Chapter

Natural Phenolic Acids and Their Derivatives against Human Viral Infections

Yi-Hang Wu, Yan Chen, An-Qi Zhuang and Shan-Mei Chen

Abstract

Natural compounds with structural diversity and complexity offer a great chance to find new antiviral agents. Phenolic acids have attracted considerable attention due to their potent antiviral abilities and unique mechanisms. The aim of this review is to report new discoveries and update pertaining to antiviral phenolic acids. The antiviral phenolic acids were classified according to their structural properties and antiviral types. Meanwhile, the antiviral characteristics and structure-activity relationships of phenolic acids and their derivatives were summarized. Natural phenolic acids and their derivatives possess potent inhibitory effects on multiple viruses in humans such as human immunodeficiency virus, hepatitis C virus, hepatitis B virus, herpes simplex virus, influenza virus and respiratory syncytial virus etc. In particular, caffeic acid/gallic acid and their derivatives exhibit outstanding antiviral properties through a variety of modes of action. In conclusion, naturally derived phenolic acids especially caffeic acid/gallic acid and their derivatives may be regarded as novel promising antiviral leads or candidates. Additionally, scarcely any of these compounds have been used as antiviral treatments in clinical practice. Therefore, these phenolic acids with diverse skeletons and mechanisms provide us an excellent resource for finding novel antiviral drugs.

Keywords: natural phenolic acid, viral infection, structure property, antiviral mechanism, structure-activity relationship

1. Introduction

Viral diseases are caused by pathogenic viruses invading the body of human. The basic process of infection includes: the infectious virions firstly attaching to the membrane of susceptible cells and then entering host cells to begin the replication of viruses [1]. Some viruses cause serious and deadly diseases including human immunodeficiency virus (HIV), hepatitis C virus (HCV), hepatitis B virus (HBV), herpes simplex virus (HSV), influenza virus (IV) and respiratory syncytial virus (RSV) etc. However, the current antiviral agents can only inhibit or reduce viral replication, while cannot clear virus infection thoroughly. Therefore, in the research area of fighting viral disorders, especially those involving potential of fatal development,

there is an urgent need for improved treatment by new antiviral drugs in the whole world.

Phenolic acids, a subclass of polyphenols, are the secondary metabolites from plants or fungi for preventing aggression by pathogens or ultraviolet radiation [2]. Recently, phenolic acids have aroused wide interest owing to their beneficial biological properties such as antiviral and anti-inflammatory activities etc., especially in the treatment of human viral diseases.

2. Structural types of phenolic acids

Phenolic acids are the various types of naturally derived aromatic acid compounds containing a phenolic ring and an organic carboxylic acid function [3]. Naturally occurring phenolic acids include two important types of derivatives of cinnamic acid (C6-C3 skeleton) and derivatives of benzoic acid (C6-C1 skeleton), which originated from non-phenolic compounds of cinnamic and benzoic acids, respectively [4]. Chemically, these compounds have at least one aromatic ring in which at any rate one hydrogen is substituted by a hydroxyl group (**Figure 1**). Phenolic acids are found to be abundant in plants. Furthermore, hydroxycinnamic acid derivatives are more common than hydroxybenzoic acid derivatives [2].

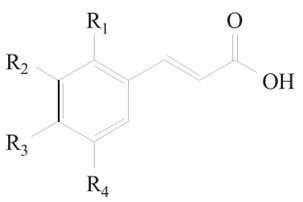
3. Antiviral effects of phenolic acids

3.1 Phenolic acids with anti-HIV activity

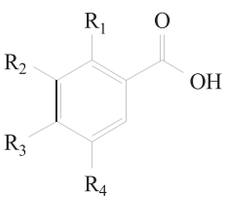
HIV is a retrovirus that invades human immune cells and causes acquired immunodeficiency syndrome (AIDS) [5]. Currently, the anti-HIV therapies include the inhibitors targeted at reverse transcriptase (RT), protease (PR) and integrase (IN). The fundamental role of RT in retroviruses replication has made the enzyme a key target in the chemotherapy of HIV infection [6]. The treatment with combinations of RT and PR inhibitors has been proven effective in reducing the levels of circulating virus to below detectable levels. HIV replication depends on the IN that mediates integration of an HIV DNA copy into the host cell genome. This enzyme represents a novel target to which antiviral agents might be directed [7].

3.1.1 Anti-HIV activities of caffeic acid derivatives

The anti-HIV effects of caffeoylquinic acids (CQAs) and caffeoyltartaric acids (CTAs) have attracted extensive attention in recent years. Thereinto, 3,5-di-*O*-CQA,



Cinamic acid derivatives (C6-C3 skeleton)



Benzoic acid derivatives (C6-C1 skeleton)

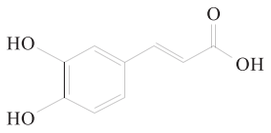
Figure 1.
Structure types of natural phenolic acids.

1-methoxyoxalyl-3,5-di-*O*-CQA (1-MO-3,5-di-*O*-CQA) and L-chicoric acid (**Figure 2**) inhibited HIV-1 IN at 0.06–0.66 μg.ml^{-1} and HIV-1 replication at 1–4 μg.ml^{-1} *in vitro*, respectively [8]. To determine whether the inhibition of IN by CQAs was limited to the 3,5 substitution, 3,4-, 4,5-, and 1,5-di-*O*-CQAs were measured for inhibition of HIV-1 replication and HIV-1 IN *in vitro*. All of the CQAs were found to inhibit HIV-1 replication at 1 to 6 μM in T cell lines. Meanwhile, these compounds suppressed HIV-1 IN at submicromolar concentrations [9]. In addition, molecular modeling of CQAs with IN showed that the most potent inhibitors filled a groove within the predicted catalytic site of IN. The change of internal free energy of the ligand/IN complex is correlated with the ability of CQAs to inhibit HIV-1 IN [9]. Thus, the CQAs are promising leads to new anti-HIV drug discovery.

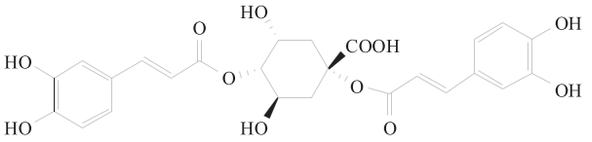
The CQAs and CTAs are highly selective HIV-1 IN inhibitors [8–10]. For instance, 4,5-di-*O*-CQA and 3,4,5-tri-*O*-CQA from *Securidaka longipedunculata* inhibited selectively the replication of HIV and inactivated viral infectivity by specific binding to gp120 which blocks HIV's interaction with CD4 on T cells [11]. However, the specificity of the CQAs and CTAs against HIV-IN remains unknown. Further studies indicated that the CQAs (3,5-di-*O*-CQA, 1-methoxyoxalyl-3,5-di-*O*-CQA, 1,3-di-*O*-CQA, 1,5-di-*O*-CQA, 3,4-di-*O*-CQA and 4,5-di-*O*-CQA) and CTA (L-chicoric acid) (**Figure 2**) inhibited HIV-1 IN at 150–840 nM and HIV replication at 2–12 μM. Their activity against RT ranged from 7 μM to greater than 100 μM. Concentrations that inhibited gp120 binding to CD4 exceeded 80 μM. No compound blocked HIV-1 RNase H by the 50% inhibition concentration (IC_{50}) value exceeding 80 μM. Furthermore, the CTAs were no effects on RT in acutely infected cells. The CQAs and CTAs exhibit >10- to >100-fold specificity for HIV IN [11, 12]. Hence, CQAs and CTAs are potential HIV inhibitors that act at a site distinct from current anti-HIV agents.

Titration experiments with HIV-1 IN or DNA substrate found that the effects of 3,4-di-*O*-CQA, 1-MO-3,5-di-*O*-CQA, and L-chicoric acid were exerted on the enzyme and not the DNA. The inhibition of retroviral INs was relatively specific, and CQAs had no effect on other DNA-modifying enzymes and phosphoryltransferases. Kinetic experiments indicated that the effect of CQAs on IN was irreversible. The inhibition was not affected by preassembling IN onto viral DNA. It suggested that the irreversible inhibition by CQAs on IN is directed toward conserved amino acid residues in the central core domain during catalysis [13]. L-Chicoric acid is a potent IN inhibitor and also inhibits entry at above 1 μM. Kinetic analyses using recombinant HIV IN showed that L-chicoric acid was consistent with a non-competitive or irreversible mechanism of inhibition. Further research demonstrated that L-chicoric acid was reversibly bound to the protein. Thus, L-chicoric acid is a noncompetitive but reversible inhibitor of HIV integration and likely interacts with amino acids other than those which bind substrate [14–16].

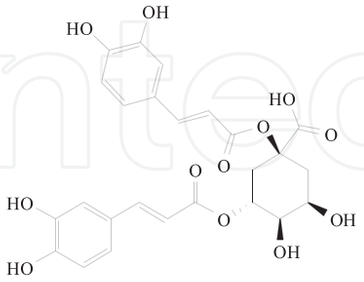
The structure-activity relationships (SAR) analyses suggested that biscatechol moieties were absolutely required for inhibition of IN, while at least one free carboxyl group was required for anti-HIV effect. These data demonstrated that the CTAs and CQAs analogs can be synthesized which have improved activity against HIV IN [17]. The CQAs and chicoric acid, both of which contain two catechol moieties, exhibit remarkable antiviral activity with high potency against IN. Among these inhibitors, hydroxylated aromatics which are contained in all sorts of natural components, have consistently shown marked potency for IN *in vitro*. Two aryl units separated by a central linker, as a common structural feature, are shared by the majority of these inhibitors [18].



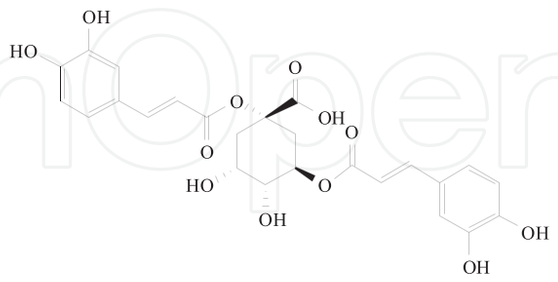
Caffeic acid



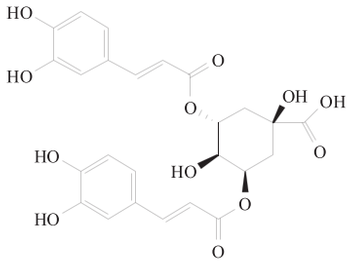
1,4-di-*O*-Caffeoylquinic acid



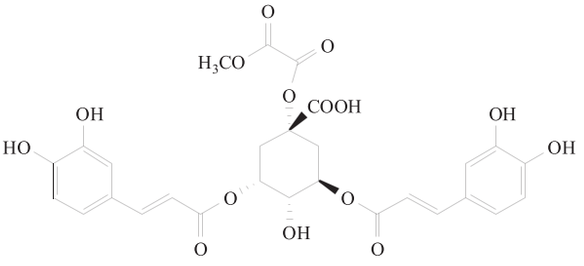
1,3-di-*O*-Caffeoylquinic acid



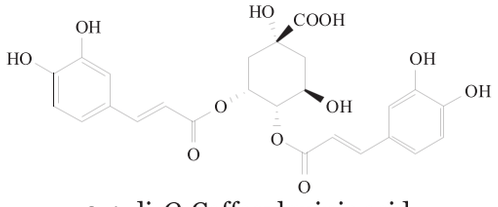
1,5-di-*O*-Caffeoylquinic acid



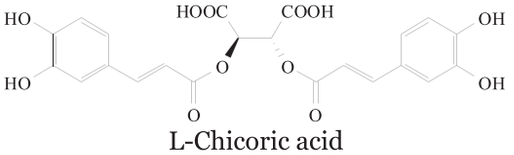
3,5-di-*O*-Caffeoylquinic acid



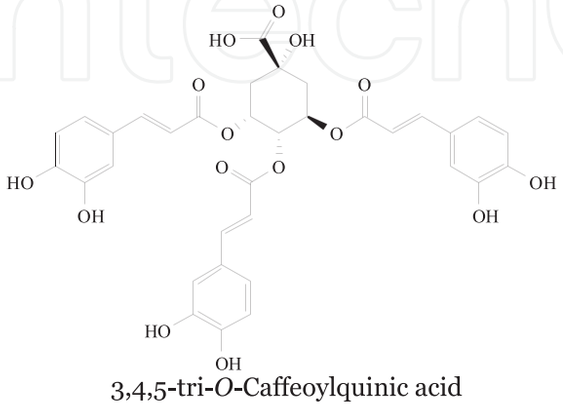
1-Methoxyoxalyl-3,5-di-*O*-caffeoylquinic acid



