenyl)–1–hydroxymethyl–2–oxo–ethyl]–5–methoxy–benzaldehyde (**612**) was isolated from the seeds of *Herpetospermum caudigerum* (Cucurbitaceae, Sichuan, China) and displayed inhibitory activity against HBV on HBsAg and HBeAg secretions with EC$_{50}$ values of 0.34 and 4.83 × 10^{-4} μM, respectively, and low cytotoxicity against HepG 2.2.15 cell line with a CC$_{50}$ value of 2.96 × 10^5 μM (Yu et al. 2014).
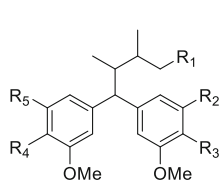
618 R$_1$ = OAc R$_2$ = R$_5$ = H R$_3$ = OH R$_4$ = OCH$_3$
619 R$_1$ = OAc R$_2$ = R$_5$ = H R$_3$ = R$_4$ = OCH$_3$
620 R$_1$ = OH R$_2$ = R$_5$ = H R$_3$ = R$_4$ = OH
621 R$_1$ = OH R$_2$ + R$_3$ = OCH$_2$O R$_4$ = R$_5$ = OCH$_3$
622 R$_1$ = H R$_2$ + R$_3$ = OCH$_2$O R$_4$ = R$_5$ = OCH$_3$
627 R$_1$ = OH R$_2$ = R$_5$ = H R$_3$ = R$_4$ = OCH$_3$
628 R$_1$ = R$_3$ = OH R$_2$ = R$_5$ = H R$_4$ = OCH$_3$

623 R$_1$ = OH R$_2$ = H
624 R$_1$ = OCH$_3$ R$_2$ = OH

625 R$_1$ = R$_4$ = OCH$_3$ R$_2$ = R$_3$ = OH R$_5$ = COOH
626 R$_1$ = OCH$_3$ R$_2$ = OH R$_3$ + R$_4$ = OCH$_2$O R$_5$ = COOH
629 R$_1$ = R$_2$ = R$_3$ = R$_4$ = OCH$_3$ R$_5$ = CH$_2$OH
630 R$_1$ = OH R$_2$ = R$_3$ = R$_4$ = OCH$_3$ R$_5$ = CH$_2$OH

Table 2 Comparison of antiviral lignan and lignoid classes from 1998–2020

Class	#[a]	# Natural	#(%) active at 1 μM or less[b]	#(%) active at 5 μM or less[b]	# Synthetic[c]
Arylnaphthalene	153	17	5 (29%)	6 (35%)	136
Aryltetralin	73	31	0 (0%)	3 (10%)	42
Dibenzylbutyrolactone	22	22	4 (18%)	7 (32%)	0
Dibenzylbutane	39	29	0 (0%)	2 (7%)	10
Tetrahydrofuranoid and tetrahydrofurofuranoid	104	104	5 (5%)	9 (9%)	0
Benzofuran	26	26	0 (0%)	0 (0%)	0
Neolignans	24	19	0 (0%)	3 (16%)	5
Dibenzocyclooctadiene lignans and homolignans	157	157	1 (1%)	20 (13%)	0
Norlignans and other lignoids	32	32	2 (6%)	8 (25%)	0

[a]Number of compounds in each class of lignan that have been tested for antiviral activity since 1998, and therefore have been included in this review

[b]The data was rounded to one significant figure to account for differences in accuracy of reported values. Only natural compounds tested for antiviral activities between 1998 and 2020 are included

[c]Number of synthetic compounds using the core structure of each class of lignan that have been tested for antiviral activity since 1998, and therefore have been included in this review

Disscussion

Hundreds of lignans with anti-viral activities were reported from 66 different plant species, belonging to 43 genera, and 34 different families (Table 1). Among them, the genera *Kadsura*, *Phyllanthus* and *Schisandra* contained numerous active lignans with anti-HIV and anti-HBV activities.

