Natural and nature-inspired stilbenoids as antiviral agents

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Abstract

Viruses continue to be a major threat to human health. In the last century, pandemics occurred and resulted in significant mortality and morbidity. Natural products have been largely screened as source of inspiration for new antiviral agents. Within the huge class of plant secondary metabolites, resveratrol-derived stilbenoids present a wide structural diversity and mediate a great number of biological responses relevant for human health. However, whilst the antiviral activity of resveratrol has been extensively studied, little is known about the efficacy of its monomeric and oligomeric derivatives. The purpose of this review is to provide an overview of the achievements in this field, with particular emphasis on the source, chemical structures and the mechanism of action of resveratrol-derived stilbenoids against the most challenging viruses. The collected results highlight the therapeutic versatility of stilbene-containing compounds and provide a prospective insight into their potential development as antiviral agents.

Keywords: antiviral, stilbenoids, resveratrol derivatives, natural compounds

Contents

1. Introduction

Viruses represent a major threat to the global health and economy. Every year emerging and re-emerging viruses from natural reservoirs constantly infect human population causing risks of viral epidemics and pandemics [1]. In 1997, avian influenza A (H5N1) directly spread from poultry to humans. In 1999 a severe encephalitis outbreak, caused by a new paramyxovirus (Nipah virus), occurred in Malaysia and Singapore. During 2002 to 2003, a novel coronavirus (CoV), known as SARS-CoV, caused more than 8000 infections, spreading to 37 countries. In 2009, a swine H1N1 influenza A virus provoked a pandemic influenza, followed by the Middle East Respiratory Syndrome (MERS), caused by a new deadly (>30% mortality) MERS-CoV in 2012. The Ebola outbreak in West Africa (2014-2016) became the deadliest occurrence of the disease since its discovery in 1976, and finally the viral pneumonia outbreak, caused by 2019-nCoV, started in China in December 2019 and officially declared as a pandemic by WHO on 11th March 2020 [2]. According to WHO, it is imperative to find new antiviral agents, including those against drug-resistant and vaccine immunity escaping viral strains [3], or finding new therapeutic indications for existing approved FDA-drugs (the so-called "drug repurposing" approach) in order to reduce time and cost for drug development for infectious diseases [4].

The urgent need of antivirals appeared since 1980s because of HIV (human immunodeficiency virus) spread causing acquired immune deficiency syndrome. Zidovudine (AZT) was the first anti-HIV drug approved in the United States in 1986. Since then, many research efforts to treat HIV led to important improvement in antiviral research and many new classes of drugs targeting a wide variety of human viruses have been introduced. Natural products from marine sponges, sea algae, arthropods and plants were largely screened as source of inspiration for new antiviral agents [5]. Indeed, natural materials, such as herbs, spices, roots, leaves, barks have been used throughout the history as traditional medicines, flavours or food preservatives. Nowadays, many clinically used drugs have been inspired by natural products, which constitute a broad biodiversity of molecules in terms of chemical space and biological properties. In the last 40 years, 185 antiviral agents were introduced. Vaccines account for 47%, but looking at small molecules, 19 were totally synthetic molecules, while 53 were natural derivatives or nature-inspired semisynthetic compounds [6].

Among natural products, stilbenoids represent a class of non-flavonoid polyphenolic compounds largely studied in the last decades because of their many bioactivities. Stilbenoids are phytoalexins, secondary metabolites produced by the plant as means of defence against pathogens or stress factors [7]. The antimicrobial activity of natural stilbenoids [8–10] and their presence in plants as both constitutive and inducible secondary metabolites suggest that these compounds may play an important role in the resistance to diseases [11]. Stilbenoids can exist as both monomers and oligomers. Monomers such as resveratrol, pterostilbene, piceatannol and oxyresveratrol (Fig. 1), are characterized by the presence of two aromatic rings linked by an olefin, and the *trans* isomer (*E*) is usually the most stable and the most common in nature. Besides the diverse number and different position of the hydroxy groups, the aromatic rings can bear prenyl, geranyl or farnesyl chains. Oligomers derive from the oxidative coupling of monomers. All the stilbenoids can be found as aglycones or as glycosylated forms [12]. The major dietary source of stilbenoids comes from grapes and wine from Vitaceae family (*Vitis vinifera* L.) but they are also present in peanuts, cocoa, blueberry, bilberry, cowberry, red currant, cranberry, strawberries [11]. Resveratrol has been largely studied in the last decades for its antioxidant, anti-inflammatory, anticancer, antidiabetic, antimicrobial activities [13]. Its antiviral activity has been also widely investigated and it has been exhaustively highlighted in the recent literature [14–18].

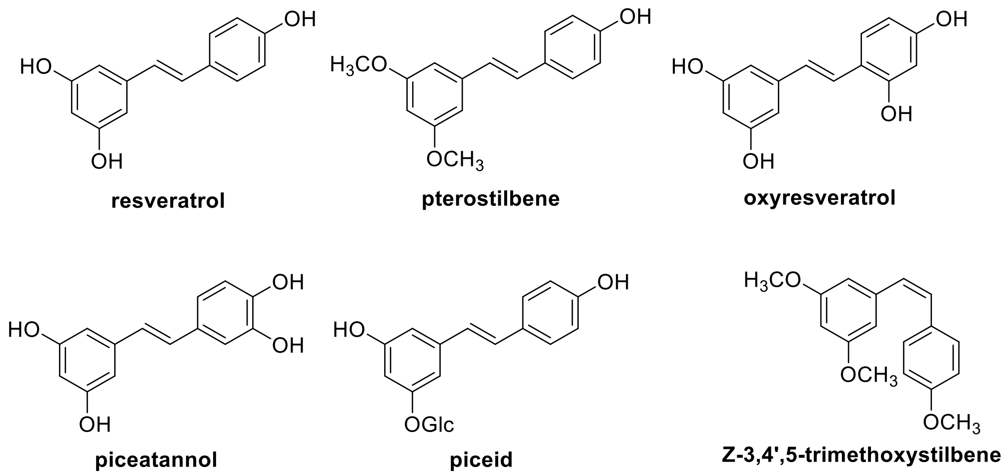


Fig. 1. Representative natural monomeric stilbenoids.

Whilst the antiviral activity of resveratrol has been extensively studied, little is known about the efficacy of its monomeric and oligomeric derivatives. In this review we provide an overview of natural resveratrol-derived stilbenoids investigated as antiviral agents, with emphasis on targets and mechanism of action.

The review also highlights the evidence of antiviral activity of synthetic resveratrol analogues designed to improve the stability and increase the potency of the natural precursors. The review is divided into sections according to the target virus. For each virus, the recent advances in the research of potentially active natural and synthetic stilbenoids are summarized.

2. Virus life cycle, targets and antiviral assays

Viruses are obligate intracellular parasites, needing a host cell to exploit cellular biochemical pathways and factors to replicate. Their genome, single or double stranded DNA or RNA, encodes for various structural and regulatory proteins, and it is contained in the protein capsid, forming the nucleocapsid. Some viral species acquire a phospholipid-containing envelope from the host cell membrane during viral budding (Fig. 2) [19]. The viral life cycle begins when the virus binds to a host cell through electrostatic adsorption to specific host cell receptors (i.e. CXCR4 and CD4 on immune system cells), structurally complementary to exterior structures of the viral particle (i.e. the

HIV envelope glycoproteins gp120 and gp41). After penetration into the host cell, viral uncoating and release of viral nucleic acids occur. Using host resources, virus starts transcription and synthesis of early viral proteins, like polymerase enzymes, followed by nucleic acids replication, and, in the case of retrovirus, the viral integrase (IN) incorporates viral nucleic acids into the host DNA. Eventually, also late viral proteins undergo transcription and translation, and their assembly leads to new viral particles, named “virions”, which can be released to infect other cells (Fig. 2). In the case of influenza virus, the viral enzyme neuraminidase (NA) is required to cleave residues on virions, allowing their release from the infected host cell. Antiviral agents block one of these steps, or may interfere with host cell functions, which facilitate viral replication [19,20]. Indeed, since viral genome encodes just for a few structural and regulatory proteins, viruses need to exploit host cell metabolism and biochemical signalling pathways to survive. In particular, NF-κB (nuclear factor-κB) pathway, regulating the expression of several proteins acting in the immune response, has been demonstrated to be an attractive target for viral pathogens because it is rapidly activated during infections and is involved in critical steps of the host cell cycle. Modulating the NF-κB pathway, viruses such as HIV, herpesviruses, and HCV, have been shown to block host cell apoptosis, thus prolonging the host cell survival and gaining time for viral replication and progeny production. Viruses such as HIV and HSV harbour NF-κB binding sites in their promoters, whose activation results in enhanced viral transcription. In these cases, molecules interfering with NF-κB pathway have been shown to have antiviral activity against both HIV-1 and HSV-1 [21,22].

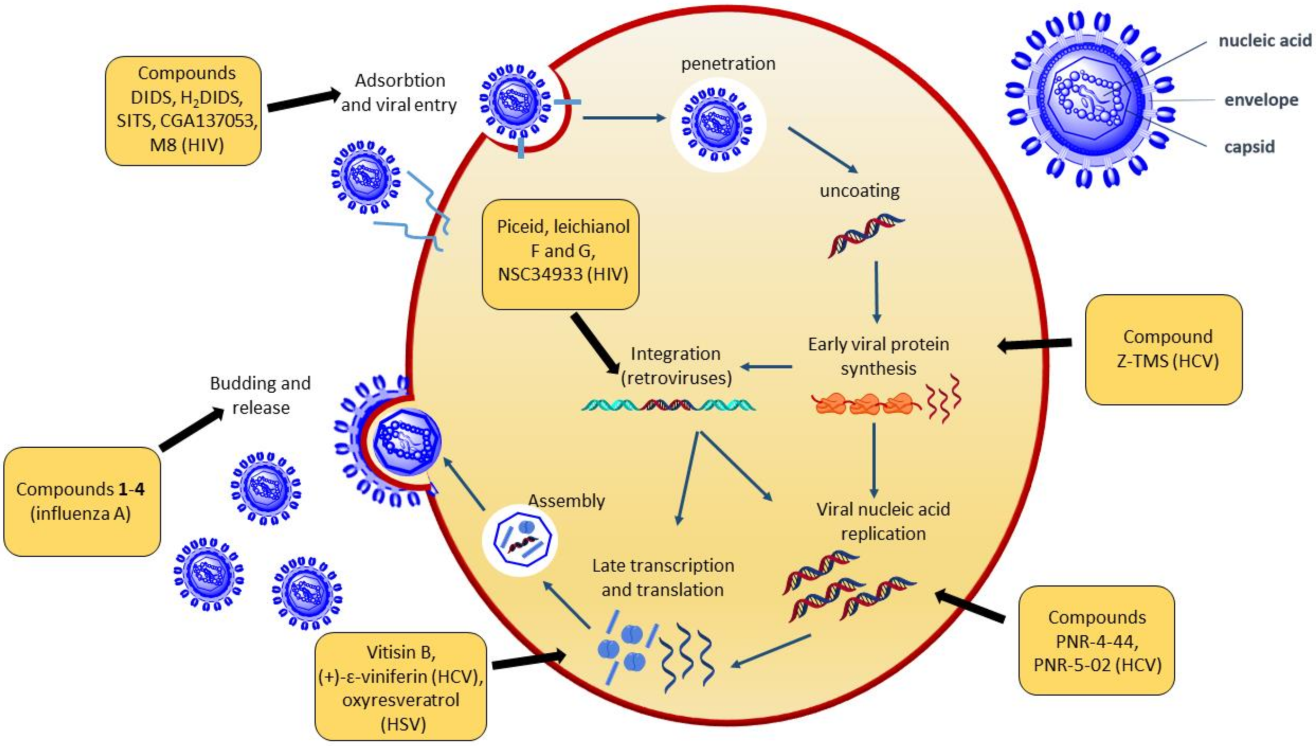


Fig. 2. Virus structure and life cycle. In the orange boxes the most representative stilbenoids acting on major sites of viral replication.