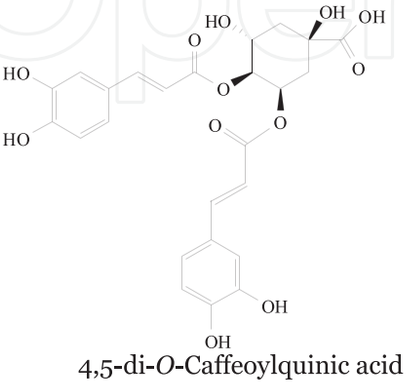
3,4-di-*O*-Caffeoylquinic acid



L-Chicoric acid



3,4,5-tri-*O*-Caffeoylquinic acid



4,5-di-*O*-Caffeoylquinic acid

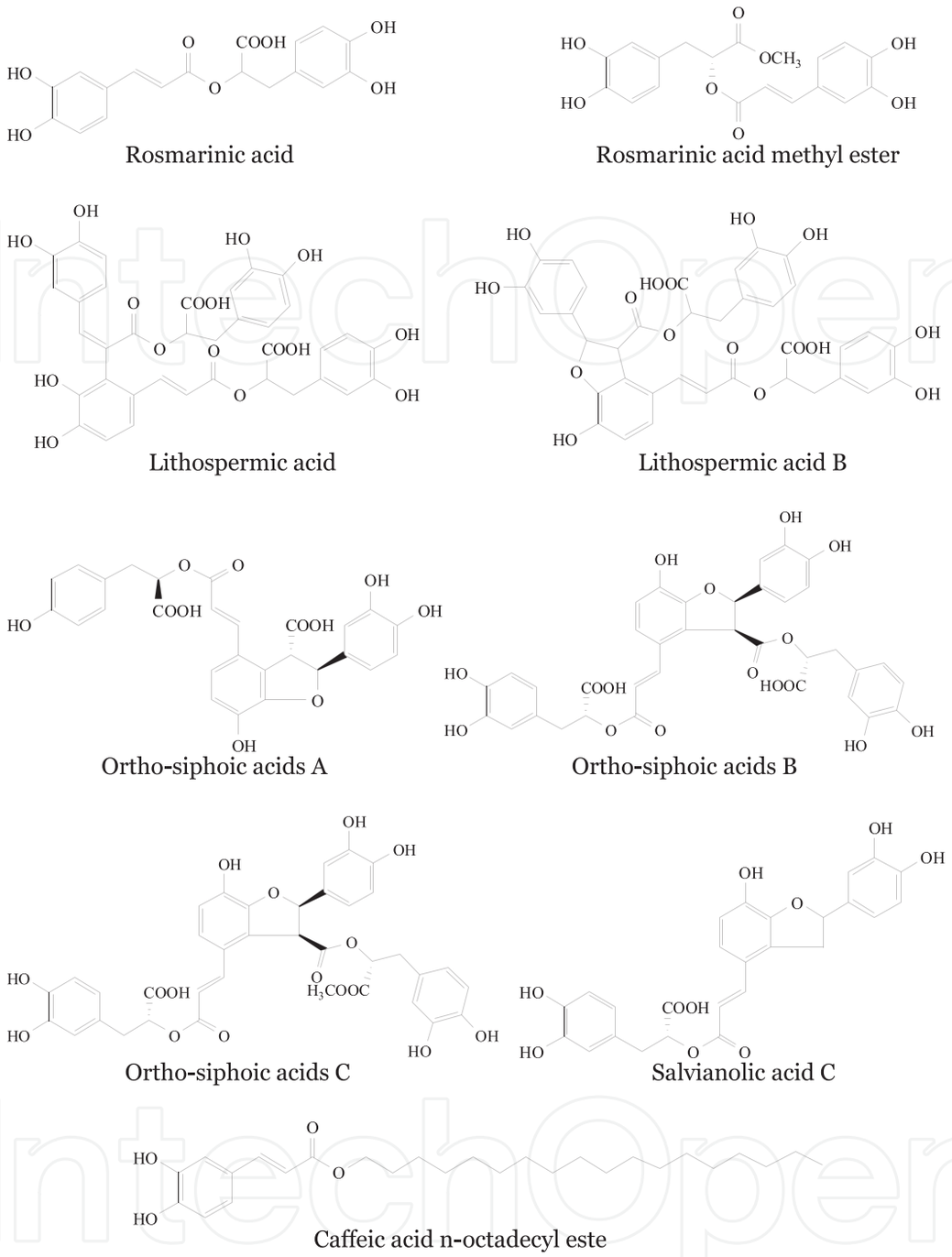


Figure 2.
Structures of natural caffeic acid and its derivatives with anti-HIV activity.

Other caffeic acid derivatives also displayed anti-HIV effects. Rosmarinic acid and rosmarinic acid methyl ester (**Figure 2**) from medicinal plants exhibited inhibitions against HIV-1 IN with IC_{50} values of 5.0 and 3.1 μM, respectively. The dimer, trimer, and tetramer of rosmarinic acid suppressed HIV-1 IN with IC_{50} values of 5.0, 1.4 and 1.0 μM, respectively [19]. Additionally, rosmarinic acid also inhibited RT directly [20]. Caffeic acid n-octadecyl ester (**Figure 2**) from *Daphne acutiloba* Rehd. showed anti-HIV activity with the 50% effective concentration (EC_{50}) value of 0.16 $\mu g.ml^{-1}$ [21]. The monopotassium and monosodium salts of isomeric caffeic acid tetramers from *Arnebia euchroma* displayed potent inhibitory activity against HIV. Furthermore, the potassium and sodium salts were proved to be important to enhance the anti-HIV

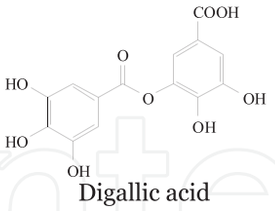
activity [22]. Acteoside and acteoside isomer from *Clerodendron trichotomum* exhibited potent inhibitory effects on HIV-1 IN with IC_{50} values of 7.8 and 13.7 μM, respectively [23].

Lithospermic acid and lithospermic acid B (**Figure 2**) from *Salvia miltiorrhiza* roots are potent anti-HIV inhibitors. The IC_{50} for inhibition of 3′-end-processing by HIV-1 IN was found to be 0.83 and 0.48 μM for lithospermic acid and lithospermic acid B, respectively. In addition, lithospermic acid and lithospermic acid B suppressed HIV-1 IN catalytic activities of 3′-joining to the target DNA with IC_{50} values of 0.48 and 0.37 μM, respectively [24]. The acute HIV-1 infection of H9 cells was strongly inhibited by lithospermic acid and lithospermic acid B with IC_{50} values of 2 and 6.9 μM, respectively. Thus, the two IN inhibitors hold promise as a novel class of anti-HIV agents [24]. Additionally, four phenolic acids (orthosiphoic acids A-C and salvianolic acid C) (**Figure 2**) from *Clerodendranthus spicatus* exhibited anti-HIV-1 protease activity with IC_{50} values of 86.9, 35.9, 38.4 and 74.2 μM, respectively [25].

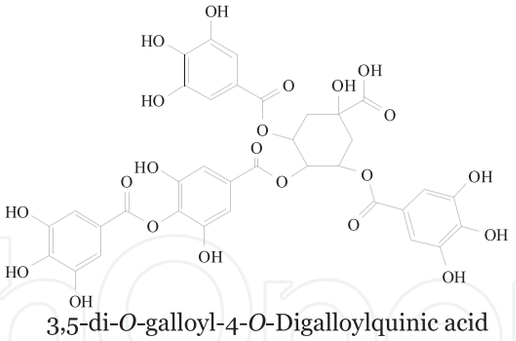
3.1.2 Anti-HIV activities of gallic acid derivatives

In searching for potential anti-HIV agents in natural products, galloylquinic acids (GQAs) were found to show potent anti-HIV activity. Four GQAs (**Figure 3**), 3,5-di-*O*-galloyl-4-*O*-diGQA, 3,4-di-*O*-galloyl-5-*O*-diGQA, 3-*O*-digalloyl-4,5-di-*O*-GQA, and 1,3,4,5-tetra-*O*-GQA, exhibited inhibitory effects on HIV RT and virus reproduction in cells at the concentrations of 10–30 μM [26]. 1,3,4-tri-*O*-GQA (**Figure 3**) was found to inhibit HIV replication and virus-cell interactions in infected H9 lymphocytes [27]. 3,4,5-tri-*O*-GQA (**Figure 3**) from *Guiera senegalensis* selectively suppressed HIV replication and RT by interaction with gp120 to prevent virus binding to CD4 receptor [11]. 3,4,5-tri-*O*-GQA from *Myrothamnus flabellifolia* was shown to inhibit HIV-1 RT. Kinetic monitoring of HIV-1 RT revealed the non-competitive inhibition of 3,4,5 tri-*O*-GQA with an IC_{50} value of 34 μM [28]. These findings suggested that GQAs and related derivatives have potential as indigenous agents for anti-HIV therapy.

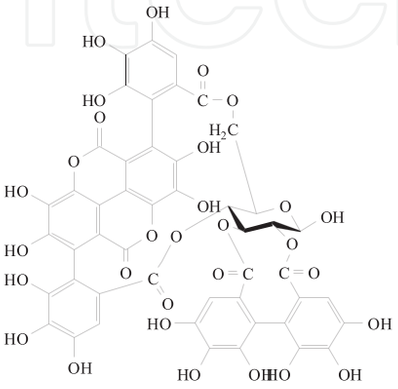
Gallic acid derivatives, 3,5-di-*O*-galloyl-shikimic acid, 3,4,5-tri-*O*-galloylshikimic acid, punicalin, punicalagin, punicacortein C, chebulagic acid and ellagitannin (**Figure 3**), were found to inhibit HIV-cell interactions. 3,5-di-*O*-Galloyl-shikimic acid, 3,4,5-tri-*O*-galloylshikimic acid, punicalin, and punicalagin suppressed the replication of HIV in infected H9 lymphocytes. The purified HIV RT was inhibited by two gallic acid derivatives punicalin and punicacortein C with IC_{50} values of 8 and 5 μM, respectively. Further research indicated that punicalin and chebulagic acid did not directly inactivate HIV in H9 lymphocytes. However, 3,5-di-*O*-galloylshikimic acid was shown to be more efficacious inhibitor among these compounds [27]. Digallic acid (**Figure 3**) from *Acacia farnesiana* inhibited significantly HIV RT by an IC_{90} value of 0.5 $\mu g.ml^{-1}$. The mode of action of digallic acid was partially competitive relative to the template, primer, and noncompetitive to the triphosphate substrate, dTTP. The Ki value of digallic acid was determined to be 0.58 μM for HIV RT [29, 30]. Further studies showed that three hydroxyl groups at the 3, 4, and 5 positions seem to be required for the inhibition of digallic acid derivatives. Besides RT, digallic acid moderately inhibited DNA polymerases α and β, whereas terminal deoxynucleotidyl-transferase and DNA polymerase γ were virtually unaffected by this compound [30]. Epigallocatechin-3-gallate (EGCG) (**Figure 3**) from green tea destructed HIV-1 particles and markedly inhibited post-adsorption entry, RT, PT kinetics, and mRNA



