RNA-dependent RNA polymerase (RdRp) natural antiviral inhibitors: a review

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Abstract

Viral diseases are the cause of many global epidemics, leading to deaths, affecting the quality of life of populations, and impairing public health. The limitations in the treatment of viral diseases and the constant resistance to conventional antiviral treatments encourage researchers to discover new compounds. In this perspective, this literature review presents isolated molecules and extracts of natural products capable of inhibiting the activity of the nonstructural protein that acts as the RNA-dependent RNA polymerase. The literature review presented natural compounds with the potential to be tested as alternative medicines or used in the development of synthetic drugs to prevent the replication of RNA viruses, such as COVID-19, hepatitis C, and dengue viruses, among others. Natural products are known to exhibit remarkable activities in mitigation of different viral diseases, in addition, they help to decrease the aggravation of infections. Consequently, reducing hospitalization time and deaths.

Keywords Antivirals · Natural products · RdRp · Dengue · Hepatitis C · SARS-CoV-2

Introduction

The RNA-dependent RNA polymerase (RdRp) is described in the literature as a promising target for the development of antiviral drugs [1]. The RdRp enzyme is part of the viral replication-transcription complex, and a specific inhibitor of this enzyme could prevent the complex from functioning properly, consequently interrupting the protein synthesis and virus multiplication. Among the positive aspects of RdRp is the fact that it has no homology with host cell proteins. Therefore, inhibitors developed for this protein may be more selective and, in turn, have few side effects and no toxicity in human cells [1, 2]. The SARS-CoV-2 virus genome has a positive-sense single-stranded RNA, which contains the orf1ab gene that encodes nonstructural proteins (NSPs) (replication-transcription complex) as well as genes that encode structural proteins. The NSPs 1 to 16 are encoded by the orf1ab gene, and nsp12 is one of the enzymes responsible for the duplication of the genome that acts as the RNA-dependent RNA polymerase (RdRp) [3]. HCV, from the Flaviviridae family, also has a positive-
sense single-stranded RNA responsible for encoding a polyprotein. This polyprotein is sequentially cleaved by host and virus proteases into mature proteins such as central, structural, ion channel, and nonstructural proteins (NSPs), named p7, NS2, NS3, NS4A, NS4B, NS5A, and NS5B [4, 5]. The NS5B enzyme is the most studied target for the development of HCV therapies [6]. The drug therapy commonly includes pegylated interferon (PEG-IFN) combined with the nucleoside analog ribavirin and direct-acting antiviral (DAA) therapy [7]. DAAs are drugs that target nonstructural proteins, especially the NS5B polymerase. DENV, from the Flaviviridae family, has four serotypes responsible for the same symptoms [8]. This virus is composed of a positive-sense single-stranded RNA molecule with an open reading frame. This structure is surrounded by untranslated regions that play structural and functional roles in the formation of RNAs (genome replication and transcription) [9]. NS5, which acts as the RdRp enzyme, is responsible for the replication of DENV and is common to its four serotypes. This makes this protein the target of choice for the development of drugs against DENV [8].

Therefore, the objective of this study was to review the literature on isolated substances and/or extracts of natural compounds that function as viral RdRp inhibitors since these compounds may have promising antiviral activities and serve as a basis for future research, such as in the development of drugs. Compounds that were reported to have this potential but did not present a half-maximal inhibitory concentration capable of inhibiting 50% of the enzyme (IC50) were excluded from this review, as well as potential inhibitors selected only with in silico data. For this purpose, several online databases like Medline, Scopus, Web of Science, Embase, Lilacs and Scielo were used with the following terms in different combinations as medicinal plant, plant extract, bioactive, phytochemical, bioactive, natural product, antiviral agents, RNA polymerase, RNA replicase inhibitor.

**Viral diseases**

Viruses are threats to public health because they can affect the physical, social, economic, and mental health of populations worldwide. The phenomenon of zoonotic spillover, climate change, and the increase in international travel are some of the factors that are directly related to the increase in the spread of viral diseases [10]. Since the first outbreak of the Severe Acute Respiratory Syndrome (SARS-CoV) in late 2002, and of the Middle East Respiratory Syndrome (MERS-CoV) in 2012, the need to develop effective therapies and vaccines has become evident. This context was intensified in December 2019, when the first cases of SARS-CoV-2 contamination were reported in China; over the next few months, the virus quickly spread to several countries and became a public health emergency [11]. The novel coronavirus (SARS-CoV-2) pandemic was declared by the World Health Organization (WHO) on March 11, 2020, and as of August 23, 2022, more than 596 million cases and 6.455.500 deaths from COVID-19 had been recorded worldwide [12]. Although several vaccines have been developed, there is currently no therapy available to treat COVID-19. Thus, an antiviral drug capable of inhibiting SARS-CoV-2 replication is needed, since the disease is now responsible for millions of deaths and is still affecting the routine and economy of the world population.