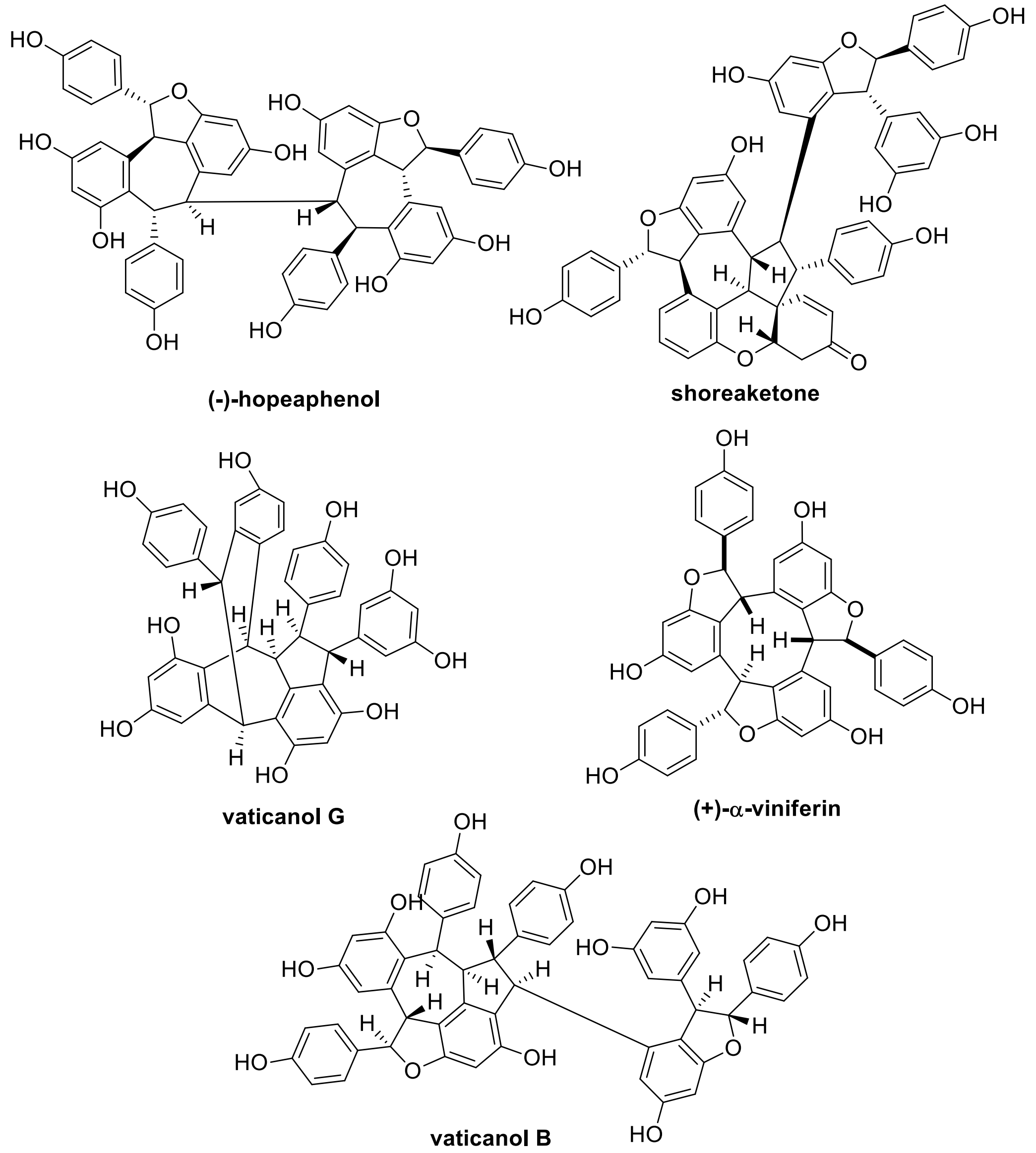
Depending on the type of virus and on the host cells, several assays are available to investigate the activity of antiviral compounds. In the plaque reduction assay (PRA), infected cells are treated with a potential antiviral agent, which should cause a decrease of the number of pfu (plaque forming units) in comparison with untreated cells, allowing the determination of IC_{50} values (the concentration of the compound able to decrease plaque numbers by 50% with respect to untreated cells). Determining compounds cytotoxicity as the concentrations reducing cell viability by 50% (CC_{50}), the selectivity index (SI) can be calculated as the ratio of CC_{50} to IC_{50} [23,24]. Cytopathic effect (CPE) reduction assays measure the IC_{50} values as the inhibitory concentrations of antivirals needed to lower by 50% the viral induced CPEs [25], which are morphological changes in host cells caused by viral invasion [26]. Time-of-addition (TOA) assays may be employed to explore which steps of viral cycle life are blocked, by adding an antiviral compound to the virus/host cells at different time points relative to viral inoculation [27]. Other methods, such as immunoassays, flow cytometry, fluorescence and transmission electron microscopy, polymerase chain reaction (PCR) techniques, enzymatic assays (i.e. NA activity assay), are also used to study viral replication, to detect viral products such as DNA, RNA, proteins, and to identify the target of the antiviral agent studied [24,28].

3. Antiviral activity of stilbenoids

3.1. Influenza viruses

Influenza viruses are responsible for acute respiratory infections in two billions of people, which may result in hundred thousands of deaths every year worldwide, according to WHO estimations [29]. Influenza viruses belong to the *Orthomyxoviridae* family. There are four types of seasonal influenza viruses (A-D), but only type A and B are the main responsible for human infections and may cause seasonal epidemics. Influenza A virus is a single-stranded, segmented RNA virus that presents different subtypes based on haemagglutin (HA1-18) and neuraminidase (NA1-11) transmembrane glycoproteins [30]. The infection occurs when the viral HA binds to the host sialic acid receptors, which mediate the virus entry by endocytosis. The moderately acidic pH of the endosome triggers the fusion of the viral and endosomal membranes and opens up the viral M2 ion channel, leading to viral ribonucleoproteins (vRNPs) release in the host cytoplasm and their transfer to the cell nucleus. After transcription and replication, mediated by the viral RNA-dependent RNA polymerase (vRdRp), the vRNPs enter the host cytoplasm to constitute new virions, which can be released to infect other cells when NA cleaves the sialic residues on the budding newly formed virions [31]. To date, there are three main families of anti-influenza A virus drugs. The first family (adamantanes) inhibits the virus uncoating and subsequent release of viral RNA in the host cells, by blocking M2. The second class (neuraminidase inhibitors) targets NA preventing the release of viral particles from infected cells. Compounds targeting NA have aroused great interest because this glycoprotein plays a fundamental role in the movement of the virus to and from sites of infection in the respiratory tract [32]. The last family consists of inhibitors of vRdRp [30].

A certain number of natural stilbenoids have been studied for their potential activity against influenza virus. Ito *et al.* tested the oligostilbenoids reported in Fig. 3, together with other representative stilbenoid compounds isolated from some species of Dipterocarpaceaeous plants, against Influenza A virus (IAV) (A/NWS/33 strain, H1N1 subtype). Hopeaphenol and shoreaketone exhibited antiviral activity, while vaticanol B, vaticanol G and α-viniferin did not show any inhibitory action against IAV. The exact mechanism of action has not been elucidated yet. However, time-of-addition (TOA) assay showed no significant difference in the SI values for any of the tested compounds between addition to the medium at the same time of viral infection and addition immediately after viral infection, suggesting that the active compounds did non inhibit the early stages of viral replication (adsorption and penetration) [33].



(-)-hopeaphenol

shoreaketone

vaticanol G

(+)-α-viniferin

vaticanol B

Fig. 3. Structures of some natural resveratrol oligomers tested against HSV and IAV [33].

In 2010, five stilbenoids were isolated together with resveratrol from the lianas of *Gnetum pendulum* (Gnetaceae) by Liu and colleagues and were evaluated by neuraminidase (NA) activity assay and CPE reduction assay [34] (Fig. 4). In the NA activity assay, all the six molecules exhibited inhibitory effects on three influenza virus NAs [A/PR/8/34 (H1N1); A/Guangdong/243/72 (H3N2); B/Jiangsu/10/2003] with IC_{50} values ranging from 5.0 (Gnetupendin B for H1N1) to 26.3 µg/mL (Gnetin D for B/Jiangsu/10/2003). The drug oseltamivir acid, a NA inhibitor, was used as positive control. In the CPE reduction assay, the anti-influenza virus activities of the six NA inhibitors against influenza virus A/Guangdong/243/72 (H3N2) in MDCK (Madin-Darby canine kidney) cells were also determined. Gnetupendin B (IC_{50} = 6.17 µg/mL, SI = 32.40) and shegansu B (IC_{50} = 11.99 µg/mL, SI = 9.60) showed anti-influenza activities, even if with higher IC_{50} than ribavirin and oseltamivir acid, used as positive controls for the antiviral activity. Notably, gnetin D

(IC$_{50}$ = 0.67 µg/mL, SI = 57.44) was the most active oligomer with an IC$_{50}$ value eightfold lower than that of ribavirin (IC$_{50}$ = 5.54 µg/mL). Notably, the methoxy group in isorhapontigenin (IC$_{50}$ = 4.28 µg/mL, SI = 8.99, Fig. 4) increased the antiviral activity with respect to resveratrol (IC5$_0$ > 22.22, SI = not determined). The obtained results showed that the tested stilbenoids exerted antiviral effects inhibiting NA [34].

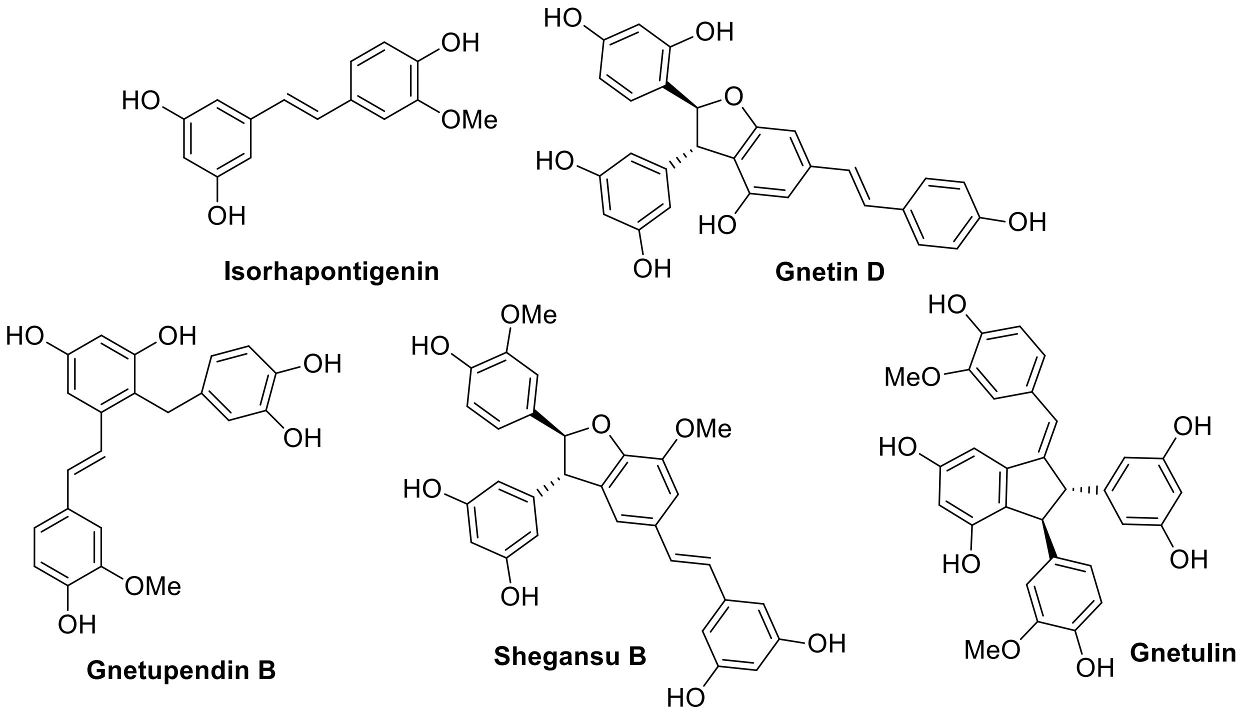
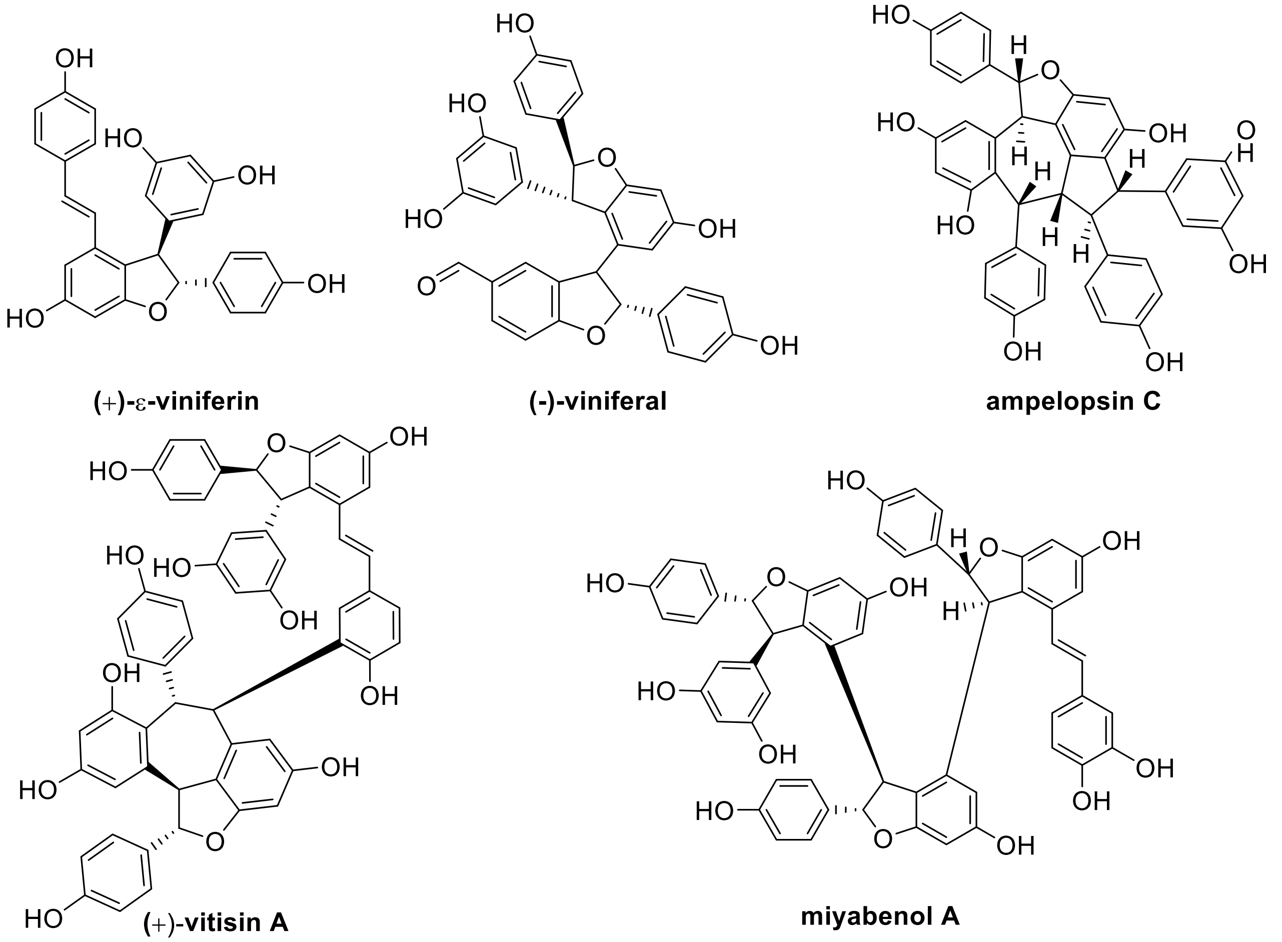


Fig. 4. Structures of stilbenoids isolated together with resveratrol from lianas of *Gnetum pendulum* and tested as anti-influenza compounds [34].