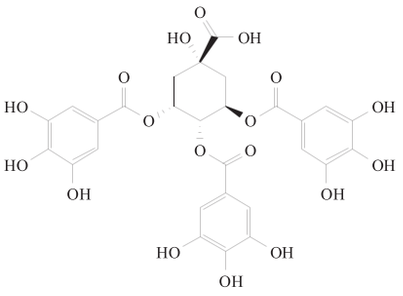
Digallic acid



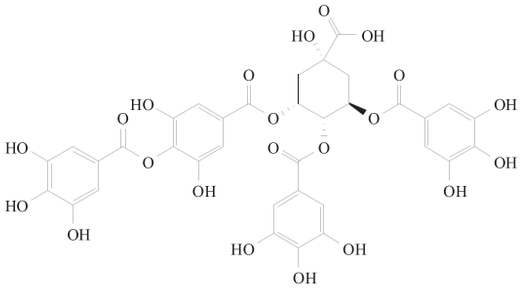
3,5-di-*O*-galloyl-4-*O*-Digalloylquinic acid



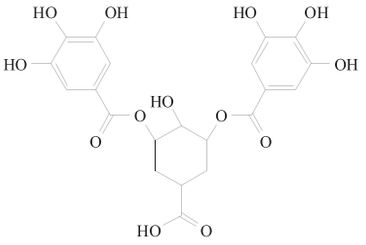
Punicalagin



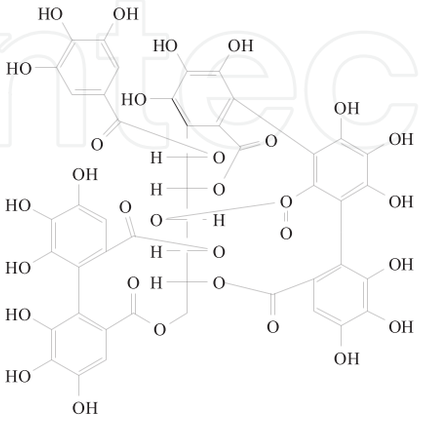
3,4,5-tri-*O*-Galloylquinic acid



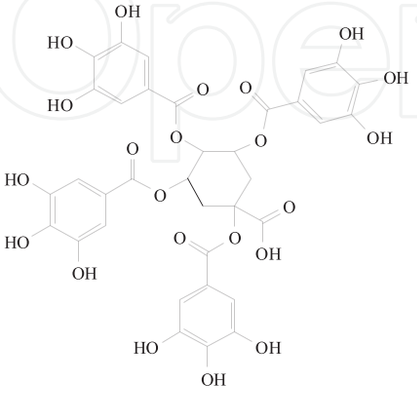
3,4-di-*O*-galloyl-5-*O*-Digalloylquinic acid



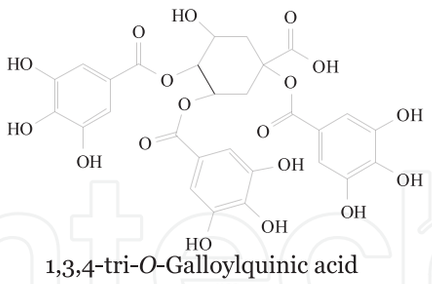
3,5-di-*O*-Galloyl-shikimic acid



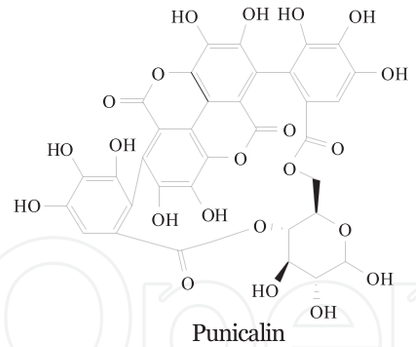
Ellagitannin



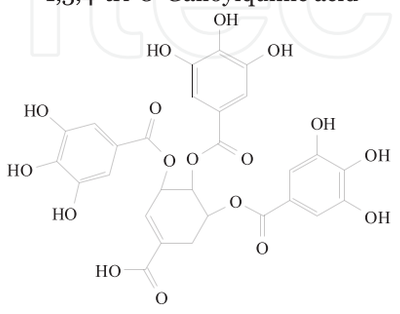
1,3,4,5-tetra-*O*-Galloylquinic acid



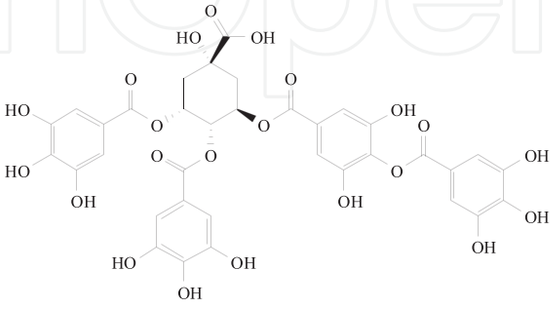
1,3,4-tri-*O*-Galloylquinic acid



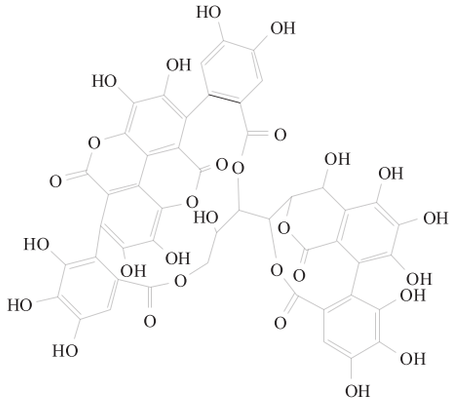
Punicalin



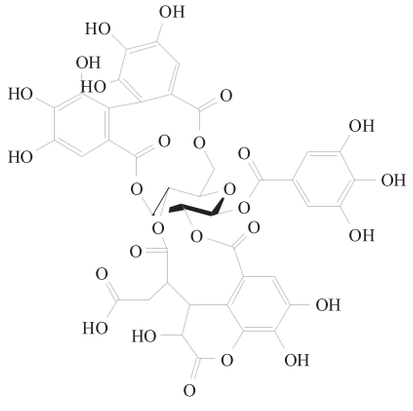
3,4,5-tri-*O*-Galloyl-shikimic acid



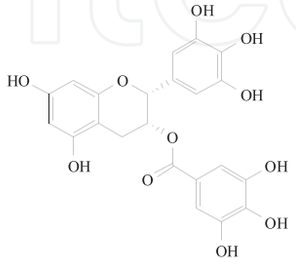
3-*O*-digalloyl-4,5-di-*O*-Galloylquinic acid



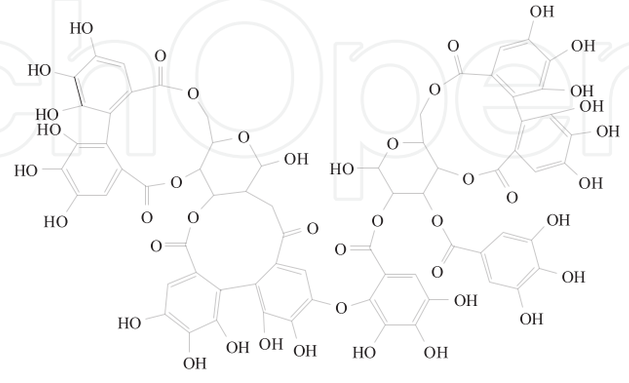
Punicacortein C



Chebulagic acid



Epigallocatechin-3-gallate



Camelliatannin H

Figure 3.
Structures of natural gallic acid derivatives with anti-HIV activity.

production at micromolar concentrations. Its anti-HIV effect may result from interactions with multiple steps in the viral cycle [31]. Camelliatannin H (**Figure 3**) from *Camellia japonica* potently inhibited HIV-1 PR with an IC_{50} value of 0.9 μM [32].

3.2 Phenolic acids with anti-HCV activity

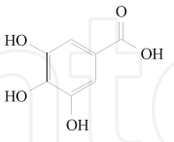
Hepatitis C is an infectious disease caused by HCV and is one of the primary causes of hepatocellular carcinoma. There are about 130–150 million people with chronic hepatitis C globally [33]. Approximately 20–30% of the patients with chronic hepatitis C develop cirrhosis, but only several antiviral agents have been approved against HCV to date [34]. General therapy is often difficult for some HCV genotypes. Hence, new anti-HCV drugs are needed. Natural products provide an abundant resource to screen for potential anti-HCV compounds for promising candidates in the clinic and to improve treatments. The nonstructural protein NS3, NS4A, and NS 5A proteases and RNA polymerase represent the key targets as they are essential for HCV replication [35].

3.2.1 Anti-HCV activities of gallic acid derivatives

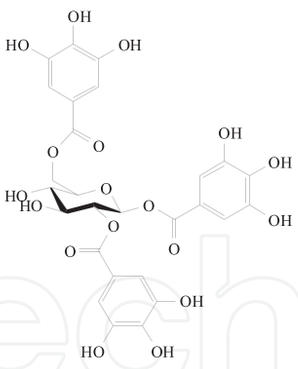
Gallic acid (**Figure 4**) is a natural phenolic acid from plants [36]. A subgenomic HCV replicon cell system was employed to study the effect of gallic acid on HCV expression. The results showed that gallic acid decreased the expression levels of HCV-RNA (∼50%) and NS5A-HCV protein (∼55%). Particularly, gallic acid reduced ROS production at the early time points of exposure in cells expressing HCV proteins. It indicated that the antioxidant ability of gallic acid might be associated with the downregulation of HCV replication [37].

Gallic acid glucosides (**Figure 4**) showed remarkable anti-HCV effect. Three gallic acid glucosides, 1,2,6-tri-*O*-galloyl-β-d-glucose, 1,2,3,6-tetra-*O*-galloyl-β-d-glucose, and 1,2,3,4,6-penta-*O*-galloyl-β-d-glucose from *Rhus chinensis* (Mill.) gallnut, inhibited HCV NS3 serine protease with IC_{50} values of 1.89, 0.75, and 1.60 μM, respectively [38]. Additionally, gallic acid and its derivatives 1,2,3,4,6-penta-*O*-galloyl-β-D-glucoside, tercatain (1,4-di-*O*-galloyl-3,6-(R)-hexahydroxydiphenoyl-β-D-glucose), 1,3,4,6-tetra-*O*-galloyl-β-D-glucose, punicafolin (1,2,4-tri-*O*-galloyl-3,6-(R)-hexahydroxydiphenoyl-β-D-glucose) and 1,3,6-tri-*O*-galloyl-β-D-glucose from *Saxifraga melanocentra* Franch possessed potent inhibition against HCV NS3 protease. The IC_{50} values of these compounds were 1.76, 0.68, 0.76, 0.81, 0.85, and 1.01 μM, respecitively. And their inhibition rates on HCV NS3 protease were 34.9, 98.7, 98.1, 95.8, 99.5%, and 94.7 at 100 $\mu g.ml^{-1}$, respectively [39].

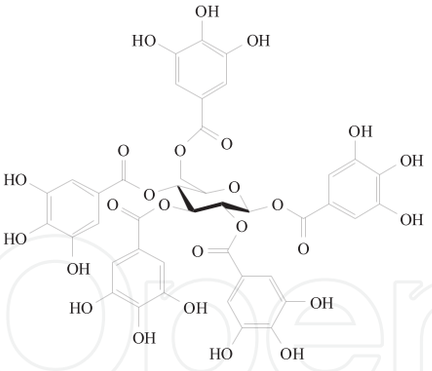
Excoecariphenol D, corilagin, geraniin, and chebulagic acid (**Figure 4**) were isolated from *Excoecaria agallocha* L. These gallic acid derivatives were measured against HCV NS3/4A proteases and HCV RNA in Huh 7.5 cells. The results showed that corilagin, excoecariphenol D, geraniin, and chebulagic acid possessed potential inhibition toward HCV NS3/4A proteases with IC_{50} values of 3.45, 6.93, 8.91, and 9.03 μM, respectively. Furthermore, corilagin and excoecariphenol D significantly inhibited HCV RNA replication with EC_{50} values of 13.59 and 12.61 μM, respectively, whereas chebulagic acid and geraniin showed moderate inhibition on HCV RNA by EC_{50} values of 22.25 and 33.19 μM, respectively [40]. Two novel gallic acid derivatives, SCH 644343 and SCH 644342 (**Figure 5**) from *Stylogne cauliflora*, suppressed HCV NS3 protease with IC_{50} values of 0.3 and 0.8 μM, respectively. Subsequent studies indicated that SCH 644343 was also active with an IC_{50} value of 2.8 μM in the HCV protease binding assay [41]. These findings suggested that HCV NS3, NS 4A, and NS5A serine proteases may be regarded as a possible pathway for anti-HCV effects of gallic acid derivatives.