Of the 630 lignans and lignoids covered in this review, 153 of them were arylnaphthalene lignans, 73 were aryltetralin lignans, 22 were dibenzylbutyrolactone lignans, 39 were dibenzylbutane lignans, 104 were tetrahydrofuranoid and tetrahydrofurofuranoid lignans, 26 were benzofuran lignans, 24 were neolignans, 157 were dibenzocyclooctadiene lignans and homolignans, and 32 were norlignans and other lignoids. Although aryltetralin and arylnaphthalene lignans have received the most attention in regards to synthesis, and structure–activity-relationship, due in large part to the clinical and commercial success of podophyllotoxin and the promising results of diphyllin (**11**) and helioxanthin (**32**), the other classes of lignans and lignoids are also deserving of increased scientific exploration as antiviral lead compounds (Table 2).

There remain multitudes of lignans and lignoids in all of the categories that have not been tested for antiviral activity, an endeavor that could reveal additional potent potential drugs. Further standardization of antiviral assays could also be beneficial in doing direct comparisons and for SAR studies (a poignant example is compound **627**, which has two EC_{50} values against HIV reported, one 44.68 μM, and one 104 μM).

Between 1963 and 2020, about 200 antiviral drugs were approved for treatment of viral infection. Most of them came from chemical synthesis or structural modifications of natural products (Clercq and Li 2016; Chaudhuri et al. 2018; FDA 2018, 2019, 2020). Although the isolated natural products normally exhibited moderate to weak antiviral activities, some did show excellent antiviral activities. For example, patentiflorin A (**153**), the 6-deoxyglucoside derivatives of diphyllin, which were isolated from *Justicia* plants, and shown to potently inhibit a broad spectrum of HIV-1 strains including some resistant strains with EC_{50} values in the range of 15–37 nM (AZT: 77–95 nM) and mosquito-borne *flavivirus* such as ZIKV, DENV1, TBEV, WNV, JEV and EBV with EC_{50} values ranged between 0.12–1.0 μM (Zhang et al. 2017a, 2017b; Martinez-Lopez et al. 2019). Helioxanthin (**32**) is an arylnaphthalene type lignan obtained from the roots of *Heliopsis scabra* Dunal

(Asteraceae, Taiwan, China) and the aerial parts of *Taiwania cryptomerioides* Hayata (Taxodiaceae, Taiwan, China). It caught the attention of chemists because of its potent inhibition against HBV gene expression in vitro with an EC_{50} value of 1 μM and an ID_{50} value of 31 μM against CEM cell line (Yeo et al. 2005). In a study focusing on the molecular mode of action of **32** on HBV gene expression, this compound was found to suppress the surface antigen promoter (SP) II and the core promoter (CP) selectively, but it had no effect on SPI or the promoter for the X gene. In addition, the suppressive effects on both SPII and CP activity were liver-specific. In another study, compound **32** reduced the DNA-binding activity of the nuclear extract of HepA2 cells to the specific *cis* element of the HBV promoter for the core antigen, including peroxisome proliferator-activated receptors (PPARs), the PPAR binding site, and the transcription factors α-fetoprotein and *specificity protein 1 (*Sp1). Moreover, the ectopic expression of PPARγ or HNF4α partially reversed the suppression of HBV RNA by **32**. Hence, compound **32** may represent a novel class of anti-HBV agents that can selectively modulate the transcriptional machinery of human liver cells to reduce HBV gene expression and replication (Tseng et al. 2008; Li et al. 2005b). More than 100 derivatives of helioxanthin were synthesised. Among them, the lactam **49** and the cyclic hydrazide derivative **59** exhibited significant inhibitory activity against wild mutant HBV with the EC_{50} values of 0.08 and 0.03 μM, respectively (Yeo et al. 2005). Compound **49** also inhibited HBV against the drug resistant mutants W10 and DM2 with the EC_{50} values of 0.004 and 0.0003 μM, respectively (Li et al. 2005b; Cheng et al. 2005a; Tseng et al. 2008). These studies revealed that natural lignans are an important source for the discovery of novel antiviral agents and should be further exploited as lead compounds. Since many lignans have demonstrated antiviral activities, extensive exploration of them through phytochemical studies, chemical synthesis, structure modification, structure–activity relationship analysis and mechanism of action studies could bring next generation of antiviral drugs.

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