Influenza A may induce the inflammation of infected airway epithelial cells, which produce several chemotactic cytokines, in particular RANTES (Regulated upon Activation, Normal T Cells Expressed and Secreted), a potent chemoattractant for monocytes and macrophages [35]. RANTES belongs to CC chemokine ligand 5 (CCL5), whose expression is affected by viral infections since its gene promoter regions contain recognition sites for many virus-activated transcription factors. Moreover, influenza A virus activates the phosphatidylinositol 3-kinase (PI3K)/Akt signal pathway, which is involved in CCL5 retinal expression in human pigment epithelial cells after viral infection [36]. Various studies demonstrated the capability of resveratrol to interfere with the function of chemoattractant receptors [37]. In 2008, Huang *et al.* isolated five oligostilbenes from the roots of *Vitis thumbergii* and evaluated their activity on influenza A virus (H1N1)-stimulated RANTES production in human alveolar epithelial cell line A549 [38]. Compounds (+)-ε-viniferin, (−)-viniferal, ampelopsin C, miyabenol A and (+)-vitisin A (Fig. 5) exhibited significant inhibitory effects of RANTES production at noncytotoxic concentration (0.1-1.0 µM) with EC$_{50}$ (half maximal effective concentration) values lower than that of resveratrol (Table 1). Notably, the tested tetramers and trimers resulted more active than dimers. In particular, (+)-vitisin A was the most active compound with EC_{50} value of 0.27 µM and low cytotoxicity (CC_{50} value of 22.4 µM). Furthermore, the authors showed that influenza A (H1N1)-induced RANTES secretion was correlated with the activation of the PI3K/Akt and the signal transducer and activator of transcription (STAT1) signaling cascades in the A549 lung epithelial cells. Western blot analysis revealed that (+)-vitisin A reduced H1N1-induced Akt phosphorylation and subsequently STAT1 activation, suggesting a potential use of (+)-vitisin A in inflammatory disorders after virus infection [38].



(+)-ε-viniferin

(-)-viniferal

ampelopsin C

(+)-vitisin A

miyabenol A

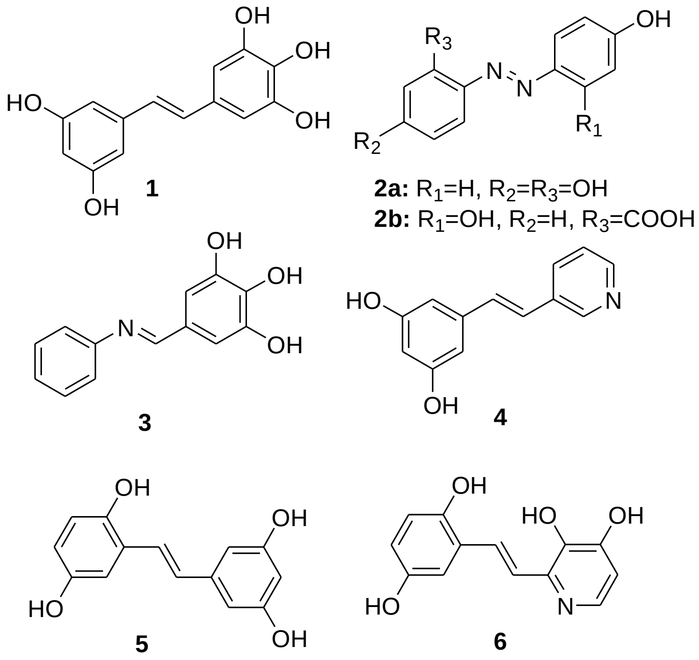
Fig. 5. Structures of oligostilbenoids isolated from *Vitis thunbergii* and tested against influenza A virus [38].

Table 1. Effects of resveratrol and five resveratrol derivatives on RANTES production and cytotoxicity in H1N1-infected human alveolar epithelial cells A549 [38]

Compounds	**RANTES production EC_{50} (µM)**	**Cytotoxicity CC_{50} (µM)**
resveratrol	28.37 ± 3.54	52.6 ± 11.2

(+)-ε-viniferin	10.11 ± 1.23	54.7 ± 9.9
(−)-viniferal	8.48 ± 0.94	> 400
ampelopsin C	0.57 ± 0.16	> 1000
miyabenol A	0.81 ± 0.05	8.4 ± 2.5
(+)-vitisin A	0.27 ± 0.04	22.4 ± 3.3

Li *et al.* evaluated a series of differently substituted resveratrol derivatives as NA inhibitors on the influenza virus strain A/PR/8/34 (H1N1) by a NA inhibition assay (Compounds **1**-**4**, Fig. 6). Thirty-five compounds were found to be active with IC$_{50}$ values ranging from 4.95 to 186 µM [39]. The active derivatives were used to develop 3D quantitative structure-activity relationship (3D QSAR) models and molecular docking in order to elucidate the molecular interaction with the target NA (X-ray structure taken from the RSCB Protein Data Bank, ID 1A4G). In the 3D QSAR studies, CoMFA (comparative molecular field analysis) and CoMSIA (comparative molecular similarity indices analysis) were applied. CoMSIA calculated the hydrophobic, H-bond donor and H-bond acceptor fields, in addition to the steric and electrostatic fields calculated also by CoMFA model. The results showed that the azo group replacing the olefin and the presence of –OH at the *para*-position, capable of donating hydrogen bonds (**2a**), increased the inhibitory activity. Moreover, a –COOH group at the *ortho*-position of the benzene ring (**2b**) seemed to be responsible for a strong hydrogen bond-reinforced ionic interaction with three residues (i.e. ARG115, TYR408, ARG373) present in the active site of NA. The results from QSAR studies were in good agreement with docking studies. The authors compared the binding mode of compound **2b** with that of the NA inhibitor zanamavir (ZNM), which formed seven hydrogen bonds in the active site. Moreover, both ZNM and compound **2b** formed hydrogen bonds with the residues GLU225, ASP128, and ARG373. To confirm the antiviral activity, the resulting active compounds were tested on A/PR/8/34 (H1N1)-infected MDCK cells. Compound **2b** showed a good anti-influenza activity (EC$_{50}$ = 7.28 ± 0.84 µg/mL, CC$_{50}$ > 100 µg/mL) in the pretreatment assay. This finding suggested that the derivatives may interact with NA, blocking the cleavage of the linkage between HA and sialic acid receptors on the host cells surface, whereby avoiding the virions release from infected cells [39].



2a: R_1=H, R_2=R_3=OH
2b: R_1=OH, R_2=H, R_3=COOH

Fig. 6. Structures of the synthetic NA inhibitors used for 3D QSAR studies (**1**-**4**) [39] and compounds tested as SARS-CoV inhibitors (**5**,**6**) [40].

3.2. Coronaviruses

Coronaviruses represent a diverse family (*Coronaviridae*) of enveloped, single-stranded positive-sense RNA viruses usually causing gastrointestinal and respiratory disorders in humans and animals. Their genome accounts for about 30000 nucleotides, making it the largest found in any RNA viruses. Human coronaviruses often lead to respiratory illnesses that may degenerate into pneumonia and severe acute lung injury [41,42]. SARS-CoV is the coronavirus responsible for the epidemic of the severe acute respiratory syndrome (SARS), emerged in November 2002 and lasted until July 2003 with 9.6% mortality rate [2].

To the best of our knowledge, there are no example in the literature of natural stilbenoids tested as SARS-CoV inhibitors. However, a series of twelve synthetic resveratrol analogues were prepared and evaluated by Li *et al.* as potential inhibitors of SARS-CoV replication in Vero E6 cells. In particular, compounds **5** and **6** (Fig. 6) did not show cytotoxicity in concentration $\geq$ 2 mg/mL (8.2 mM) and were able to inhibit the cytopathic effect (CPE) in concentration < 0.5 mg/mL (2.05 mM). Possible lower doses were not investigated [40].

MERS-CoV (Middle East Syndrome Coronavirus) is a viral pathogen causing respiratory illnesses, with a 34% mortality, firstly identified in Saudi Arabia in 2012 [43]. Up to date, there are still no effective anti-MERS drugs or vaccines approved on the market [44]. In *in vitro* studies Lin *et al.* [45] investigated the effect of resveratrol on MERS-CoV infection and showed that the cytotoxicity of MERS-CoV-infected Vero E6 cells (CRL-1586) was reduced by resveratrol treatment (250 µM) to 25%. To determine where the resveratrol action occurred, they found that MERS-CoV RNA replication was suppressed and MERS titers were significantly reduced. Moreover, they showed that resveratrol significantly inhibited MERS nucleocapsid (N) protein translation, fundamental for MERS-CoV replication, in a dose dependent manner, in the concentrations ranging from 125 to 250 µM. Since MERS-CoV is well known to induce cell apoptosis [46] and high levels of cleaved Caspase 3 were reported after MERS-CoV infection as apoptosis indicator [47], Lin *et al.* found that resveratrol decreased Caspase 3 cleavage dose-dependently, suggesting that resveratrol reduced the MERS-CoV mediated cells apoptosis [45]. The exact mechanism needs further investigations, but it is known that resveratrol may reduce inflammation by interfering with the NF-κB (Nuclear Factor-Kappa B) pathway [48] and it could down-regulate fibroblast growth factor 2 (FGF-2) signalling [49], involved in MERS-CoV-induced apoptosis [50].

3.3. Hepatitis C virus

Hepatitis C virus (HCV) is a bloodborne positive single-stranded RNA virus, belonging to the *Flaviviridae* family in the *Hepacivirus* genus [51]. HCV causes hepatitis C that can be a mild illness lasting a few weeks (acute) or a lifelong and serious disease (chronic). Hepatitis C may degenerate into cirrhosis and HCV is the major cause of liver cancer. Worldwide 71 million people have chronic HCV infection [52]. HCV exists in seven genotypes and more than 80 subtypes, which differ in the pathogenesis and response to treatments. Because of its high genetic variability, due to a high replication rate and lack of proofreading activity by the HCV RNA-dependent RNA polymerase (vRdRp), so far there is no effective vaccine against hepatitis C, and new antivirals able to overcome the drug-resistance and to reduce the side effects in the long treatment are needed [51,52]. HCV infection starts with HCV nanoparticles attachment to the liver cells through a multistep-process involving the viral glycoproteins E1 and E2 and cellular receptors. Then, HCV particles internalization occurs by clathrin-mediated endocytosis. Upon the release of the RNA into the cytoplasm, the viral RNA is translated as a single polypeptide that undergoes co- and post-translational processes by viral and cellular proteases to yield structural (Core, E1, E2) and seven non-structural (NS) proteins. The NS proteins include NS5B (vRdRp), key enzyme in RNA synthesis and one of the main targets of the direct-acting antivirals (DAAs). The other NS proteins are fundamental in the formation of the replication complex and virus assembly. In particular, HCV NS3 protein plays a significant role in the viral life cycle. [51,53,54].

The effect and the mechanism of action of resveratrol as anti-HCV agent was reported in the review by Abba *et al.* [14]. More recently, Nguyen *et al.* [55] studied the anti-HCV and antitumoral activities of the natural compound Z-3,5,4'-trimethoxystilbene (Z-TMS, Fig. 1), isolated for the first time from the bark of *Virola elongate* [56]. The compound was tested on hepatoma cell lines (GS5 and FCA4) expressing HCV-1b subgenomic replicons. Z-TMS was 100 times more potent than resveratrol in downregulating the levels of HCV NS5B polymerase in a dose-dependent manner, without displaying cytotoxicity to human hepatocytes *in vitro* or in mice liver. The authors demonstrated that Z-TMS interfered with the cancer stem cell (CSC) marker DCLK1, microtubule dynamics and induced autophagy, G_2-M arrest, and nuclear fragmentation [55].

Other natural stilbenoids were identified as potent anti-HCV. In the last years, Lee *et al.* published two papers about this topic. In 2016, they observed the inhibitory effect of an extract from the roots of *Vitis vinifera* on HCV infected- Huh7.5 hepatocarcinoma cells and identified five oligostilbenes as responsible for the suppression of HCV replication exerted by the extract. The compounds were two resveratrol dimers, ampelopsin A (Fig. 7) and (+)-ε-viniferin (Fig. 5), and three resveratrol tetramers, vitisin A (Fig. 5), wilsonol C and vitisin B (Fig. 7). Also in this case, compounds with more complex structures (tetramers) demonstrated higher potency in comparison to simpler ones (dimers). In particular, vitisin B resulted to be the most potent oligostilbene, displaying its activity by directly binding the NS protein HCV NS3, dramatically decreasing viral replication at nanomolar concentrations (EC_{50} value = 6 nM) (Table 2). Moreover, the authors verified that vitisin B, combined with an NS5B polymerase inhibitor, sofosbuvir, exhibited a synergistic or at least additive antiviral activity. Eventually, in *in vivo* pharmacokinetic studies, after intraperitoneal injection in rats, vitisin B showed a preferred tissue distribution in the liver, which is a major organ of HCV replication [57]. Because of the difficulties to obtain the pure compound in substantial amounts for further investigation, studies on infected mice were not included [58].