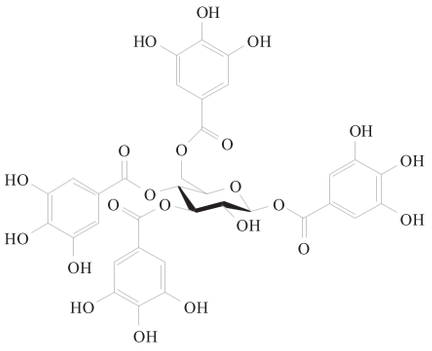
Gallic acid



1,2,6-tri-*O*-Galloyl-β-D-glucose



1,2,3,4,6-penta-*O*-Galloyl-β-D-glucose



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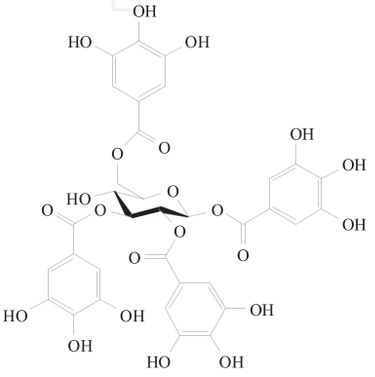
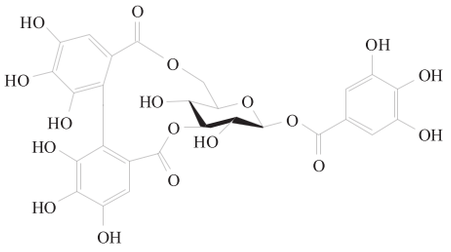
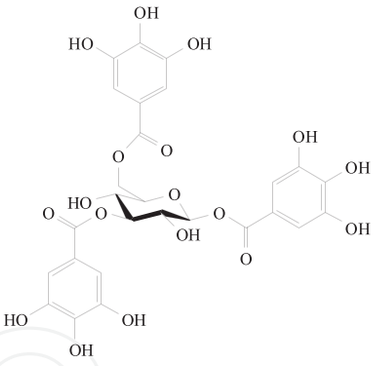


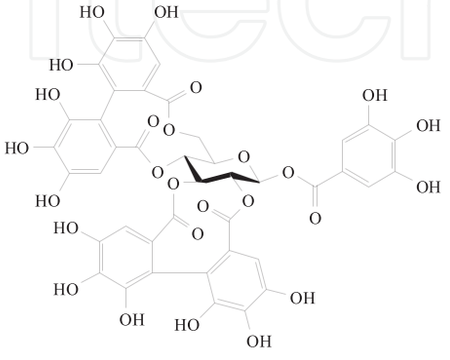
1,2,3,6-tetra-*O*-Galloyl-β-D-glucose



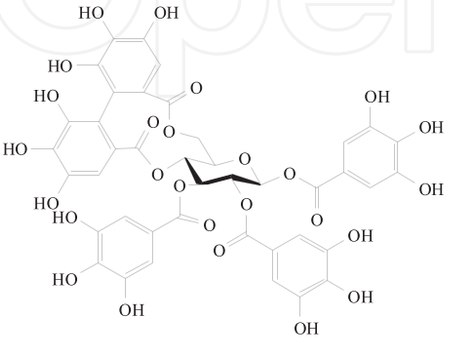
Corilagin



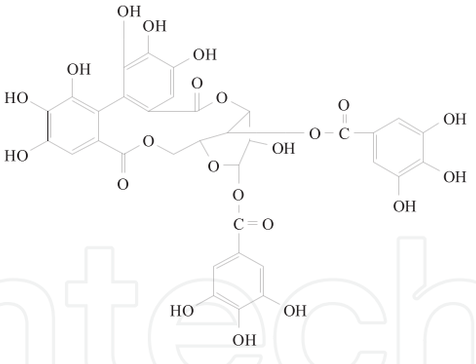
1,3,6-tri-*O*-Galloyl-β-D-glucose



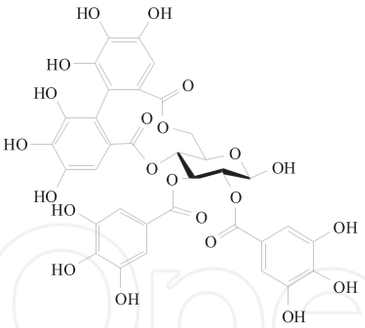
Casuarictin



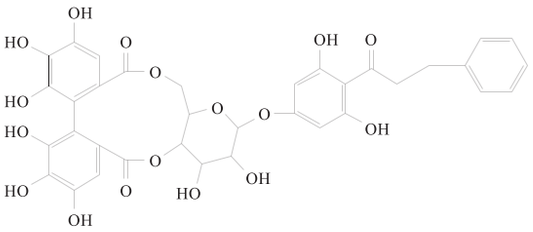
Eugeniin



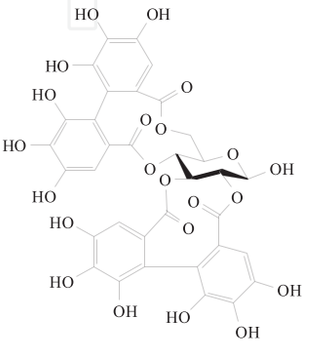
Tercatain



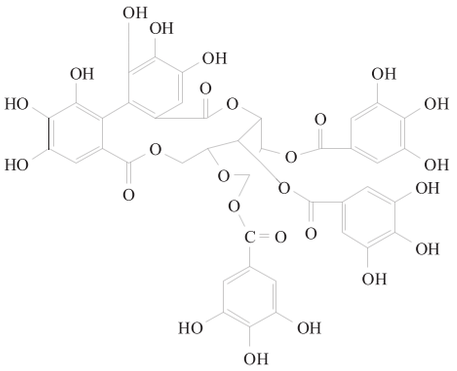
Tellimagrandin I



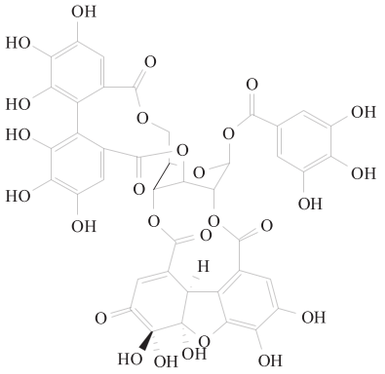
SCH 644342



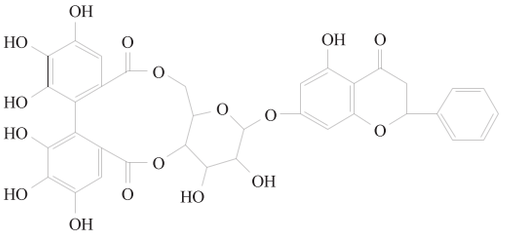
Pedunculagin



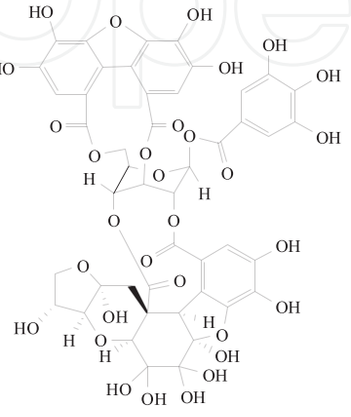
Punicafolin



Geraniin



SCH 644343



Excoecariphenol D

Figure 4.
Structures of natural gallic acid and its derivatives with anti-HCV activity.

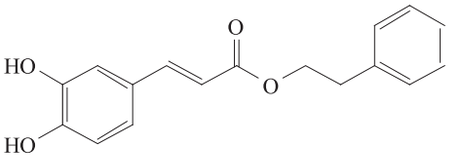


Figure 5.
Structure of natural caffeic acid phenethyl ester (CAPE) with anti-HCV activity.

Four gallic acid analogs (**Figure 4**), tellimagrandin I, eugeniin, and casuarictin from *Rosa rugosa* Thunb together with pedunculagin from *Juglans regia*, were proved to be potent HCV invasion inhibitors using the model virus that expressed HCV envelope proteins E1 and E2 [42]. The mechanisms of anti-HCV action of chebulagic acid and punicalagin (**Figure 4**) from *Terminalia chebula* Retz. were studied during the attachment and entry steps of infection. The results showed that two gallic acid derivatives were effective in abrogating HCV infection at micromolar concentrations [43]. EGCG at a concentration of 50 μM inhibited HCV infectivity at an early step by over 90%. EGCG disrupted the initial step of HCV entry to block viral attachment to the cell, probably by acting on viral particle directly. Besides, it also suppressed cell-to-cell virus spread. Therefore, EGCG as an HCV entry inhibitor might be a promising antiviral strategy aimed at HCV reinfection [44–46]. Taken together, it suggests the potential of gallic acid and its derivatives for developing anti-HCV drugs.

3.2.2 Anti-HCV activities of caffeic acid derivatives

The effect of caffeic acid (**Figure 2**) on HCV propagation was evaluated using a naïve HCV particle infection and production system in Huh 7.5.1–8 cells. The amount of HCV particles released into the medium was significantly reduced at 3 and 4 days post-infection when the cells were cultured with 0.1% caffeic acid for 1 h after HCV infection. HCV-infected cells were treated with 0.001% caffeic acid for 4 days, which was adequate to decrease the amount of HCV particles released into the medium. Caffeic acid treatment suppressed the initial stage of HCV infection including HCV genotypes 1b and 2a, thus suggesting the inhibition of caffeic acid on HCV propagation [47].

Caffeic acid phenethyl ester (CAPE) (**Figure 5**) and CAPE derivatives exhibited anti-HCV activity in HCV replicon cell line of genotype 1b with EC_{50} values from 1.0 to 109.6 μM. Caffeic acid n-octyl ester showed the strongest anti-HCV activity with an EC_{50} value of 1.0 μM and a selectivity index (SI) value of 63.1. SAR analyses indicated that the length of the n-alkyl side chain and catechol moiety are responsible for the anti-HCV activities of these derivatives [48].

3.3 Phenolic acids with anti-HBV activity

Hepatitis B is a very harmful and epidemic disease caused by HBV. It can cause chronic infection and puts patients at high risk of death from cirrhosis and hepatocellular carcinoma [49]. Although an effective vaccine can prevent HBV infection at present, chronic HBV infection poses still a huge health burden in the whole world [50]. The current anti-HBV drugs have their limitations without exception. There is no effective drug or therapeutic method that can really and truly cure hepatitis B so far [49].