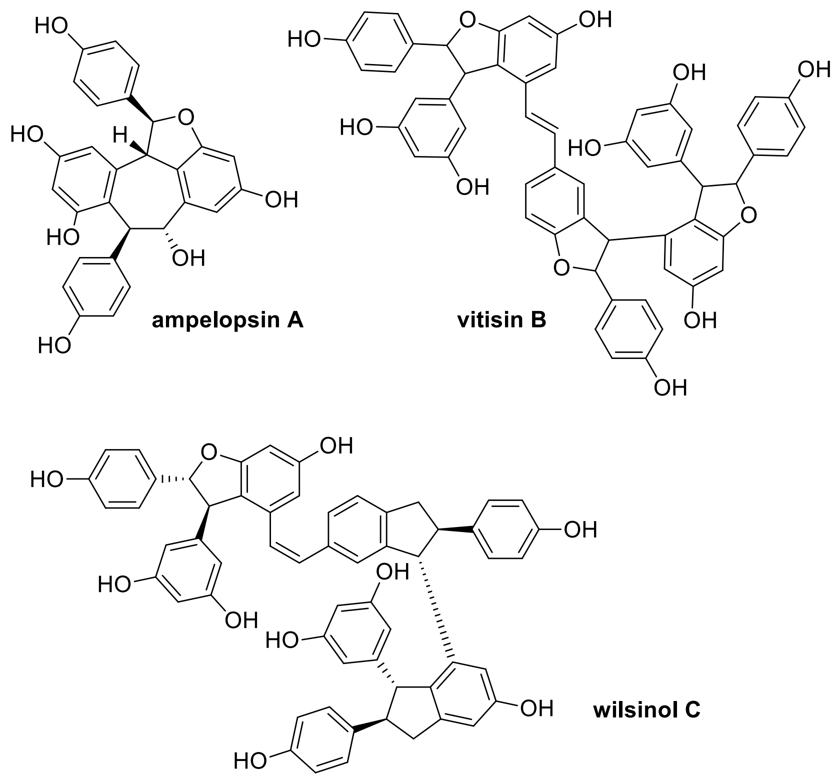


Fig. 7. Natural stilbenoids isolated from the roots of *Vitis vinifera*, together with (+)-ε-viniferin and vitisin A, tested against HCV [57].

Table 2. Antiviral activity and cytotoxicity of oligostilbenes on HCV infected-Huh7.5 hepatocarcinoma cells [57].

Compound	**EC_{50} (µM)**	**CC_{50} (µM)**
Ampelopsin A	5.740	>10
(+)-ε-viniferin	0.159	>10
Vitisin A	0.035	>10
Wilsonol C	0.016	>10
Vitisin B	0.006	>10

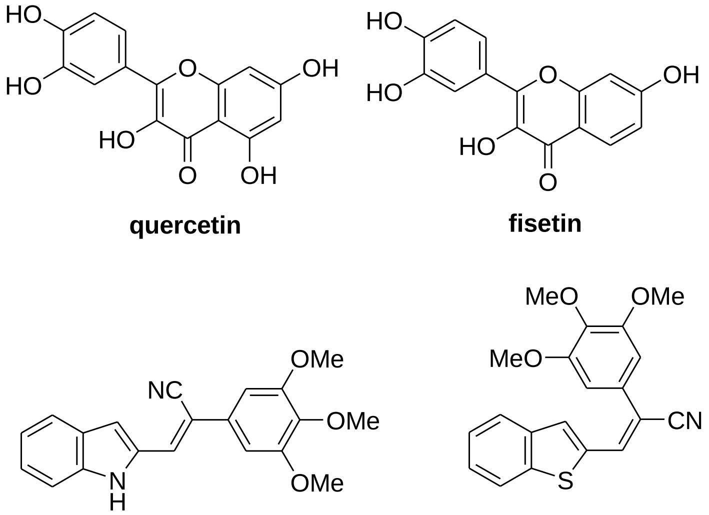
In 2019, the same authors confirmed the inhibitory capability of (+)-ε-viniferin against HCV [58]. The pure enantiomer (+)-ε-viniferin ((+)-ε-VF) (Fig. 5) was isolated from the extract of roots of *Vitis vinifera* and, thanks to an efficient synthetic methodology, substantial amounts of (±)-ε-viniferin ((±)-ε-VF) and penta-acetylated (±)-ε-viniferin ((±)-ε VF-5Ac) were made available. All the three compounds showed potent anti-HCV activity in 2a and 1b HCV genotype replicon cells with low cytotoxicity (CC_{50} > 10 µM). The results from genotype 2a luciferase reporter assay showed that (+)-ε-VF exerted the most potent antiviral effects with an EC_{50} of 0.1 µM, followed by the racemates (±)-ε-VF (EC_{50} = 0.2 µM) and (±)-ε-VF-5Ac (EC_{50} = 2.37 µM). In general, the pure enantiomer (+)-ε-VF exhibited 2.0- and 3.2-fold higher antiviral activity than that of the racemate in both genotypes 2a (RT-PCR and Western blot). These data suggested a lower potency of (–)-ε-viniferin. However, similar experiments on genotype 1b HCV replicon cells showed that (±)-ε-VF displayed higher antiviral activity (EC_{50} = 1.7 µM) in comparison to (+)-ε-VF (EC_{50} = 7 µM). Additionally, the authors confirmed that (+)-ε-VF suppressed HCV NS3 helicase activity, using a GO-based NS3 helicase assay described by Jang [59] and comparing the effect to resveratrol activity. The pharmacokinetic profile of (±)-ε-VF were studied on mice after oral and intraperitoneal administration. The intraperitoneal dosing resulted in much higher plasma concentrations than those after oral administration, suggesting that the low oral bioavailability of (±)-ε-VF is due to poor absorption through the intestinal epithelium and to intestinal first pass effects. [58].

3.4. Dengue virus (DENV)

Dengue virus (DENV) is a mosquito-borne virus, causing a wide spectrum of diseases, which can vary from mild fever to acute-flu like illness and life-threatening haemorrhagic fever (severe dengue). DENV belongs to the *Flaviviridae* family, possessing a single-stranded RNA genome, and includes four serotypes (DENV-1-4). 100-400 million dengue virus infections are estimated each year. Dengue affects in particular South-East Asia (about 70% of the global burden) and Western Pacific regions, but it has rapidly spread worldwide in recent years. So far, there is no specific treatment for dengue fever [60,61]. Various polyphenols have exhibited anti-dengue activity, such as quercetin and fisetin (Fig.9) [62,63]. In 2019, Jasso-Miranda and coworkers studied a collection of polyphenols, including resveratrol, for their potential beneficial effects against dengue virus. Unfortunately, resveratrol did not exhibit antiviral activity for U937-DC-SIGN cells infected with DENV-2 and DENV-3, although showing low toxicity [64].

Han *et al.* evaluated the antiviral activity of other twenty-six resveratrol analogues, originally synthesized as anti-cancer agents [65,66]. In particular, the compounds PNR-4-44 and PNR-5-02 showed a dose-dependent inhibition of DENV2-induced cytopathic effect (CPE) in Huh 7 cells, with an EC_{50} of 8.12 ± 0.82 nM and 7.22 ± 0.85 nM, respectively (Fig. 8). The cytotoxicity was also low, with CC_{50} values of 1.7 µM and 1.9 µM, resulting in SI values of 209 and 263, respectively. In the time-of-addition (TOA) assay, the compounds resulted inactive when added 12 hours after the infection, suggesting an activity in the post-entry and fusion events, such as viral translation, replication, or events prior to viral proteins assembly. Both compounds were found to inhibit RNA viral synthesis in DENV2 replication, but they resulted inactive against the viral RdRp.

In a pretreatment cells study, only PNR-5-02 affected the DENV2 replication, implying at least partially interactions with host cell factors required for viral replication. On the other hand, PNR-4-44, inactive in the pretreatment, seemed to directly target the virus. The exact mechanism of action is not known. Interestingly, Dengue virus belong to the same family of HCV, sharing a similar NS3 protein [67]. Since vitisin B and ε-viniferin were found to inhibit HCV NS3 [57,58], Dengue virus NS3 could be likely one of the possible target. The key molecular features of resveratrol analogues involved in the anti-DENV activity still need to be elucidated and the authors underlined that SAR studies are still needed to improve their activity-cytotoxicity profile [66].



quercetin **fisetin**

PNR-4-44 **PNR-5-02**

Fig. 8. Quercetin, fisetin and synthetic resveratrol analogues endowed with anti-DENV activity [66].

3.5 Human immunodeficiency virus (HIV)

Human immunodeficiency virus type 1 (HIV-1) is an enveloped single-stranded RNA virus of the *Lentiviridae* family [68], responsible for the acquired immunodeficiency syndrome (AIDS), which currently affects more than 37 million people [69]. HIV infects CD4-positive T-helper through viral envelope glycoproteins (gp120 and gp41) that recognize and bind the CD4 receptor and other coreceptors (CCR5, CXCR4). Once inside the cells, the virus exploits a reverse transcriptase (RT) to transcribe its RNA into DNA that is incorporated in the cell host genome by a viral integrase. At this point, as an integrated provirus, HIV can remain latent for years. The transition from latency to HIV replication and subsequent infection occurs when host cellular transcription factors are activated along with regulatory HIV proteins [5]. Antiretroviral drugs effectively control viral replication, but the high mutation rate of HIV-1, along with the huge number of viral particles produced by host cells, has led to drug resistance and expedited the development of novel drug therapies [69,70].

Although resveratrol showed various antiviral activity for several viruses, it did not exhibit any inhibition against wild-type HIV-1 replication in activated T cells or in transformed T cell lines [70]. On the contrary, together with nucleoside analogue reverse transcriptase inhibitors (NRTIs) such as tenofovir, didanosine and zidovudine, resveratrol seemed to improve the inhibition of cellular ribonucleotide reductase (RNR) [71]. In 2017, Chan *et al.* confirmed the inefficiency of resveratrol as anti-HIV in activated T cells and in transformed T cell line Jurkat [72]. Surprisingly, the authors found that resveratrol prevented productive infection of resting CD4 T cells in a dose-dependent manner. Moreover, four natural stilbenoids, pterostilbene, piceid, piceatannol and isorhapontigenin (Fig. 1, 3), were tested for anti-HIV-1 activity on resting CD 4 T cells. Pterostilbene was active at all concentrations tested, piceid and isorhapontigenin inhibited productive infection at a concentration 30 µM, while piceatannol was less potent at the same concentrations[72]. This finding suggests that in the tested monomers the free hydroxy groups reduce the antiviral potency.

Pflieger *et al.* confirmed this observation in another study. In 2013, they isolated a collection of stilbenoids, consisting of monomers and oligomers (Fig. 1, Fig. 9) from stalks of *Vitis vinifera* and from stem bark of *Millicia excelsa*, and the compounds were tested on two different models of polynucleotidyl transferases, HIV-1 integrase (IN) and eukaryote MOS-1 transposase, for further modelling of new agents against IN [73]. Seven out of the 17 compounds resulted completely inactive, while pterostilbene, piceid, leachianol F and leachianol G exhibited a good inhibitory efficiency comparable to that of raltegravir, an anti-integrase compound. These data highlighted that glycosylation or methylation in resveratrol monomers increased the ability to inhibit HIV-1 integrase [73].