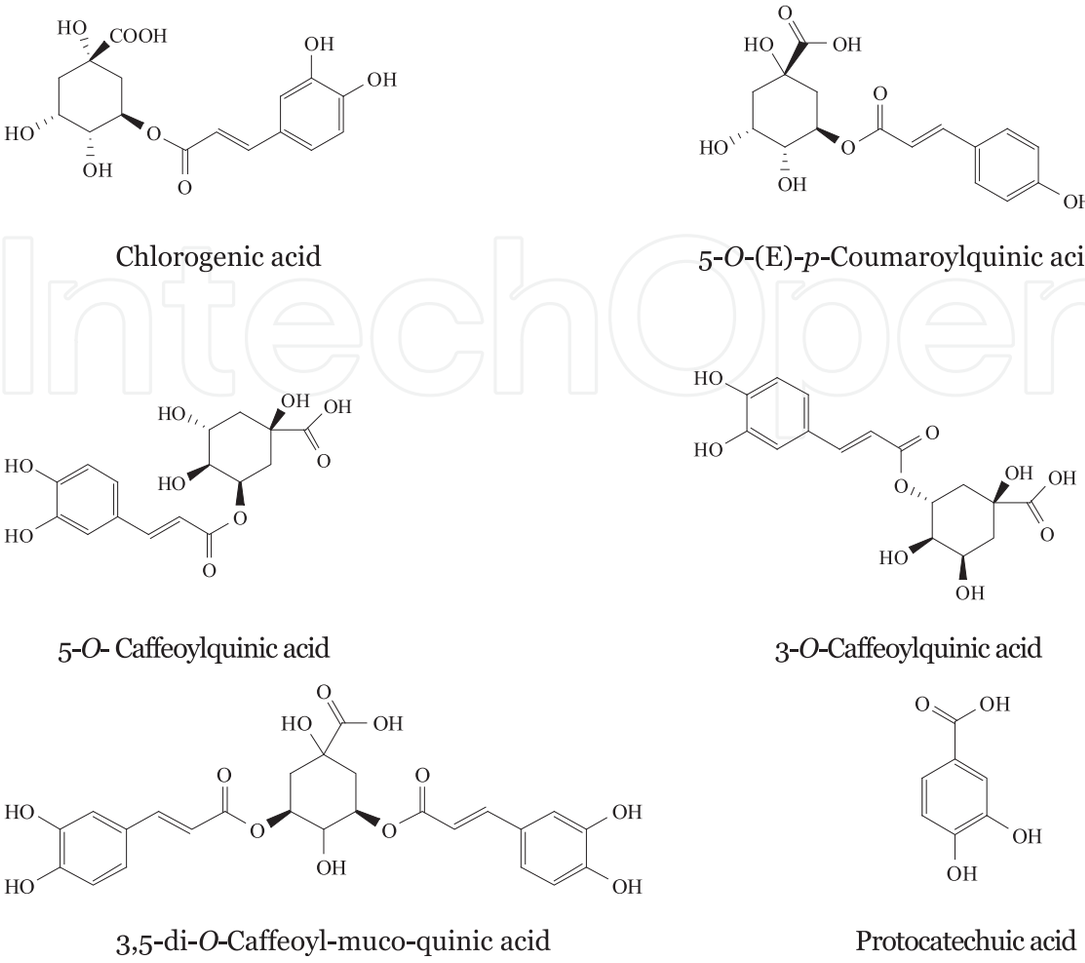


Figure 6.
Structures of anti-HBV phenolic acids.

Some naturally originated phenolic acids have potent anti-HBV activity. Seven caffeoylquinic acid derivatives from *Lactuca indica L.*, including 3-*O*-CQA, 5-*O*-CQA, 5-*O*-(*E*)-*p*-coumaroylquinic acid, 3,4-di-*O*-CQA, 3,5-di-*O*-CQA, 3,5-di-*O*-caffeoyl-muco-quinic acid, and 4,5-di-*O*-CQA (**Figures 2** and **6**), significantly decreased the level of HBV DNA in HepG2.2.15 cells, and treatment with 5-*O*-(*E*)-*p*-coumaroylquinic acid, 3,4-di-*O*-CQA, and 3,5-di-*O*-caffeoyl-muco-quinic acid respectively caused a remarkable decline in the level of the extracellular HBV DNA [51]. Caffeic acid and chlorogenic acid (**Figures 2** and **6**) in the fruits and leaves of dicotyledonous plants have a variety of antiviral activities. Caffeic acid and chlorogenic acid suppressed HBV DNA replication as well as hepatitis B surface antigen (HBsAg) production in HepG2.2.15 cells. Furthermore, the two phenolic acids also reduced the serum level of duck hepatitis B virus (DHBV) in a DHBV-infected duck model [52].

Two caffeic acid derivatives, 3,4-di-*O*-CQA and 3,5-di-*O*-CQA (**Figure 2**) from *Laggera alata*, markedly inhibited hepatitis B envelope antigen (HBeAg) and HBsAg expressions with inhibitory rates of 81.01, 72.90 and 89.96, 86.90%, respectively. Moreover, 3,4-di-*O*-CQA significantly reduced the content of HBV covalently closed circular DNA (HBV cccDNA) and markedly upregulated the expression of heme oxygenase-1 (HO-1) in HepG2.2.15 cells and HBV transgenic mice [53]. 3,5-di-*O*-CQA exhibited a similar effect as 3,4-di-*O*-CQA [54]. Due to the destabilization of HO-1 on

the HBV core protein, suggests that the overexpression of HO-1 may be involved in the anti-HBV activities of two CQAs by reducing the stabilization of HBV core protein, which blocks the replenishing of HBV cccDNA in nuclear [53, 54]. Cichoric acid from *Cichorium intybus* leaves at 10–100 μg.ml^{-1} decreased markedly the expression levels of HBsAg and HBeAg in HepG2.2.15 cells and produced the maximum inhibitory ratios of 76.41% and 79.94%, respectively [55].

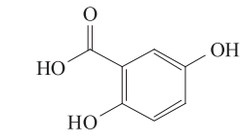
Gallic acid and its derivatives punicalagin and punicalin could be used for suppressing the expressions of HBsAg and HBeAg [56]. EGCG down-regulated the HBeAg and HBV pre-core mRNA expressions, and reduced the levels of both HBV cccDNA and DNA replicative intermediates in HepG2.2.15 cells, thus suggesting that the inhibition of EGCG on HBV replication results in decreasing production of HBV cccDNA by impairing the synthesis of HBV DNA replication intermediates [57]. Additionally, the inhibitory effect of protocatechuic acid on HBV replication was exhibited by activating the extracellular-signal-related kinase 1/2 pathway and then downregulating the HNF4α and HNF1α expressions in HepG2.2.15 cells [58].

3.4 Phenolic acids with anti-HSV activity

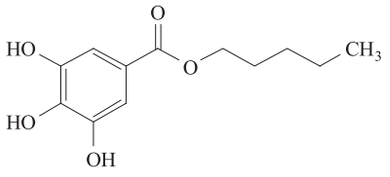
HSV-1 and HSV-2 are two members of herpesvirus family that infect humans [59]. There are about 3.7 billion people infected with HSV-1 worldwide, whereas approximately 417 million people with HSV-2 infection globally. Some antiviral agents such as valacyclovir, acyclovir, and famciclovir can reduce the frequency and severity of symptoms of people with HSV, but they cannot cure the infections [60]. Besides, human herpesvirus 4, also called Epstein-Barr virus (EBV), as a common human virus, is an important member of the herpes-virus family.

Gallic acid (**Figure 4**) and its derivative pentyl gallate (**Figure 7**) decreased the replication of HSV-2 when either incubated with HSV-2 prior to the addition of the mixture to cells or added to and cultured with cells after infection [61]. The virucidal effects of gallic acid and pentyl gallate on virus particles may contribute to their anti-HSV-2 activities by partial inhibition of HSV-2 attachment to cells and subsequent cell-to-cell spread [61, 62]. Eugeniin (**Figure 4**) from *Syzygium aromaticum* and *Geum japonicum* exhibited anti-HSV activity in mice and suppressed the reproduction of thymidine kinase-deficient HSV-1, acyclovir-phosphonoacetic acid-resistant HSV-1 and wild HSV-2, also inhibited purified HSV-1 DNA polymerase activity, viral DNA and late viral protein syntheses in HSV-infected Vero cells. Thus, viral DNA synthesis is one of its major targets of inhibitory action. Therefore, eugeniin may be developed as a novel anti-HSV agent which is different from anti-HSV nucleoside analogs [63].

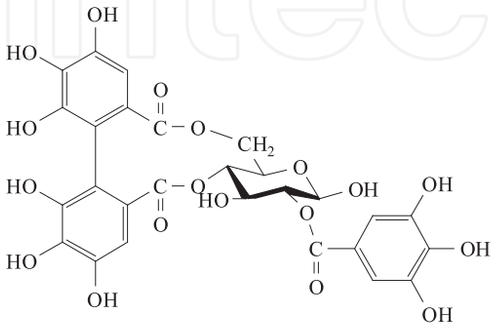
Hippomanin A (**Figure 7**) from *Phyllanthus urinaria* Linnea was shown to suppress HSV-2 infection by the plaque reduction assay and its inhibitory effect on HSV-2 multiplication was exhibited with an IC_{50} value of 28.2 μM [64]. Geraniin and 1,3,4,6-tetra-*O*-galloyl-β-D-glucose (**Figure 4**) from *P. urinaria* were tested for their inhibitory activities against HSV-1 and HSV-2 *in vitro*. The results showed that geraniin actively suppressed HSV-2 infection with an IC_{50} value of 18.4 μM, whereas 1,3,4,6-tetra-*O*-galloyl-β-D-glucose effectively inhibited HSV-1 infection with an IC_{50} value of 19.2 μM. Hence, the two gallic acid derivatives have different magnitudes of potency against HSV-1 and HSV-2 multiplications [65]. Excoecarianin (**Figure 7**) from *P. urinaria* Linnea protected Vero cells from HSV-2 infection with an IC_{50} value of 1.4 μM. Moreover, its inhibitory effect on HSV-2 infection was the strongest when excoecarianin was simultaneously added to the virus. Further studies showed that excoecarianin prevented viral infection by inactivation of HSV-2 virus particles.



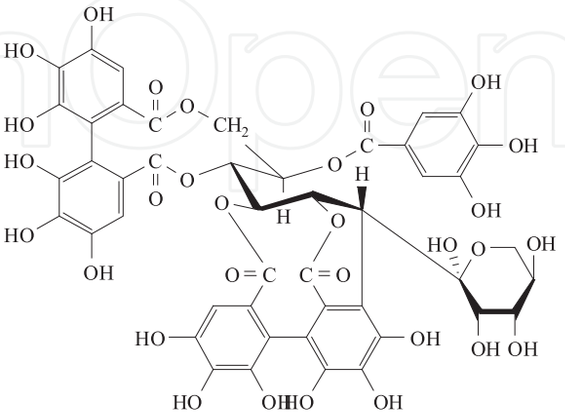
2,5-Dihydroxybenzoic acid



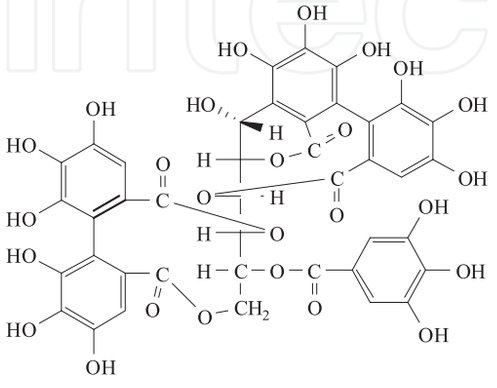
Pentyl gallate



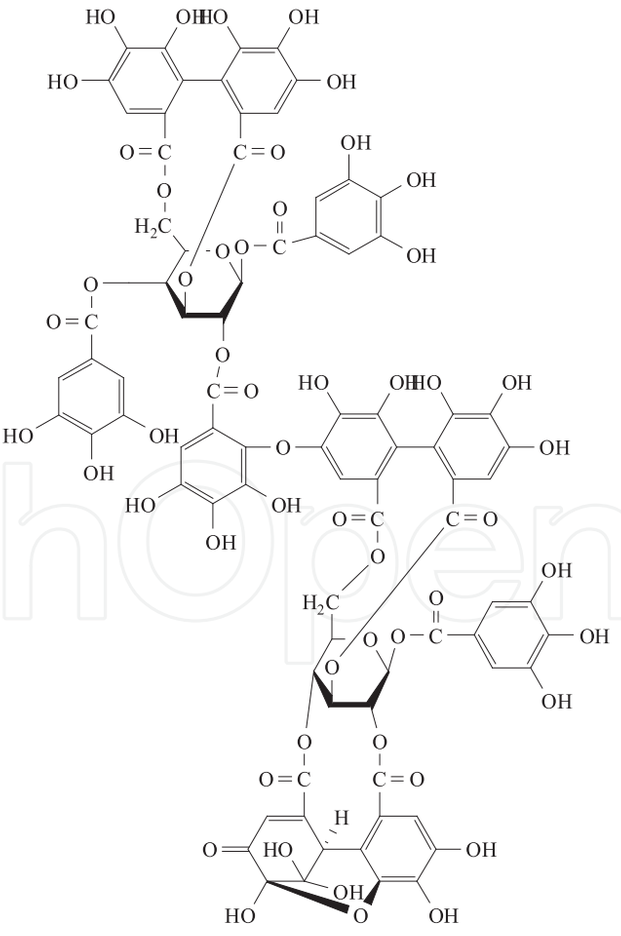
Hippomanin A



Pterocarnin A



Casuarinin



Excoecarianin

Figure 7.
Structures of natural phenolic acids and their derivatives with anti-HSV activity.