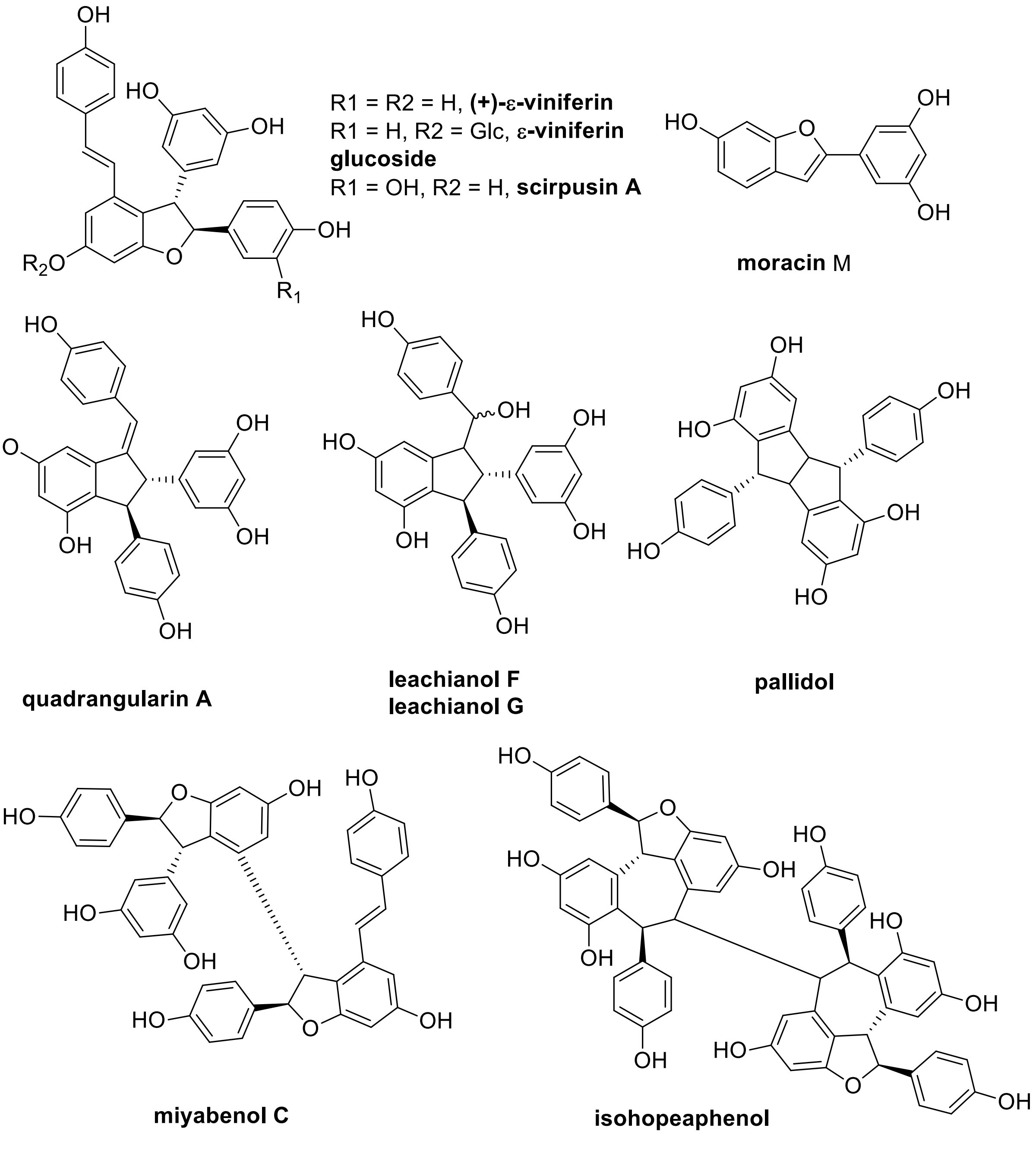
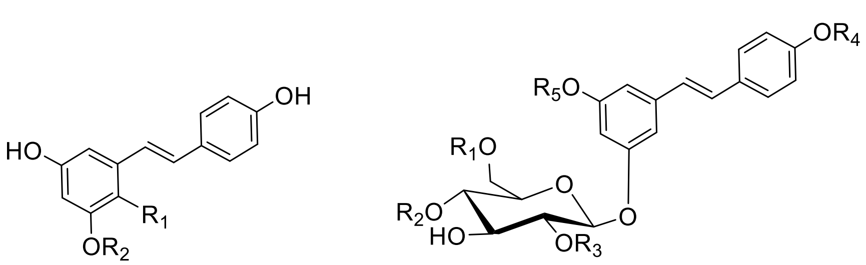


Fig. 9. Structures of stilbenoid compounds isolated from *Vitis vinifera* and *Millicia excelsa*, together with vitisin B, hopeaphenol, resveratrol, piceid, pterostilbene and piceatannol, tested as anti-HIV agents [73].

Resveratrol along with various glucopyranoside derivatives was extracted and isolated from *Polygonum cuspidatum* and *Polygonum multiflorum* by Lin *et al.* [74]. The compounds were tested on cell line C8166 as anti-HIV-1 agents. Resveratrol showed the greatest inhibitory activity against HIV replication with EC_{50} 4.37 μg/mL and therapeutic index value (TI = CC_{50}/EC_{50}) of 8.14, while the glycosylated derivatives showed a severe decrease of potency with respect to their corresponding aglycones (Fig. 10, Table 3). Among the glycosylated compounds, the position of sulphate group did not influence the antiviral activity. Conversely, the stereochemistry of the double bond seemed to affect the activity, as the *cis* isomer **14** (EC_{50} = 84.77 µg/mL) was more active than the *trans* isomer **13b** (EC_{50} > 200 µg/mL), even if more cytotoxic (CC_{50} = 98.82 µg/mL and CC_{50} = 812.88 µg/mL for **14** and **13b**, respectively) [74]. Interestingly, compounds **14** is characterised by a *cis* configuration at the double bond, which likely favors the interaction with the target, thus increasing the antiviral activity.



resveratrol $R_1,R_2 = H$
piceid $R_1 = H, R_2 = Glc$
12 $R_1 = OGlc, R_2 = Glc$

13a $R_1 = SO_3^-Na^+, R_2,R_3,R_4,R_5 = H$
13b $R_2 = SO_3^-Na^+, R_1,R_3,R_4,R_5 = H$
13c $R_3 = SO_3^-Na^+, R_1,R_2,R_4,R_5 = H$
13d $R_4 = SO_3^-Na^+, R_1,R_2,R_3,R_5 = H$
13e $R_5 = SO_3^-Na^+, R_1,R_2,R_3,R_4 = H$

14

Fig. 10. Structures of resveratrol derivatives isolated from *Polygonum cuspidatum* and *Polygonum multiflorum* tested as anti-HIV agents [74].

Table 3. Anti-HIV-1 activities of resveratrol derivatives tested by Lin *et al.* [74].

Compound	CC_{50} (µg/mL)	EC_{50} (µg/mL)	TI
resveratrol	35.57 ± 1.73	4.37 ± 1.96	8.14
piceid	> 200	> 200	
12	> 200	176.26 ± 24.26	> 1.13
13a	745.85 ± 10.84	> 200	< 3.73
13b	812.88 ± 18.90	> 200	< 4.06
13c	> 2000	153.42 ± 19.25	> 13.04
13d	> 2000	> 200	
13e	526.52 ± 2.61	89.66 ± 1.65	5.87
14	98.82 ± 6.23	84.77 ± 4.09	1.17

Looking for natural products as anti-HIV agents, Dai *et al.* isolated from the organic extract of the leaves of *Hopea malibato* Foxw. (Dipterocarpaceae) oligostilbenes malibatols A and B, dibalanocarpol, and balanocarpol (Fig. 11). The isolated compounds were tested in the NCI (National Cancer Institute) primary anti-HIV screen: dibalanocarpol and balanocarpol showed modest HIV-inhibitory activity with EC_{50} values of 46 and 20 µM, respectively, while malibatols A and B were only cytotoxic [75]. In this case, the dihydrobenzofuran ring of balanocarpol and dibalanocarpol with respect to the benzofuran ring of malibatol A and B seemed to play a key role in the anti-HIV activity.

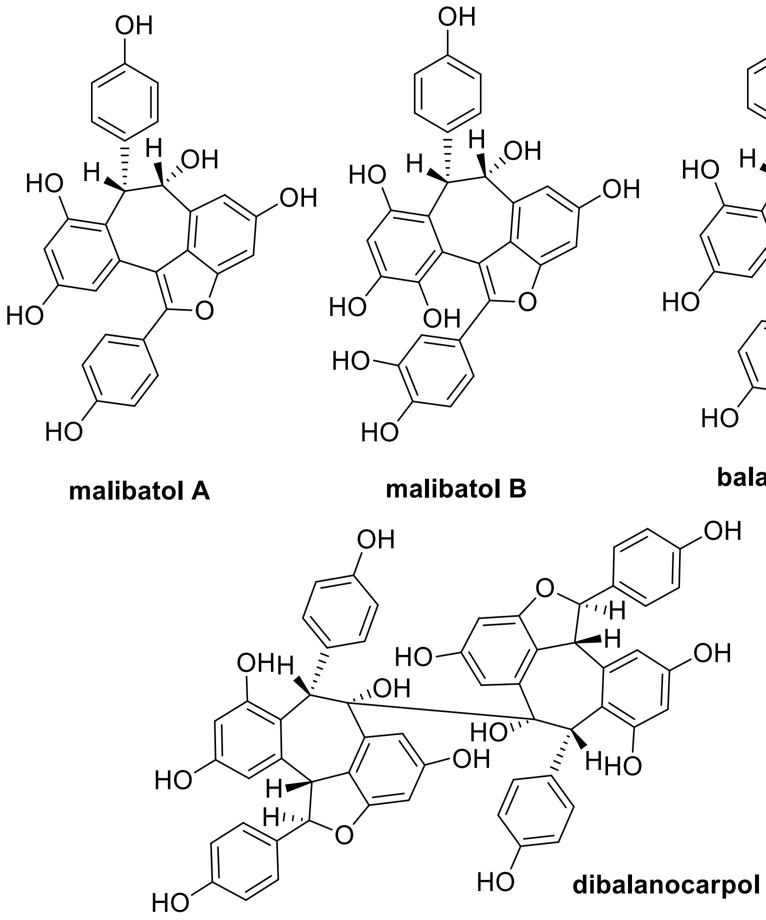
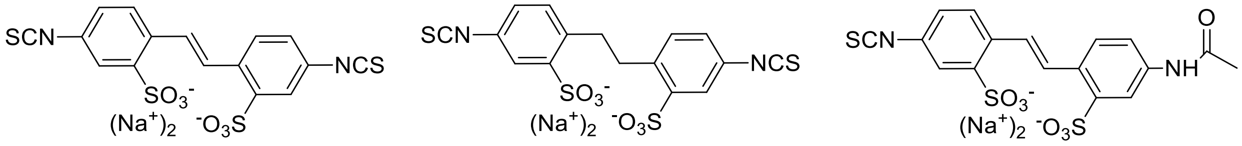


Fig. 11. Structures of resveratrol derivatives isolated from *Hopea malibato Foxw* as anti-HIV agents [75].

Cardin *et al.* studied the stilbene disulfonic acids 4,4’-diisothiocyanato- stilbene-2,2’-disulfonic acid (DIDS), 4,4’-diisothiocyanatodihydrostilbene-2,2’-disulfonic acid (H_2DIDS), and 4-acetamido-4’-isothiocyanatostilbene-2,2’-disulfonic acid (SITS) as CD4 antagonists (Fig. 12). CD4 is the receptor expressed on the cell surface of T helper lymphocytes and macrophages, involved in the activation of immune system response, but also mediator of the HIV fusion, binding the viral envelope glycoprotein gp120. All the three compounds inhibited the growth of HIV-1 strain RF in C8166 and MT4 cells, and GB8 strain in JM cells. In particular, DIDS and H_2DIDS seemed to covalently bind a lysine residue in the CDR-3 domain of CD4, a region that is not closely involved in CD4-immune system response activation, thus blocking the CD4-gp120 interaction. Hence, the two diisothiocianate functions were fundamental in the interaction with the target, since SITS resulted less active. DIDS resulted the most active compound, maybe due to the constraint conferred by the double bond with respect to the less rigid dihydrostilbene H_2DIDS [76].



4,4'-diisothiocyanatostilbene-2,2'-disulfonic acid **(DIDS)**

4,4'-diisothiocyanatodihydro-stilbene-2,2'-disulfonic acid **(H_2DIDS)**

4-acetamido-4'-isothiocyanato-stilbene-2,2'-disulfonic acid **(SITS)**

Figure 12. Structures of synthetic resveratrol analogues with anti-HIV activity [76].

In a more recent study, other stilbene disulfonic acids resulted to inhibit IN by a novel mechanism [77] (Fig. 13). IN is an essential enzyme for HIV-1 replication, catalysing the insertion of the newly synthesized viral DNA into the host chromosome by two steps: 3' processing (3'P), that is the IN-catalysed cleavage of the terminal dinucleotide at the 3'-end of the viral DNA mimic, and strand transfer (ST), that is integration of the 3'P product in the host DNA. Clinical integrase ST inhibitors, like raltegravir (RAL), bind the IN active site [78]. However, IN tends to mutate giving rise to drug resistance. Therefore, Aknin *et al.* used a high-throughput screening approach to find ST inhibitors targeting IN outside of its catalytic site. In a preliminary screening they identified NSC34931 (stilbenavir, Fig. 13), a compound already known for its cytopathic effects on HIV-1 [79], as the most active among the molecules that showed an inhibitory activity on ST step. Notably, NCS34931 consisted of a chemical scaffold different from that of the known ST inhibitors. SAR studies were performed on the selected compounds and the naphthalene moiety resulted to be fundamental for the activity. Indeed, NSC163 and NSC163175 (Fig. 13), lacking aromatic rings, were completely inactive at the highest concentrations tested, and replacing the naphthalene ring with an ethoxybenzene caused a 10-fold decrease of potency in NSC47745 (Fig. 13). NSC34933, with just some rearrangements in the naphthalene substitution pattern with respect to NSC34931, appeared to maintain the sub-micromolar activity of the parent compound and to be even less cytotoxic (Fig. 13, Table 4). The two compounds were tested against clinically relevant mutants resistant to conventional IN inhibitors and the stilbene derivatives maintain their activity at sub-micromolar concentration, representing a potential therapeutic alternative. Indeed, they were found to compete with DNA in binding IN, especially involving the *C*-terminal domain (CTD), at concentrations 10 times lower than that necessary to inhibit 3'P and ST [77].

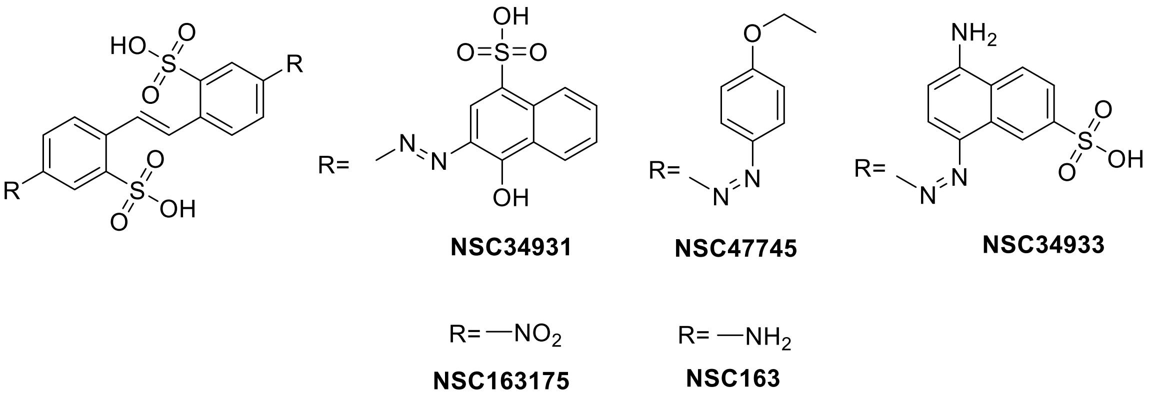
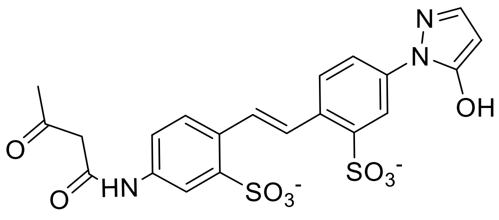


Fig. 13. Structures of disulfonic acid derivatives with anti-HIV activity [77].

Table 4. Summary of stilbene disulfonic acid derivatives activities from [77].

	In vitro (μM, IC_{50} ± SD)		**Ex vivo (μM)**		
Compound	**3’P**	**ST**	**EC_{50}**	**CC_{50}**	**SI**
NSC34931	0.32 ± 0.12	0.18 ± 0.07	3.07	59.0	19.2
NSC34933	1.1 ± 0.3	0.5 ± 0.2	0.60	>100	>166
NSC47745	3.2 ± 1.5	3.2 ± 1.7	15.3	>100	>6.5
NSC163175	>111	>111	ND	ND	ND
NSC163	>111	>111	ND	ND	ND

Cellular proteins, like NF-κB, and regulatory viral proteins, like Tat (transactivator of transcription), are involved in the reactivation of HIV-provirus after latency by binding sites in the HIV-1 long terminal repeat (LTR) [80]. NF-κB transcription factors take part to several biological processes such as immune and inflammatory responses, cell transformation, apoptosis, embryonic liver development, and transcription of viral genes, including HIV. NF-κB is highly produced upon activation of the primary human T cells, the primary HIV target, and it activates a complex array of systems resulting in increased transcriptional activation and virus multiplication, binding target sequences in the LTR. Since NF-κB is a normal part of human cells, it should not mutate, like viral targets [68]. On the other hand, Tat is a viral regulatory protein, which recruits cellular factors binding the enhancer region of the HIV-LTR, like NF-κB, enhancing virus replication. Moreover, Tat induces the HIV-coreceptor expression, such as CXCR4 and CCR5, and the release of chemokines, which attract monocytes and CD4 T lymphocytes to perpetuate the infection [81]. In 2000, a synthetic stilbene compound, CGA137053 (Fig. 14), was found to bind directly Tat protein and to prevent the upregulation of the HIV coreceptor CXCR4. The two negative charged sulfonate groups, the spacer between them, and the pyrazolic nucleus of CGA137053 seemed to be fundamental in the interaction with Tat. The inhibition of Tat protein was demonstrated to work intracellularly and to inhibit HIV-1 replication on HIV-infected, primary human leucocytes (PBL) and macrophages in a dose-dependent manner (EC_{90}, 90% effective concentration, ranging from 0.5 to 5 µM depending on the HIV strains) [82].



CGA137053

Fig.14. Structure of the synthetic stilbene compound CGA137053 binding directly Tat protein. [82].

Lethal mutagenesis is another antiviral approach that takes advantage of the high rate of RNA virus mutation by intentionally further increasing it so that the virus becomes unable to replicate its genome with enough fidelity to maintain its infectiousness [83]. Clouser *et al.* studied the synergistic effect of resveratrol in combination with decitabine (5-aza-2'-deoxycytidine, 5-aza-dC), a deoxyribonucleoside analogue able to lethally mutagenize HIV-1 in a cell culture system [70]. In a previous study, the same research group demonstrated the synergistic effect between a nucleoside analogue and a ribonucleotide reductase inhibitor (RNRI) in increasing the HIV mutation rate, resulting in HIV infectivity decrease [84]. Indeed, resveratrol has been reported to inhibit HIV-1 replication by interacting with SIRT1 [15] and to be an inhibitor of ribonucleotide reductase, the enzyme involved in the reduction of ribonucleotides into the corresponding deoxyribonucleotides [85]. Therefore, Clouser *et al.* synthesized fifteen resveratrol derivatives and screened them on HIV-1-infected 293T-cells alone and in combination with decitabine. Piceatannol and **23a** showed an improved activity against HIV-1 infection, maintaining a low cytotoxicity (Fig. 15, Table 5). Replacing the double bond with a heterocycle (**20-22**, **23e-23f**) or with an α, β-unsaturated ketone (**19**) did not improve the potency of resveratrol. The 2-hydroxy-naphthalene (**23c**) and the isoquinoline (**23d**) moieties were also ineffective in improving the potency. Conversely, hydroxy groups seemed to play a key role in the antiviral activity since piceatannol, bearing four hydroxy functions, was one of the most active compound, whereas compound **7**, differing from the most active compound **23a** only in the pyridine ring in place of a 4-hydroxy phenyl ring, completely lost potency. The benzofuran and benzothiophene derivatives (**10a**, **b-11a**, **b**), bearing three hydroxyl groups, demonstrated a better activity than resveratrol, having however a low SI. Overall, the distance between the aromatic rings bearing at least three hydroxy group and the resulting conformation of the compounds seemed to influence the antiviral effects. On the other hand, only resveratrol demonstrated a synergism with decitabine, increasing HIV-1 mutant frequency [70]. However, in 2016 the same authors studied combinations of resveratrol and 5-azacytidine (5-aza-C), the decitabine riboside analogue, and they found that the synergistic activity at low concentration of resveratrol as RNRI is mainly due to decreased accumulation of RT products rather than to increased viral mutagenesis [86].

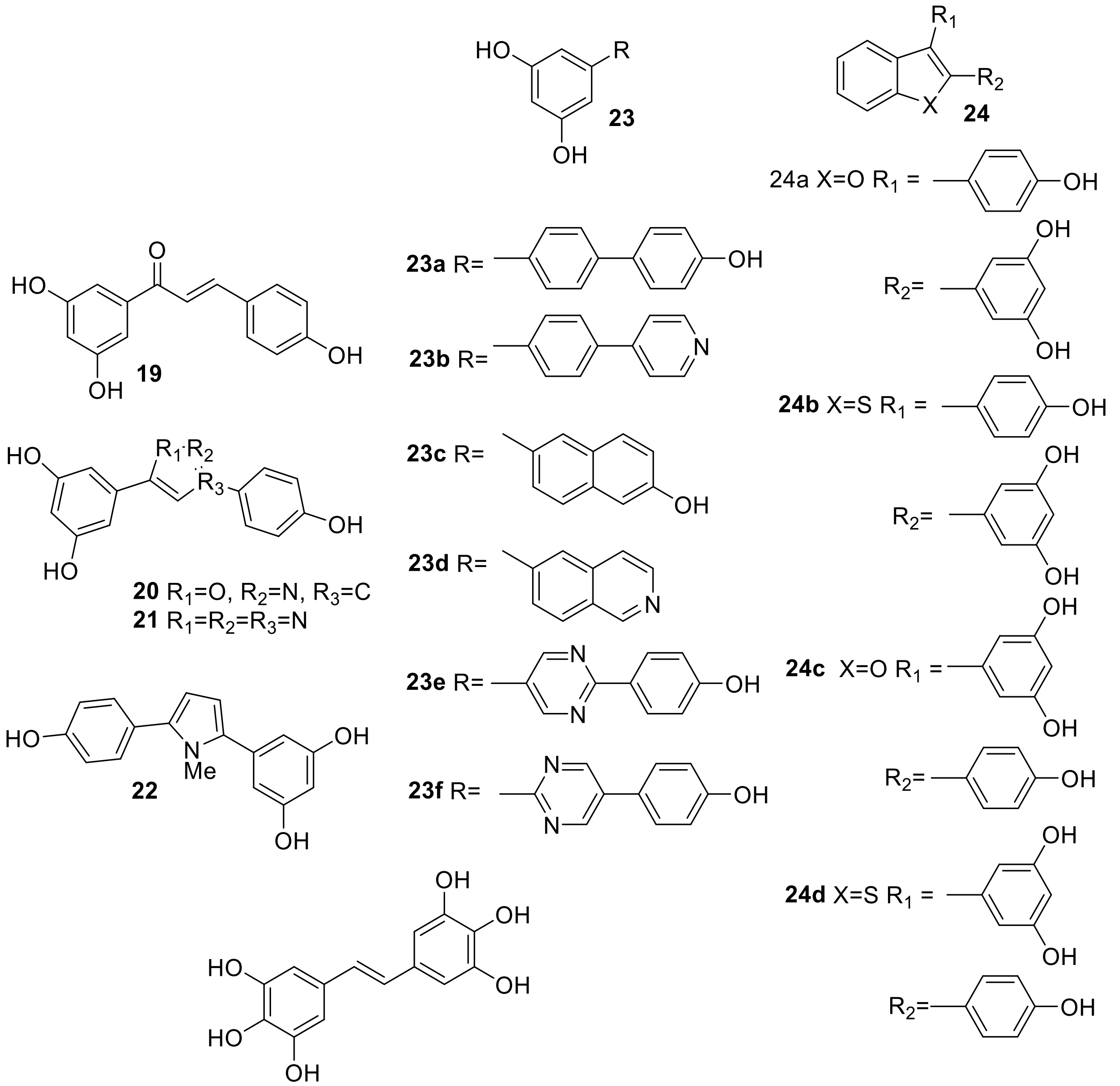


Fig. 15. Structures of resveratrol derivatives screened on HIV-1 [84], [87].

Table 5 Anti-HIV-1 activity (EC_{50}), toxicity (TC_{50}), and SI of resveratrol and derivatives from [84].

Compound	EC_{50} (μM)	TC_{50}^{a} (μM)	SI^{b}
resveratrol	>75	>300	ND
piceatannol	21.4	>400	>18.7

19	>75	ND	ND
20	>75	ND	ND
21	>75	ND	ND
22	>75	ND	ND
23a	8.8	179	20.3
23b	>100	ND	ND
23c	>75	ND	ND
23d	>75	ND	ND
23e	>75	ND	ND
23f	>75	ND	ND
24a	35.0	84.8	2.4
24b	34.4	131	3.8
24c	65.1	108	1.5
24d	45.1	118	2.6

[a] *Concentration of compound that induces toxicity in 50% of the host cells,* [b] *Selectivity index:* TC_{50}/EC_{50}.

In 2015, Han *et al.* reported the anti-HIV-1 properties of a synthetic resveratrol analogue termed 3,3',4,4',5,5'-hexahydroxy-*trans*-stilbene M8 (Fig. 15). The compound showed a dose-dependent inhibition of cytopathic effect (CPE) in MT-4 and TZM-bl cells, infected with HIV-1 NL 4-3 or BaL variants, with an EC_{50} = 0.29-1.69 µM (Table 6). M8 seemed to inhibit the viral attachment to host cells. Indeed, firstly in TOA assays, M8 did not show any activity when added 2h after the infection, suggesting that M8 targets an early step in HIV-1 replication. Secondly, quantitative real-time PCR analysis showed a decrease level of early viral reverse transcription products in a dose-dependent manner. Lastly, in a post-attachment assay, authors demonstrated that compound M8 was able to block virus attachment to cells before the fusion step [87].

Table 6. Antiretroviral activity of M8 against laboratory strains of HIV-1 in different cells from [87].

Variant	**Cell line**	**Assay**	**EC_{50} (µM)[a]**	**CC_{50} (µM)**	**SI**
NL 4-3 (X4)	MT-4	MTT	0.74 ± 0.081	11.9 ± 1.1	16
NL 4-3 (X4)	TZM-bl	Luc	0.29 ± 0.031	20.1 ± 1.9	69
Bal (R5)	TZM-bl	Luc	1.69 ± 0.17	20.1 ± 1.9	12

[a] EC_{50}*: 50% effective concentration, determined in MT-4 cells against NL4-3 HIV-1 by MTT or luciferase activity (Luc) in TZM-bl cells.*

3.6. *Norovirus*

Norovirus (NV) is a single-stranded positive-sense RNA virus within the family of *Caliciviridae* [88], and human NV (HNV) is considered the major cause of epidemic acute gastroenteritis worldwide, leading to 685 million cases per year. To date, there are no vaccines or specific drugs in NV-infection treatment [89]. The noroviruses are subdivided into six different genotypes (GI-VI), and GI, II and GIV are responsible for human infections. Virions, consisting of an icosahedral nucleocapsid and RNA, enter the target cells and release their genomes, which bind to the cell ribosomes and proteins, and are transcribed by the viral RNA-polymerase [88,90].

Harmalkar *et al.* performed the total synthesis of the natural gramistilbenoids A, B, C, and of their analogues (**25-27**) (Fig. 16) [91]. The stilbenoid **26** bearing a vinyl group displayed a moderate inhibitory activity against HNV replication on HG23 cells. Therefore, SAR studies were performed on **26**, and it was observed that a vinyl moiety and –OMe groups on ring A, a substituent at the *para*-position on ring B, and the *trans* configuration of the double bond were crucial for the antiviral activity. An optimum of antiviral potency, low cytotoxicity and highest metabolic stability in human and mouse liver microsomes was achieved in compound **28** (EC_{50} = 2.43 µM, CC_{50} < 100 µM). **28** inhibited the viral RNA genome replication probably involving the heat shock factor 1 (HSF-1) dependent stress inducible pathway, a host signal target and a new mechanism of action that may lead to the development of new anti-HNV drugs [91].