Additionally, a synergistic antiviral assay indicated that excoecarianin could be potential for combinatorial therapy with nucleoside analogs such as acyclovir in HSV-2 infection. These data revealed that excoecarianin as an entry inhibitor against HSV-2 merits to be further investigated [66].

Chebulagic acid and punicalagin (**Figure 3**) from *T. chebula* Retz. suppressed HSV-1 entry in A549 human lung cells. Two derivatives could inactivate HSV-1 viral particles and prevent binding, penetration, and cell-to-cell spread, as well as secondary infection. Both compounds targeted HSV-1 glycoproteins and blocked interactions between HSV-1 glycoproteins and cell surface glycosaminoglycans. Consequently, chebulagic acid and punicalagin may be used as competitors for glycosaminoglycans in HSV-1 infection and help decrease the risk for development of viral resistance to nucleoside analogs [67]. Casuarinin (**Figure 7**) from *Terminalia arjuna* Linn., an isomer of casuarictin, exhibited anti-HSV-2 activity with IC_{50} values of 3.6, 1.5 μM and SI values of 25, 59 for XTT and plaque reduction assays, respectively. Casuarinin also showed to prevent the attachment of HSV-2 to cells and inhibit viral penetration. Interestingly, casuarinin at 25 μM reduced viral titers up to 100,000-fold. Thus the anti-HSV activity of casuarinin was performed by disturbing the late events of infection and inhibiting viral attachment and penetration [68]. Pterocarnin A (**Figure 7**) from *Pterocarya stenoptera* was shown to actively inhibit HSV-2 multiplication from attaching and penetrating into cells. These observations suggested that pterocarnin A suppressed both early and late stages in the HSV-2 replication cycle [69]. The anti-HSV activity of EGCG exhibited a direct effect on the virion by binding to the envelope glycoproteins gB and gD or another envelope glycoprotein [70]. Ellagitannins from *P. urinaria* and *P. myrtifolius* showed an anti-EBV effect at micromolar concentration [71]. These studies reveal that gallic acid derivatives may be regarded as potential candidates for developing anti-HSV agents.

Caffeic acid (**Figure 2**) from *Plantago major* L. exhibited potent activity against HSV-1 (EC_{50} = 15.3 $\mu g.ml^{-1}$, SI = 67.1) and HSV-2 (EC_{50} = 87.3 $\mu g.ml^{-1}$, SI = 118). Its mode of action against HSV-2 was at multiplication stages at 0–12 h postinfection of HSV-1, suggesting the potential use of this compound for treatment of HSV infection [72, 73]. Rosmarinic acid (**Figure 2**) from *Melissa officinalis* inhibited HSV-1 attachment to host cells for acyclovir-sensitive and resistant strains [74]. In addition, 2,5-dihydroxybenzoic acid (**Figure 7**) from *Origanum vulgare* had a weak effect against HSV-1 with an IC_{50} value of 32.7 μM [75]. Protocatechuic acid (**Figure 6**) from *Hibiscus sabdariffa* displayed anti-HSV-2 activity *in vitro* (EC_{50} = 0.92 $\mu g \bullet ml^{-1}$, SI > 217) [76].

3.5 Phenolic acids with anti-IV activity

Influenza is an infectious disease caused by IV and spreads around the world in a yearly outbreak, resulting in about 3–5 million severe cases and 250,000 to 500,000 deaths [77]. IVs that infect people include three types of A, B, and C. The vaccine made for 1 year may not be effective in the following year, since the virus evolves rapidly [78]. Despite anti-IV drugs such as oseltamivir and zanamivir have been used to treat influenza, the lack of excellent agents intensifies the importance of novel anti-IV drugs development.

Caffeic acid (**Figure 2**), which is abundant in nature, has a variety of potential pharmacological effects especially antiviral activity [79]. Some natural products containing the fragment of caffeic acids, such as chlorogenic acid and its analogs also show inhibitory effects on influenza neuroaminidases (NAs) [80]. Chlorogenic acid,

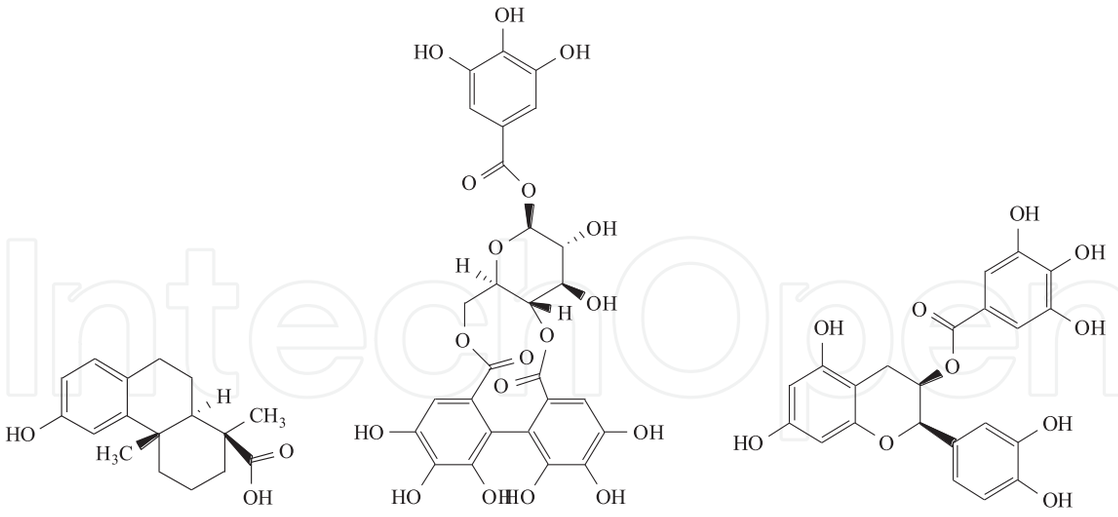


Figure 8.
Structures of natural phenolic acids and their derivatives with anti-IV activity.

caffeic acid, and their derivatives (**Figures 2** and **6**) have been found to exert antiviral effects against NAs from H5N1. Chlorogenic acid and related derivatives exhibited high activities against NAs. The catechol group from caffeic acid may be important for the activity [81]. Caffeic acid, chlorogenic acid, 3,4-di-*O*-CQA, 3,5-di-*O*-CQA, 4,5-di-*O*-CQA, and 3,4,5-tri-*O*-CQA (**Figures 2** and **6**) from the propolis showed effective anti-IV activity [82]. A caffeic acid derivative, caffeic acid phenethyl ester (**Figure 5**) was found to have anti-IV properties *in vitro*. Caffeic acid derivatives seem to be a promising source to find potent NA inhibitors [83, 84].

Rosmarinic acid methyl ester (**Figure 2**) from *Salvia plebeian* exhibited potent inhibition against H1N1 NA with an IC_{50} value of 16.65 μM and reduced cytopathic effect of H1N1 during replication, thus suggesting the potential of the compound to be new lead for developing novel NA inhibitor [85]. Gallic acid and its derivatives possess an inhibitory effect on human avian influenza [56]. Strictinin (**Figure 8**), which is a natural gallic acid derivative, prevented influenza A viruses (IAV) replication with IC_{50} values from 0.09 to 0.28 μM. Further studies showed that strictinin inhibited IAV-induced hemifusion and also exhibited antiviral activities against influenza B virus (IBV) and parainfluenza virus type-1 *in vitro*. Thus strictinin may be a useful antiviral agent [86, 87]. Podocarpic acid (**Figure 8**) from *Dacrydium cupressinum* and its derivatives exhibited inhibitory activity against H1N1 IAV at nanomolar concentrations and suppressed multicycle replication of influenza A/Kawasaki/86 (H1N1) virus *in vitro* [88, 89]. EGCG and (−)-epicatechin gallate (ECG) (**Figures 3** and **8**) from green tea showed potent inhibitory effects on IV replication and effectively inhibited neuraminidase activity [90].

3.6 Phenolic acids with anti-RSV activity

RSV is a syncytial virus that causes respiratory tract infections. It is also a significant pathogen in infants, young children, the elderly, and the immunocompromised [91]. Despite its global impact on human health, there are relatively few therapeutic options available to prevent or treat RSV infection. To date, no effective vaccine or therapeutic agent has been developed [92].

The inhibitory activities of 3,4-di-*O*-CQA and 3,5-di-*O*-CQA (**Figure 2**) from *Schefflera heptaphylla* against RSV were verified by a plaque reduction assay with IC_{50} values of 2.33 and 1.16 μM, respectively. Their anti-RSV modes were performed by the suppression of virus-cell and cell-cell fusion in the early stage and at the end of viral reproduction in turn [93]. Five caffeic acid derivatives from *Markhamia lutea*, luteoside A, luteoside B, luteoside C, verbascoside, and isoverbascoside, exhibited potent antiviral activity against RSV *in vitro* [94]. Two gallic acid derivatives, chebulagic acid and punicalagin (**Figure 3**), abrogated RSV infection at micromolar concentrations by inhibiting viral attachment, penetration, and spread. Two compounds may be of value as antivirals for limiting emerging/recurring viruses to engage host cell GAGs for entry [43].

Carnosic acid (**Figure 9**) from *Rosmarinus officinalis* displayed potent activities against both RSV A- and B-type viruses. The compound efficiently suppressed the replication of RSV and inhibited viral gene expression without inducing type-I interferon production. Furthermore, the addition of carnosic acid at 8 h after infection still blocked the expression of RSV genes, further suggesting that carnosic acid might directly inhibit the replication of RSV [95]. Sekikaic acid (**Figure 9**) from *Ramalina farinacea* exhibited potent inhibition toward a recombinant RSV strain with an IC_{50} value of 5.69 $\mu g.ml^{-1}$ and RSV A2 strain with an IC_{50} value of 7.73 $\mu g.ml^{-1}$, and clearly interfered with viral replication at a post-entry step [96].

3.7 Phenolic acids against other viruses

Enterovirus 71 (EV71) is a causative agent that causes hand, foot, and mouth disease, a highly contagious viral infection that affects young children. It can also cause severe neurological or cardiac complications [97]. To date, no approved antiviral agents have been developed for the treatment of EV71 infection. The anti-EV71 activity of gallic acid (**Figure 4**) from *Woodfordia fruticosa* Kurz flowers was evaluated in Vero cells. Gallic acid exhibited a high anti-EV71 activity with an IC_{50} value of 0.76 $\mu g.ml^{-1}$, thus suggesting that gallic acid may be used as a potential anti-EV71 agent [98].

Adenoviruses (ADVs) can cause mild infections involving the gastrointestinal tract, upper or lower respiratory tract, and conjunctiva. The infections of ADVs are more common in young children, owing to lack of humoral immunity. No reliable therapy or vaccine is available to civilians [99]. Caffeic acid (**Figure 2**) from *P. major* L. exhibited the strongest activity against ADV-3 (EC_{50} = 14.2 $\mu g.ml^{-1}$, SI = 727), whereas chlorogenic acid (**Figure 6**) from *P. major* L. possessed potent anti-ADV-11 activity (EC_{50} = 13.3 $\mu g.ml^{-1}$, SI = 301). The mode of action of caffeic acid against ADV-3 was at multiplication stage, suggesting the potential of the compound against ADV infection [72, 73]. EGCG reduced ADV yield with an IC_{50} value of 25 μM in Hep2 cells and its anti-ADV activity indicated itself through several mechanisms, including multiple steps both outside and inside the cell in virus infection [100].

Dengue virus (DENV) causes a spectrum of human diseases ranging from mild dengue fever to dengue hemorrhagic fever and dengue shock syndrome in severe cases [101]. Measles virus (MV) can cause a severe infection characterized by high fever, coryza, cough, exanthema, and conjunctivitis [102]. Cytomegalovirus (CMV) is a member of the herpes family of viruses. Most of the patients with CMV do not cause symptoms, but it can be fatal for the immunocompromised such as newborn infants or HIV-infected patients [103]. Currently, there is no effective antiviral therapy available for DENV, MV, and CMV. Hence, it is very important of finding an effective

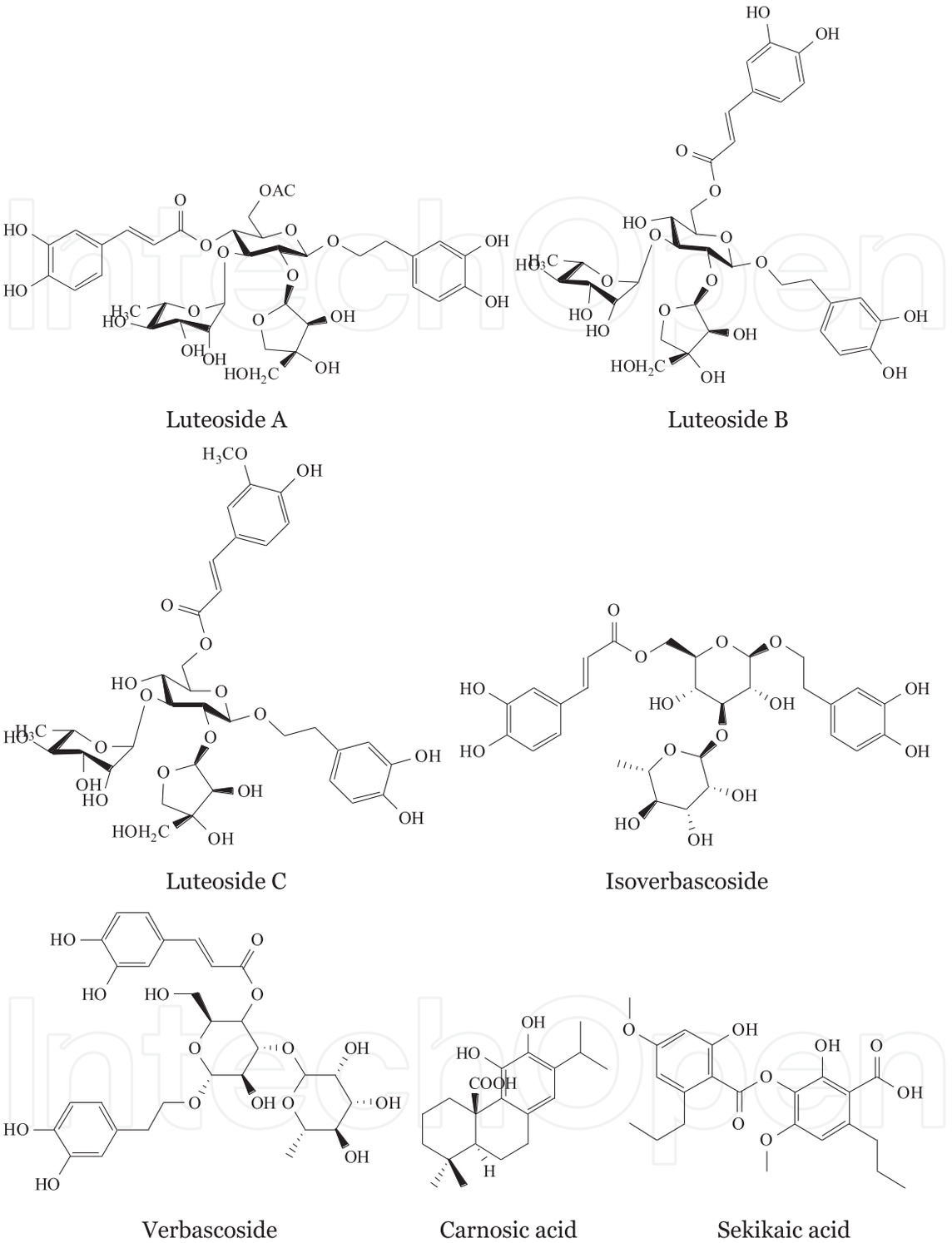


Figure 9.
Structures of anti-RSV phenolic acids.

compound against these viruses. Chebulagic acid and punicalagin (**Figure 3**) were effective in abrogating infections by DENV, MV, and HCMV at micromolar concentrations. Furthermore, these compounds blocked viral attachment, penetration, and spread for MV and HCMV infections. Hence, as the broad-spectrum antivirals, two gallic acid derivatives may be useful for limiting emerging/recurring viruses to engage host cell GAGs for entry [43].

Human papillomaviruses (HPVs), as a family of more than 180 related viruses, cause lots of diseases including condyloma acuminatum by HPV type 6 and 11 infection mainly [104, 105]. EGCG exhibited an anti-HPV effect by inhibiting the HPV11 E6 and E7 mRNA expressions in the recombinant HPV11.HaCaT cells [106].

4. Structural and antiviral properties

From the perspective of the structural properties of natural phenolic acids, caffeic acid, and its derivatives exhibited strong inhibitory activities against multiple viruses (**Table 1**), such as caffeic acid derivatives, including 1,3-di-*O*-CQA, 1,4-di-*O*-CQA, 1,5-di-*O*-CQA, 3,4-di-*O*-CQA, 3,5-di-*O*-CQA, 1-MO-3,5-di-*O*-CQA, 4,5-di-*O*-CQA, L-chicoric acid, rosmarinic acid, rosmarinic acid methyl ester, caffeic acid n-octadecyl ester, lithospermic acid, lithospermic acid B, orthosiphoic acids A-C and salvianolic acid C, possessed remarkable anti-HIV acitvity [8–16, 19–21, 23–25]. SAR suggested that two catechol moieties were required to inhibit HIV IN, while at least one free

Stuctural type	Compounds	Antiviral types	Structure-activity relationship	Reference
Caffeic acid and its derivatives	Caffeic acid	Anti-HCV; Anti-HBV; Anti-HSV; Anti-IV; Anti-ADV	① Biscatechol moieties were required for inhibition of IN, while at least one free carboxyl group was required for anti-HIV effect; Two aryl units separated by a central linker, as a common structural feature, is shared by the majority of these inhibitors. ② The potassium and sodium salts were found to be essential to increase the anti-HIV abilities of caffeic acid tetramers. ③ Chicoric acid derivatives lacking one carboxyl group and with 3,4,5-trihydroxycinnamoyl sidechains replacing caffeoyl group had the most strongest inhibition of HIV replication and end-processing activity ④ The length of the n-alkyl side chain and catechol moiety are responsible for the anti-HCV activities of caffeic acid derivatives. ⑤ The catechol group from caffeic acid seems to be important for the anti-IV activity. ⑥ The caffeoyl group may be indispensable for the anti-IV effects of CQAs.	[45, 51, 70, 71, 77, 79, 80]
	Chlorogenic acid	Anti-HBV; Anti-IV; Anti-ADV		[50, 70, 71, 78–80]
	3-*O*-CQA	Anti-HBV		[45]
	5-*O*-CQA	Anti-HBV; Anti-IV		[49, 82]
	5-*O*-(*E*)-*p*-Coumaroylquinic acid	Anti-HBV		[49]
	1,3-di-*O*-CQA	Anti-HIV		[12]
	1,4-di-*O*-CQA	Anti-HIV		[16]
	1,5-di-*O*-CQA	Anti-HIV		[12]
	3,4-di-*O*-CQA	Anti-HIV; Anti-HBV; Anti-IV; Anti-RSV		[12, 13, 49, 51, 80, 91, 107]
	3,5-di-*O*-CQA	Anti-HIV; Anti-HBV; Anti-IV; Anti-RSV		[12, 49, 52, 80, 91]
	1-MO-3,5-di-*O*-CQA	Anti-HIV		[12, 13]
	3,5-*O*-Dicaffeoyl-muco-quinic acid	Anti-HBV		[49]
	4,5-di-*O*-CQA	Anti-HIV; Anti-HBV; Anti-IV		[11, 12, 49, 80]
	3,4,5,-tri-*O*-CQA	Anti-HIV; Anti-IV		[11, 80]

Stuctural type	Compounds	Antiviral types	Structure-activity relationship	Reference
	Chicoric acid	Anti-HIV, Anti-HBV		[12, 14, 55, 108]
	Rosmarinic acid,	Anti-HIV; Anti-HSV		[17, 18, 72]
	Rosmarinic acid methyl ester	Anti-HIV; Anti-IV		[17, 83]
	Caffeic acid n-octadecyl ester	Anti-HIV; Anti-HCV		[19, 46]
	Caffeic acid phenethyl ester	Anti-HCV; Anti-IV		[46, 81, 82]
	Lithospermic acid	Anti-HIV		[21]
	Lithospermic acid B	Anti-HIV		[21]
	Orthosiphoic acids A-C	Anti-HIV		[22]
	Salvianolic acid C	Anti-HIV		
	Caffeic acid tetramers	Anti-HIV		[20]
	Luteoside A, B, C	Anti-RSV		[94]
	Verbascoside/ Acteoside, Isoverbascoside/ Isoacteoside	Anti-HIV, Anti-RSV		[23, 94]

Table 1.
Antiviral types and structure-activity relationship of natural caffeic acid and its derivatives.

carboxyl group was required for anti-HIV effect. Most of the inhibitors have two aryl units separated by a central linker. Meanwhile, hydroxylated aromatics seem to play an important role in inhibiting IN [17, 18]. The salts of isomeric caffeic acid tetramers showed potent anti-HIV activity. Moreover, the potassium and sodium salts were found to be essential to increase their anti-HIV abilities [22]. SAR of chicoric acid indicated that chicoric acid derivatives lacking one carboxyl group and with 3,4,5-trihydroxycinnamoyl sidechains replacing caffeoyl group had the strongest inhibition of HIV replication and end-processing activity [109]. Caffeic acid and its related compounds also displayed anti-HCV effects, while SAR demonstrated that the length of the n-alkyl side chain and catechol moiety is responsible for their anti-HCV activities [47, 48]. The derivatives of caffeic acid, including 3-*O*-CQA, 5-*O*-CQA, 5-*O*-(*E*)-*p*-coumaroylquinic acid, 3,4-di-*O*-CQA, 3,5-di-*O*-CQA, 3,5-di-*O*-caffeoyl-muco-quinic acid, 4,5-di-*O*-CQA and chicoric acid, had potent anti-HBV activity [51, 52, 55]. Caffeic acid exhibited potent inhibitory activity against HSV [72, 73]. Rosmarinic acid inhibited HSV-1 attachment to host cells [74]. Caffeic acid and its analogs such as chlorogenic acid, 5-*O*-CQA, 3,4-di-*O*-CQA, 3,5-di-*O*-CQA, 4,5-di-*O*-CQA, 3,4,5-tri-*O*-CQA, and CAPE showed inhibitory effect on IV [79–84]. The catechol group from caffeic acid seems to be important for the anti-IAV activity [81, 84]. The caffeoyl group may be indispensable for the anti-IV effects of CQAs [82]. 3,4-di-*O*-CQA and

3,5-di-*O*-CQA exhibited inhibitory activity against RSV infection [93]. Luteoside A-C, verbascoside and isoverbascoside displayed potent anti-RSV effect [94]. Additionally, caffeic acid and chlorogenic acid displayed anti-ADV activity [72, 73]. Other caffeoyl conjugates such as echinacoside also have antiviral effect [110].