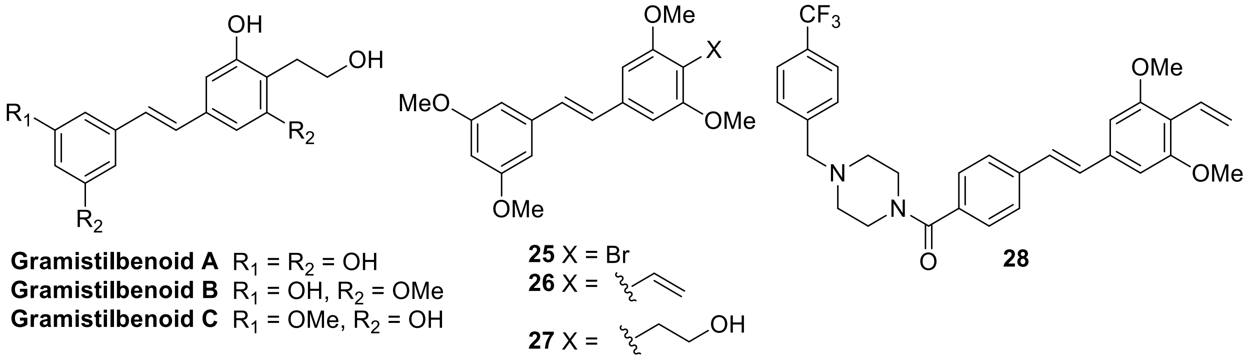


Fig. 16. Structures of gramistilbenoids A, B, C, and of their analogues **25-28** [91].

3.7. *Enterovirus*

The genus *Enterovirus*, belonging to the large family of *Picornaviridae*, includes enteroviruses (EVs), coxsackie A (CVA) and B (CVB) viruses, echoviruses, polioviruses (PV), and rhinoviruses (RV). This wide class of viruses is responsible for several illnesses, such as hand-foot-and-mouth (HFM) disease, encephalitis, paralysis, respiratory diseases, poliomyelitis, affecting millions of people worldwide. Enteroviruses are non-enveloped small positive-strand RNA viruses, encapsulated by an icosahedral capsid. The life cycle starts when the virus binds to a surface cell receptor, and it is internalized by endocytosis into the cell. The RNA is released into the cytosol and translated into a polyprotein, which is cleaved by the viral proteases to yield the structural and NS proteins. The NS proteins are involved in the replication of RNA via a negative strand intermediate that works as template for the synthesis of new positive strands. The new synthesized RNAs may be further translated and replicated, or directly encapsulated in the viral capsid proteins to form new infectious virions. The viral proteases trigger also host cell factors, which help virus replication, reproduction and proliferation [92,93].

Resveratrol and *cis*-resveratrol isolated from the methanol extract of the twigs of *Caesalpinia latisiliqua* were tested for the antiviral activity against HRV1B-, CVB3- and EV71-infections by Oh *et al.* Resveratrol showed antiviral activity against HRV1B with IC_{50} values of 29.7 µM. Conversely, *cis*-resveratrol exhibited significant antiviral activity in CVB3 infection with IC_{50} value of 12.2 µM and in EV71 infection with IC_{50} value of 37.6 µM [94].

Segun *et al*. reported the anti-enteroviral activity of three stilbenoids (mappain, vadelianin and schweinfurthin G; Fig. 17) isolated from the leaves of *Macaranga barteri* (Euphorbiaceae) [95]. The pure compounds were tested against echovirus 7, 13 and 19 serotypes and were inactive against echovirus E13, while a good activity was reported on E19. In particular, vadelianin exhibited an IC_{50} value of 0.0036 nM and the best selectivity profile with SI value of 216.7 [95].

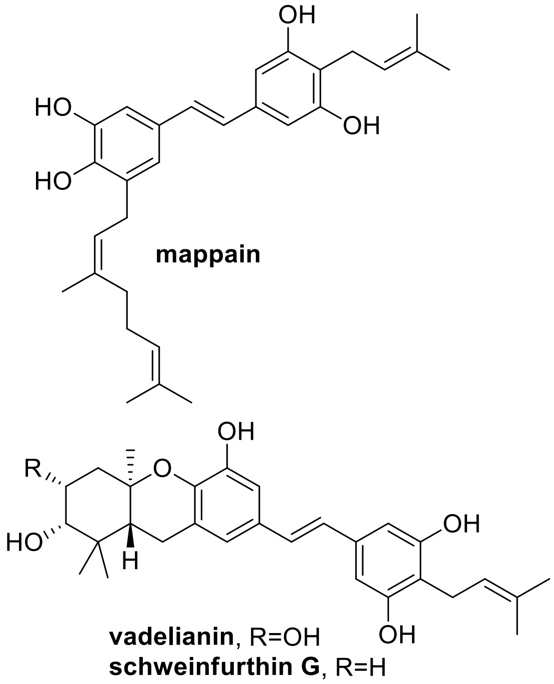


Fig. 17. Structures of mappain, vadelianin and schweinfurthin G [95].

3.8. Herpes Simplex Virus

Herpes simplex viruses (HSVs) belong to *Herpesviridae* family, *Alphaherpesvirinae* subfamily. Differently from all the other viruses treated above, they are double-stranded DNA viruses and exist as two types: HSV-1 and HSV-2 [96]. HSV-1 is the most common form of herpes. More than 60% of the human population contract orofacial infections, that can lead to infectious blindness and viral encephalitis in adults [97]. On the other hand, HSV-2 infection affects the genital area and is a major cause of sexually transmitted diseases (STD), such as HIV and human papillomavirus (HPV) [98]. The transmission of herpes viruses occurs from person to person by direct contact with infected secretions [99]. The infections may be latent and appear periodically, due to the virus capability to infect neurons, in particular the sensorial nerve termini, then traveling in a retrograde manner. Therefore, HSV may reactivate a lytic-replication cycle leading to a recurrent infection, viral shedding and transmission to new hosts [17,96]. Nucleoside analogues, such as acyclovir and pencyclovir, are administered as therapeutic agents against HSV. However, it is necessary to develop new antiherpetic compounds due to the growth of herpes simplex virus strains resistant to acyclovir [100]. An exhaustive overview on resveratrol as novel anti-herpes simplex virus was reported by Annunziata *et al.* [17].

In 2016, Ma *et al.* [23] demonstrated the anti-HSV activity of some stilbene derivatives isolated from Mulberry (*Morus alba* L.) leaves. All the compounds (Fig. 18) were tested against HSV-1 (15577 and a clinical strain) and HSV-2 (333 strain), and resulted to have good IC_{50} values ranging from 2.5 to 25.0 µg/mL, but low SI in many cases. In particular, mulberrofuran G resulted in SI values of 3.6 and 4 on the HSV-1 tested strains, and 3.5 on HSV-2. Kuwanon X was the best compound of the series with IC_{50} values of 2.2, 1.5 and 2.5 µg/mL and SI values of 37, 55 and 32 for HSV-1 15577, HSV-1 clinical strain and HSV-2 standard, respectively. For this reason, the authors deeply analyzed the mechanism of action of kuwanon X against HSV-1 by various experiments, including virucidal assay, inhibition of attachment and penetration assay and TOA assay. They concluded that kuwanon X was active as anti-HSV with multiple mechanisms of action, including inhibition of viral adsorption and penetration, reduction of immediate-early (IE), late (L) gene expression and viral DNA biosynthesis, and inhibition of the NF-κB activation induced by HSV. Indeed, NF-κB has been demonstrated to be highly activated by HSV-1 and HSV-2 in many cell lines, being necessary for initiation of viral replication and viral protein synthesis. The NF-κB pathway suppression has been revealed to inhibit HSV replication [21, 23, 101, 102].

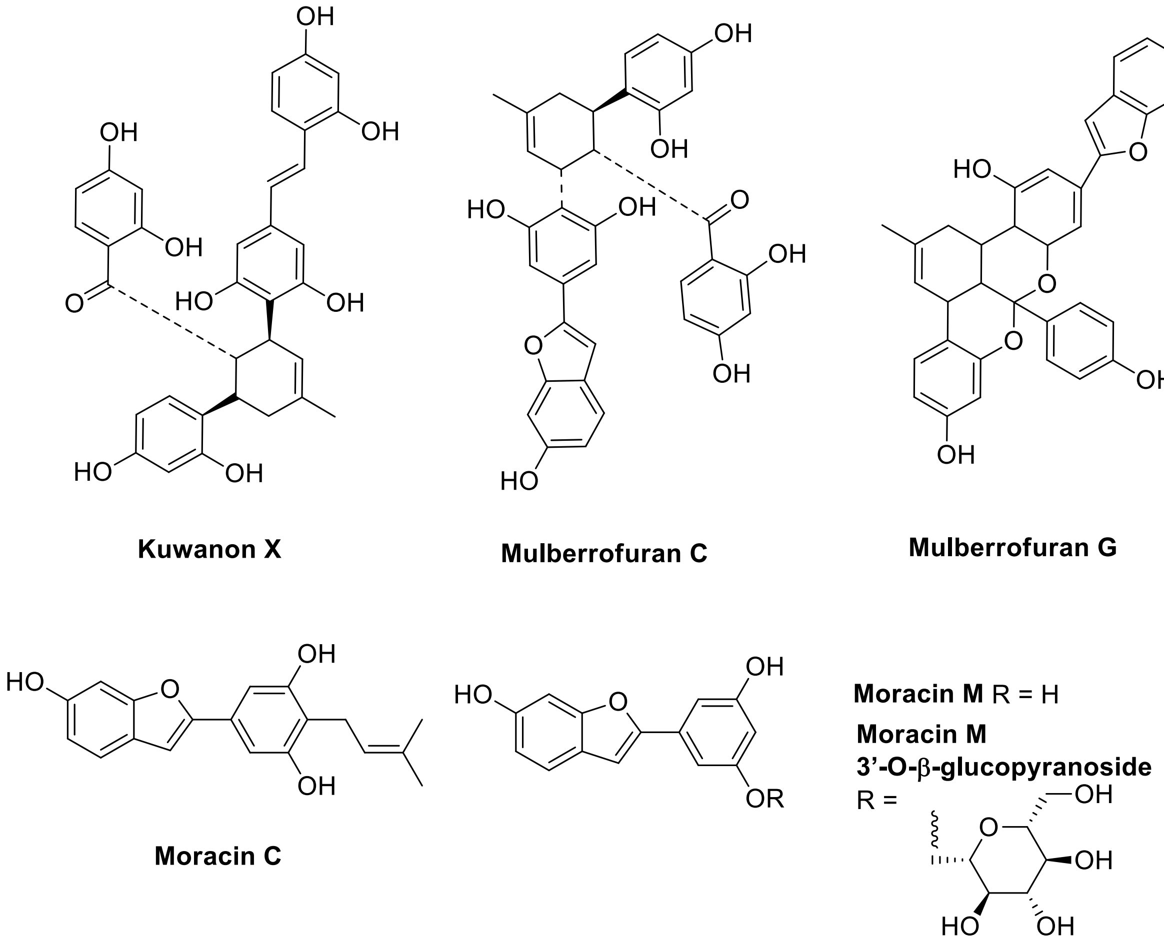


Fig. 18. Structures of compounds isolated from Mulberry tested as anti-HSV agents [23].

Ito *et al.* reported the *in vitro* antiviral activity against HSV-1 and HSV-2 of some oligostilbenoids isolated from *Shorea uliginosa* (Dipterocarpaceae) and other plants belonging to the same family [33]. Among the compounds tested also against IAV (Fig. 3), (−)-hopeaphenol, shoreaketone, vaticanol B, vaticanol G and α-viniferin showed a potent inhibitory effect towards the replication of HSV-1 and HSV-2. (–)-Hopeaphenol and shoreaketone showed the same IC_{50} value (2.8 µM) against HSV-1, while IC_{50} values of 6.4 µM and 6.8 µM against HSV-2, respectively, with SI ranging from 55 to 180. Additionally, the authors performed TOA assays to outline the drug-sensitive phase of HSV-2 replication to hopeaphenol and shoreaketone in comparison with acyclovir (ACV). The two oligostilbenoids acted as potent virucidal when added to the medium during viral infection, and throughout the incubation thereafter, or immediately after infection, whereas ACV exhibited a lower effect. This study suggested that the antiviral activity of these compounds is due to a different mode of action in comparison with that of the current clinically-used drug ACV [33].

In 2012, another collection of dimeric and oligomeric resveratrol derivatives (Fig. 19), previously isolated from plants of *Hopea* genus, was screened as anti-HSV-1 and anti-HSV-2 agents by Chen. *et al.* [103]. In general, the compounds were more active against HSV-2 infection than that from HSV-1. Vaticaffinol, a tetramer with reported antifungal properties, was one of the most promising compounds, with an IC_{50} value of 3.2 µM against HSV-2. The results of this study showed a potent, dose-dependent antiviral effect of the compounds, which promoted ROS production, coinciding with suppression of HSV-1 and HSV-2 replication in treated cells [103].