In addition, gallic acid and its derivatives exhibited potent inhibitory effects on several viral infections (**Table 2**), such as gallic acid derivatives, including 3,5-di-*O*-galloyl-4-*O*-diGQA, 3,4-di-*O*-galloyl-5-*O*-diGQA, 3-*O*-digalloyl-4,5-di-*O*-GQA, 1,3,4,5-tetra-*O*-GQA, 1,3,4-tri-*O*-GQA, 3,4,5-tri-*O*-GQA, 3,5-di-*O*-galloyl-shikimic acid, 3,4,5-tri-*O*-galloylshikimic acid, punicalin, punicalagin, punicacortein C, chebulagic acid, ellagitannin, EGCG and camelliatannin H, were found to possess potent anti-HIV effect [11, 26–28, 31, 32, 111]. Digallic acid and its derivatives

Stuctural type	Compounds	Antiviral types	Structure-activity relationship	Reference
Gallic acid and its derivatives	Gallic acid	Anti-HCV; Anti-HBV; Anti-HSV-2; Anti-IV; Anti-EV71	① The docking analysis of gallic acid derivatives indicated that the gallic acid-based inhibitor could be effectively targeted for designing HIV-1 PR inhibitors. ② Three hydroxyl groups at the 3, 4, and 5 positions seem to be required for the inhibition of digallic acid derivatives. ③ SAR analysis of the hydrolysable tannins elucidated that the galloyl groups on C-2 and C-3 and the hexahydroxydiphenyl group bridged between C-4 and C-6 increased inhibitory ability for HCV invasion. ④ The 3-galloyl group of EGCG skeleton plays a significant role on its antiviral effect, whereas the 5'-OH at the trihydroxy benzyl moiety at 2-position plays a secondary role. ⑤ The essential pharmacophore of ellagitannins exits in the corilagin moiety and the outer carboxylic acid moieties seem to serve only as auxopharmacore.	[35, 37, 53, 59, 60, 93]
	3,4-di-*O*-galloyl-5-*O*-diGQA	Anti-HIV		[24]
	3,5-di-*O*-galloyl-4-*O*-diGQA	Anti-HIV		[24]
	3-*O*-digalloyl-4,5-di-*O*-GQA	Anti-HIV		[24]
	1,3,4-tri-*O*-GQA	Anti-HIV		[25]
	3,4,5-tri-*O*-GQA	Anti-HIV		[11, 26]
	1,3,4,5-tetra-*O*-GQA	Anti-HIV		[24]
	3,5-di-*O*-galloyl-shikimic acid	Anti-HIV		[25]
	3,4,5-tri-*O*-galloylshikimic acid	Anti-HIV		[25]
	Punicalin,	Anti-HIV; Anti-HBV		[25, 53]
	Punicalagin	Anti-HIV; Anti-HBV; Anti-HSV-1; Anti-RSV; Anti-DENV; Anti-MV; Anti-HCMV		[25, 41, 53, 65]
	Punicacortein C	Anti-HIV		[25]
	Chebulagic acid	Anti-HIV; Anti-HSV-1; Anti-RSV; Anti-DENV; Anti-MV; Anti-HCMV		[25, 38, 41, 65]
	Ellagitannin	Anti-HIV		[25]
	Digallic acid	Anti-HIV		[27, 28]
	Camelliatannin H	Anti-HIV-1		[32]
	1,2,6-tri-*O*-galloyl-β-d-glucose	Anti-HCV		[36]

Stuctural type	Compounds	Antiviral types	Structure-activity relationship	Reference
	1,3,6-tri-*O*-galloyl-β-D-glucose	Anti-HCV		[37]
	1,2,3,6-tetra-*O*-galloyl-β-d-glucose	Anti-HCV		[36]
	1,3,4,6-tetra-*O*-galloyl-β-D-glucose	Anti-HCV; Anti-HSV		[37, 63]
	1,2,3,4,6-penta-*O*-galloyl-β-D-glucoside	Anti-HCV		[36, 37]
	Tercatain	Anti-HCV		[37]
	Punicafolin	Anti-HCV		[37]
	Excoecariphenol D	Anti-HCV		[38]
	Corilagin,	Anti-HCV		[38]
	Geraniin	Anti-HCV; Anti-HSV		[38, 63]
	SCH 644343	Anti-HCV		[39]
	SCH 644342	Anti-HCV		[39]
	Tellimagrandin I	Anti-HCV		[40]
	Eugeniin	Anti-HCV; Anti-HSV		[40, 61]
	Casuarictin	Anti-HCV		[40]
	Pentyl gallate	Anti-HSV-2		[59, 60]
	Hippomanin A	Anti-HSV-2		[62]
	Excoecarianin	Anti-HSV-2		[64]
	Casuarinin	Anti-HSV-2		[65]
	Pterocarnin A	Anti-HSV-2		[66]
	Strictinin	Anti-IV		[84, 85]
	Epigallocatechin-3-gallate	Anti-HIV; Anti-HCV; Anti-HBV; Anti-HSV; Anti-IV; Anti-ADV; Anti-HPV		[29, 42–44, 54, 68, 88, 99, 105]

Table 2.
Antiviral types and structure-activity relationship of natural gallic acid and its derivatives.

displayed significant anti-HIV and anti-HSV activities. All three hydroxyl groups at the 3, 4, and 5 positions seem to be responsible for their inhibitory activities [29, 30, 61, 62]. The docking analysis of gallic acid derivatives indicated that the gallic acid-based inhibitor could be effectively targeted for designing HIV-1 PR inhibitors [108]. Gallic acid glucosides and other derivatives, including 1,2,6-tri-*O*-galloyl-β-D-glucose, 1,3,6-tri-*O*-galloyl-β-D-glucose, 1,2,3,6-tetra-*O*-galloyl-β-D-glucose, 1,3,4,6-tetra-*O*-galloyl-β-D-glucose, punicafolin, 1,2,3,4,6-penta-*O*-galloyl-β-D-glucose, 1,2,3,4,6-

penta-*O*-galloyl-β-D-glucoside, excoecariphenol D, tercatain, corilagin, geraniin, chebulagic acid, tellimagrandin I, eugeniin, casuarictin, chebulagic acid, punicalagin, SCH 644343, SCH 644342 and EGCG, possessed marked anti-HCV activity [38–45]. Gallic acid and its derivatives punicalagin, punicalin, and EGCG were found to inhibit HBV replication [56, 57]. Ten gallic acid derivatives such as eugeniin, hippomanin A, casuarinin, geraniin, 1,3,4,6-tetra-*O*-galloyl-β-D-glucose, excoecarianin, chebulagic acid, punicalagin, pterocarnin A and EGCG showed remarkable inhibitory activity against HSV infection [63–70]. Ellagitannins exhibited anti-EBV activity. SAR analysis indicated that their essential pharmacophores exist in the corilagin moiety and the outer carboxylic acid moieties seem to serve only as auxopharmacore [71]. Gallic acid and its derivatives also showed antiviral activity against human avian influenza [56]. Strictinin, EGCG, and ECG have potent inhibitory activity against IAV infection [86, 87, 90]. Two gallic acid derivatives, chebulagic acid and punicalagin, exhibited strong inhibitory effects on RSV, DENV, MV, and HCMV infections, respectively [43]. Gallic acid had high potency against EV71 [98]. EGCG showed potent anti-ADV and anti-HPV activities [100, 106].

As regards antiviral characteristics or mechanism of action, several naturally originated phenolic acids exhibited new targets or modes of antiviral action. Firstly, caffeic acid and its derivatives have special antiviral mechanisms. CQAs and CTAs, as highly selective HIV IN inhibitors, act at a site distinct from that of current anti-HIV agents [8–12]. The irreversible inhibition of CQAs on HIV IN is directed toward conserved amino acid residues in the central core domain during catalysis [13]. The reversible and noncompetitive inhibition of L-chicoric acid on HIV IN may interact with amino acids other than those which bind substrate [14]. Rosmarinic acid suppressed HIV-1 IN and also inhibited RT directly [19, 20]. The primary target of L-chicoric acid and its analogs against HIV is the viral entry in cells [107]. Salvianolic acid C and orthosiphoic acids A-C displayed anti-HIV-1 PR effect [25]. The anti-HBV effects of 3,4-di-*O*-CQA and 3,5-di-*O*-CQA are associated with the upregulation of HO-1 by decreasing HBV core protein stability, which blocks HBV cccDNA refill [51, 52]. The antiviral effects of caffeic acid against HSV-2 and ADV-3 were at viral multiplication stages [72, 73]. Caffeic acid, chlorogenic acid, and their derivatives exerted antiviral effects against Nas from H5N1 [81–84]. The ability of 3,4-di-*O*-CQA to clear IAV infection was performed by increasing tumor necrosis factor-related apoptosis-inducing ligand [112]. The anti-RSV effects of 3,4-di-*O*-CQA and 3,5-di-*O*-CQA were exerted by the suppression of virus-cell and cell-cell fusion in the early stage and at the end of viral reproduction in turn [93].

Secondly, gallic acid and its derivatives possess new antiviral characteristics. GQAs and other gallic acid derivatives displayed inhibitory activities against HIV RT, virus reproduction, and virus-cell interactions [26, 27]. 3,4,5-tri-*O*-GQA selectively inhibited HIV replication and non-competitively suppressed HIV RT by interaction with gp120 to block virus binding to CD4 receptor [11, 28]. Digallic acid inhibited HIV RT and DNA polymerases α/β. Its mode of action against HIV was partially competitive relative to the template and primer, and also noncompetitive to the triphosphate substrate and dTTP [29, 30]. Gallic acid reduced ROS production at the early time points of exposure in cells expressing HCV proteins, thus suggesting that the antioxidant capacity of the compound may be involved in anti-HCV replication [37]. Meanwhile, HCV NS3/4A and NS5A proteases are possible pathways for gallic acid derivatives to inhibit HCV [37–41]. The anti-HCV mechanisms of gallic acid derivatives chebulagic acid and punicalagin may be related to suppressing the attachment and entry steps of infection [43]. EGCG inhibited HCV entry by acting directly on the

virions, leading to the structural alteration of viral particles, which could impair the attachment to the surface of hepatocyte [113]. Gallic acid and its derivatives against HSV infection were ascribed to their virucidal effects on virus particles by partial inhibition of the virus attachment to cells and its subsequent cell-to-cell spread [61, 62]. Eugeniin may be a promising novel anti-HSV agent by targeting viral DNA synthesis [63]. Excoecarianin, as an entry inhibitor against HSV-2, contributes to improving combinatorial drug treatment with nucleoside analogs [66]. Chebulagic acid and punicalagin blocked interactions between cell surface glycosaminoglycans and HSV-1 glycoproteins, and thus they may be used as competitors for glycosaminoglycans and improve drug resistance to nucleoside analogs [67]. Casuarinin exhibited anti-HSV activity by inhibiting viral attachment and penetration and also disturbing the late events of infection [68]. Pterocarnin A inhibited both early and late stages in HSV-2 replication cycle [69]. Strictinin suppressed IAV-induced hemifusion and prevented IAV replication, and also showed antiviral activities against IBV and human parainfluenza virus type-1 infections [86, 87]. Chebulagic acid and punicalagin blocked viral attachment, penetration, and spread for RSV, MV, and HCMV infections [43]. The anti-HPV effect of EGCG was performed by inhibiting HPV11 E6 and E7 mRNA expressions [106].

Additionally, other phenolic acids also possess antiviral properties. Protocatechuic acid showed anti-HBV and anti-HSV-2 activities [58, 76]. 2,5-Dihydroxybenzoic acid had a weak anti-HSV-1 effect [75]. Podocarpic acid and its derivatives suppressed the replication of H1N1 IAV and influenza A/Kawasaki/86 (H1N1) virus [88, 89]. Carnosic acid suppressed viral gene expression and RSV replication [95]. Sekikaic acid showed potent inhibition toward RSV and clearly interfered with viral replication at a viral post-entry step [96].

5. Conclusion

Viral infections are an important part of human disorders and their treatments are still difficult. The approved antiviral drugs have their limitations without exception. Many viral diseases lack efficient vaccines and antiviral therapies so far, which are often perplexed by the development of drug resistance and the generation of viral mutation. Hence, it is urgently needed to discover novel antiviral drugs. Naturally originated compounds especially phenolic acids are an excellent source for finding new antiviral agents because of their potent activities and unique antiviral mechanisms [114, 115]. In this review, the naturally occurring phenolic acids with antiviral activity are discussed according to their structure properties and antiviral types such as anti-HIV, anti-HCV, anti-HBV, anti-HSV, anti-IV, anti-RSV, *etc*. These natural phenolic acids and their derivatives may be cited as promising antiviral leads or candidates.

To summarize, naturally originated phenolic acids and their derivatives exerted potent antiviral effects on multiple viruses in humans. In particular, caffeic acid/gallic acid and their derivatives exhibited prominent antiviral properties and special targets or mechanisms of action, thus suggesting these compounds can be regarded as novel promising leads or candidates for the development of new antiviral agents. In addition, these natural phenolic acids with antiviral effects are mostly limited to the *in vitro* results to date. Furthermore, scarcely any of them have been used as antiviral drugs in clinical practice. Therefore, naturally derived phenolic acids with diverse skeletons and different targets or mechanisms, as a powerful resource for novel antiviral agent development, are worthy to be further studied and explored in the future.

Conflict of interest

The authors have no conflict of interest. The partial content of this manuscript was published in *Current Medicinal Chemistry* (2017, 24(38): 4279–4302).

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