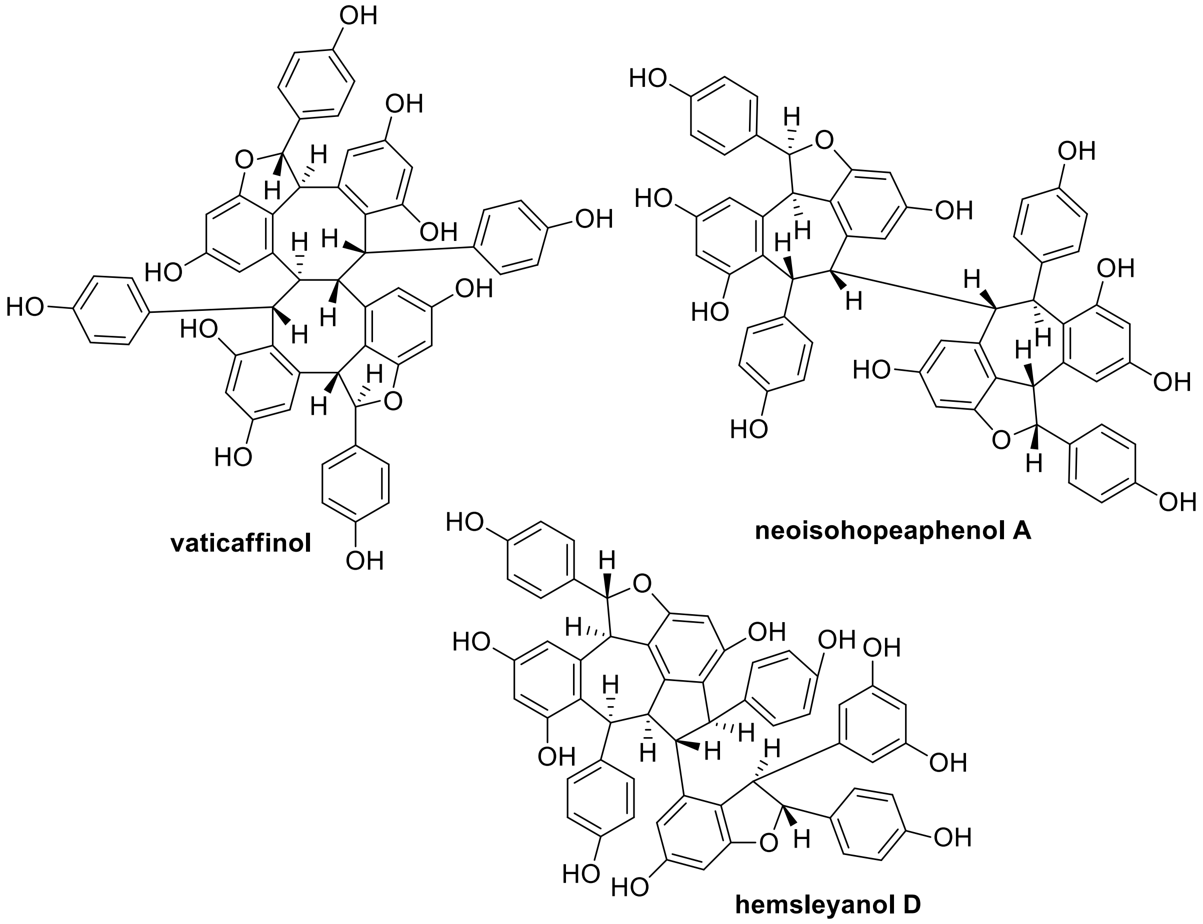


Fig. 19. Structures of some natural oligomers tested as anti-HSV agents by Chen. *et al.* [103].

After the reported studies on the beneficial effects of Thai traditional plants for the treatment herpes simplex virus, Chuanasa *et al.* investigated the antiviral activity of oxyresveratrol (Fig. 1), the major constituent of the heartwood of *Artocarpus lakoocha* (Moraceae), and its mechanism of action. The activity was determined against HSV-1 (7401H and KOS) and HSV-2 (Baylor 186) on infected Vero cells, with IC_{50} values of 19.8 µg/mL, 24.0 µg/mL and 18.7 µg/mL, respectively. In particular, oxyresveratrol showed a better anti-HSV activity than ACV in the plaque reduction assay against thymidine kinase (TK)-deficient (ACV-resistant) strain. Indeed, ACV is a nucleoside analogue, which exerts its antiviral action after TK phosphorylation [104]. This finding suggested that oxyresveratrol displayed a different mechanism of action than ACV, probably inhibiting the late viral protein synthesis, similarly to resveratrol. Moreover, in *in vivo* studies the authors demonstrated that HSV-1-infected mice orally treated with oxyresveratrol (125 mg/kg/dose), showed a significant delay in herpetic skin lesions development, while the topical administration of 30% oxyresveratrol ointment five times per day significantly retarded skin lesions, preventing mice death. Therefore, oxyresveratrol may be a suitable anti-HSV agent in topical treatment [105].

4. Conclusions

Nowadays, huge efforts are required to face emerging and re-emerging viruses that constantly infect human population, threating global public health and economy. Viruses easily undergo mutations, leading to drug resistance and increasing the need of new antiviral compounds with new mechanisms of action. In this scenario, targeting viruses with compounds from natural sources represents a promising strategy. Stilbenoids are a class of natural products endowed with several biological activities. Stilbenoids are synthesized by plants as means of protection against pathogens, whereby the potential antiviral properties of this class of natural compounds have attracted interest in the last years. Resveratrol has received massive attention for its potential health benefits, including anticarcinogenesis, anti-aging, antimicrobial and also antiviral properties. In this review we focused on the studies concerning other natural stilbene monomers and oligomers, which in most cases demonstrated to be more active than resveratrol itself. Notably, many compounds were discovered to exploit new mechanisms of action, interacting directly with the virus or modulating different pathways involved in the immune response, which may overcome virus drug resistance. However, though many *in vitro* studies provided promising results on this wide class of compounds, a limited number of *in vivo* studies has been performed so far.

This is mainly due to the difficulty of obtaining substantial amount of desired pure compounds, necessary for *in vivo* model biological evaluation, by extraction and purification procedures [13, 106, 107]. To overcome this problem, in the last decade, a number of research groups have focused on the development of versatile synthetic procedures to selectively produce pure derivatives [9, 10, 58, 107–110], taking advantage in many cases of chemo-enzymatic approaches. In this respect, biocatalysis has a number of important advantages such as high efficiency, mild reaction conditions, versatility and high selectivity (chemo-, regio- and stereoselectivity). Notably, preliminary *in vivo* studies reported in the literature have shown that in general, stilbenoids show low bioavailability and undergo extensive metabolism and it has been pointed out that bioconverted forms of polyphenols, (phase I and II metabolism) may probably have more importance than the parent compound found in the diet or administered in therapy. In many cases, synthetic efforts produced stilbene derivatives with greater potency than their parent compounds, allowing to expand knowledge on modes of action and to deepen structure-activity relationship studies of the most active compounds [39, 70, 76, 77, 82, 91].

Despite the promising results reported in the cited studies, future efforts, involving complementary expertise of chemists, nutritionists, molecular biologists, pharmacologists, are still needed to carry out *in vivo* experiments and remain of primary importance to confirm the antiviral potential of stilbenoids for clinical applications.

Table 7. Antiviral activity of the most active stilbenoids

Compound	Virus	Target	Activity (µM) and cell lines	Ref.
Hopeaphenol	Influenza A (A/NWS/33, H1N1)	NI	IC_{50} = 6.4 µM on MDCK	Ito, [33]
Gnetin D	- A/PR/8/34 (H1N1) - A/Guangdong/243/72 (H3N2) - B/Jiangsu/10/2003	NI	IC_{50} = 0.67 µg/mL (6.4 µM) (H3N2) on MDCK	Liu, [34]
(+)-Vitisin A	Influenza A (A/PR/8/34, H1N1)-	↓ RANTES	EC_{50} = 0.27 µM on Human alveolar epithelial A549	Huang, [38]
2b	Influenza A (A/PR/8/34, H1N1)	Neuraminidase	EC_{50} = 7.28 µg/mL (28 µM) on MDCK	Li, [39]
Resveratrol	MERS-CoV (HCoV-EMC/2012)	Interference with NF-κB pathway	Vero E6 (CRL-1586)	Lin, [45]
5	SARS-CoV	NI	Vero E6	Li, [40]
6		NI		
Z-3, 4’, 5-trimethoxy stilbene (Z-TMS)	- HCV-1b replicon (FCA4), JFH1 - HCV-2a (HCVcc)	↓ HCV NS5B	Hepatoma Huh7-derived (Huh7.5, GS5 and FCA4) FCA4-HCV$^+$DCLK1$^+$	Nguyen, [55]
Vitisin B	- HCV-2a (Rluc-J6/JFH1, J6/JFH1), - HCV-1b Con1 sequence (Bart79I) - HCVcc expressing an HCV NS5A-GFP fusion protein	↓ HCV NS3	EC_{50} = 0.003 µM (2a genotype) EC_{50} = 0.001 µM (1b genotype) on Huh7.5	Lee, [57]
(+)-ε-Viniferin		↓ HCV NS3	EC_{50} = 2.9 µM (2a genotype) EC_{50} = 7.0 µM (1b genotype) on Huh7.5	Lee, [58]
(±)-ε-VF		↓ HCV NS3	EC_{50} = 9.3 µM (2a genotype) on Human hepatoma Huh7.5 EC_{50} = 1.7 µM (1b genotype)	Lee, [58]
(±)-ε-VF-5Ac		NI	EC_{50} = 4.7 µM (2a genotype) EC_{50} = 10.4 (1b genotype) ** on Huh7.5	
PNR-4-44	DENV-2-induced CPE	↓ RNA viral synthesis	EC_{50} = 8.12 nM (0.00812 µM)	Han, [66]
PNR-5-02		↓ RNA viral synthesis and host cell factors interference	EC_{50} = 7.22 nM (0.00722 µM)	
Pterostilbene	HIV-1	↓ integrase, prevents CD4 T cells infection	Activated T and transformed T Jurkat (clone E6), IL-4 treated CD4 T and Resting CD4	Chan, [72]
Leachianol G	HIV-1	↓ integrase	293T	Pflieger, [73]

Resveratrol	HIV-1	Prevents CD4 T cells infection, synergism with RNR inhibitors	EC_{50}= 4.37 µg/mL (19 µM) on C8166	Lin, [74]
14		NI	EC_{50}= 84.77 µg/mL (172 µM) on C8166	
Dibalanocarpol	HIV-1	NI	EC_{50}= 46 µM on CEM-SS	Dai, [75]
Balanocarpol		NI	EC_{50}= 20 µM on CEM-SS	
DIDS	HIV-1 strain RF	Binding to coreceptor CD4	IC_{50}= 20 µM on JM	Cardin, [76]
H_2DIDS	HIV-1 strain GB8		IC_{50}= 40 µM on JM	
NSC34931 (stilbenavir)	HIV-1	↓ Integrase	IC_{50}= 0.32 µM EC_{50}= 3.07 µM on MT4-LTR-eGFP	Aknin, [77]
NSC34933	HIV-1	↓ Integrase	IC_{50}= 1.1 µM EC_{50}= 0.60 µM on MT4-LTR-eGFP	
CGA137053	HIV-1	Binding to Tat protein	EC_{90}= 0.5 – 5 µM on Human leucocytes (PBL) and macrophages	Hamy, [82]
23a	HIV-1	NI	EC_{50}= 8.8 µM) on 293T	Clouser, [70]
M8	HIV-1 NL 4-3 or BaL variants	↓ viral attachment	EC_{50}= 0.29 – 1.69 µM on MT-4 and TZM-bl cells	Han, [87]
28	HNV	↓ RNA viral replication	EC_{50}= 2.43 µM on HG23 cells	Harmalkar, [91]
Resveratrol	HRV1B CVB3 EV71	NI	IC_{50}= 29.7 µM (HRV1B) on Hela	Oh, [94]
***cis*-resveratrol**		NI	IC_{50}= 12.2 µM (CVB3) IC_{50}= 37.6 µM (EV71) on Vero	
Vadelianin	EV 7, 13 and 19 serotypes	NI	IC_{50}= 0.0036 nM (0.0036 • 10^{-3} µM) on Human rhabdomyosarcoma (RD)	Segun, [95]
Kuwanon X	HSV-1 (15577 and clinical strains) HSV-2 (333 strains)	↓ viral adsorption, penetration, proteins, DNA biosynthesis, NF-κB pathway	IC_{50}= 2.2 µg/mL (3.77 µM) (15577 strain) IC_{50}= 1.5 µg/mL (2.57 µM) (clinical strain) IC_{50}= 2.5 µg/mL (4.29 µM) (333 strain) on Vero and Hela	Ma, [23]
(−)-hopeaphenol	HSV-1 HSV-2	NI	IC_{50}= 2.8 µM (HSV-1) IC_{50}= 6.4 µM (HSV-2) on MDCK	Ito, [33]
Shoreaketone			IC_{50}= 2.8 µM (HSV-1) IC_{50}= 6.8 µM (HSV-2) on MDCK	
Vaticaffinol	HSV-1 (strain 17) HSV-2 strain G (VR-734)	Promotes ROS production	IC_{50}= 3.2 µM (HSV-2) on HeLa, Vero, and H1299	Chen, [103]
Oxyresveratrol	HSV-1 (7401H and KOS) HSV-2 (Baylor 186) TK-deficient HSV-1 strain (B2006 strain) and PAA-resistant strain	Inhibition of late viral proteins	IC_{50}= 19.8 µg/mL (81.0 µM) (7401H) IC_{50}= 24 µg/mL (98.2 µM) (KOS) IC_{50}= 18.7 µg/mL (76.6 µM) (Baylor 186) on Vero (ATCC CCL81)	Chuanasa, [105]

NI= Not Identified.

Declaration of competing interest

The authors declare no competing financial interest.

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