The hepatitis C virus (HCV) is also included in the statistics of the viruses that most affect global health, with the aggravating factor that the infection develops gradually, originating diseases such as liver fibrosis, cirrhosis, and hepatocellular carcinoma [5]. Anti-HCV antibodies are produced during the acute phase of infection; however, HCV can evade them, rendering the host immunity system ineffective. These immune events have not been fully elucidated [7]. This condition, alongside treatment interruption, contributes to approximately 71 million people presenting chronic hepatitis C worldwide [7, 13]. To date, there are no HCV vaccines [14].

Dengue (DENV) is the most prominent mosquito-borne viral disease and falls into the category of public health problems in tropical and subtropical countries. Dengue has existed for several decades; however, its occurrence increased 30-fold in the last 50 years. To prevent cases, it is necessary to fight the proliferation of the dengue mosquito, since there is no available chemotherapy so far [8] and the tetravalent dengue vaccine (Dengvaxia®) [15] is restricted to people who have already had contact with the virus [13]. The rapid antiviral drug resistance and the lack of preventive vaccines motivate the search for new substances; therefore, there is an increasing number of studies on natural compounds [4, 16, 17].

**Molecular structures of isolated compounds with the potential to inhibit RdRp-HCV and RdRp-DENV**

The substances in a plant extract promote a synergistic effect, which can contribute to the inhibition of multi-site enzymes. RdRp-HCV (NS5B), for instance, has five different small-molecule binding sites, which shows that there is great benefit in using a natural product extract, whether combined with other drugs or not [18]. In addition to synergism from several compounds against the same target, the antiviral action can result from the synergism of different molecules that act on different targets but with the same purpose. An extract can have several molecules that...
present different mechanisms of action, including blocking the entry of the virus into the cell, blocking enzyme synthesis, and inhibiting viral replication [19, 20]. However, it is necessary to isolate the compounds that constitute extracts, even if the purified form has no synergistic effect. Fractionation and purification allow us to characterize an active molecule and evaluate its activity and/or potential in different experimental models [18]. In Fig. 1 we present the molecular structures and names of the isolated compounds mentioned in the studies that were included in this review. Further on, some inherent characteristics of isolated compounds will be discussed. These features make it easier to understand the nature of the interactions between isolated compounds and the viral polymerase (RdRp), in addition to trying to indicate promising compounds that can be explored in the future.

Compound 26 (IC$_{50}$: 7.4) was isolated from the extract of *Tripterygium hypoglaucum*. In a study that compared the inhibitory activity of compound 26 with that of other compounds isolated from the same plant on the hepatitis C virus RNA-dependent RNA polymerase (RdRp-HCV), the researchers correlated the presence of structural elements of compound 26 with the inhibitory activity; the structural elements include the presence of a carboxylic acid in the E-ring and the aldehyde and hydroxyl groups in the A-ring (Fig. 1) [6]. Based on the results from an assay on the polymerase inhibitory activity of mono- and dialkylated flavanones isolated from the bark extract of *Cryptocarya chartacea*, [21] observed both more and less active components and correlated the presence of arylheptanoid side chains at C-6 and C-8 in compounds 21 and 18 with the inhibitory activity [21]. Important data on the structures of the carneic acids (compounds 15, 16, 14, 12, 13) were listed in a polymerase bioassay, in which the authors suggested some relevant features for the inhibitory activity on dengue virus RNA-dependent RNA polymerase (RdRp-DENV). Among these features are the presence of the 1-methylopropenyl unit in position C-15 (Fig. 1) and the lower inhibitory potential of the compounds when this subunit is oxidized at C-18. They further listed the β-OH group at C-9 in compound 15 as likely responsible for the activity of this compound on the polymerase [22]. The literature indicates that some molecules selected from the *Dacrydium balansae* species did not show the same potential as isolated biflavonoids (compounds 28, 36, 7, 29), thus suggesting, through the comparison of chemical structures, the importance of the dimeric nature of biflavonoids (Fig. 1). Furthermore, the comparison between isolated biflavonoids led the authors to hypothesize that 4’-methoxylation decreases the potency of some of biflavonoids [8].

Compound 40 strongly inhibited RdRp (NS5B) activity (Table 1) [18] found that, in a cell culture system, 10 μM of this compound was able to inhibit more than 80% of NS5B expression [18]. In the same study, the authors also found that compounds 40 and 30 (Fig. 1) showed structural similarities and synergistic effect when inhibiting the polymerase activity [18]. Aside from being present in *Eclipta Alba*, compound 40 is also the main metabolite of the *Eclipta prostrata* species [23]. The literature reports that this compound can inhibit the secretion of interleukins and suppress the transcription of inflammatory genes [24]. The following biological effects were also cited: anti-fibrotic, anti-free radical, and antioxidant [23].

Compound 7, isolated from the *Dacrydium balansae* species, inhibits the inflammatory, which is an adaptor protein involved in inflammatory signaling. This protein complex detects pathogenic microorganisms, causing the rapid activation of the immune system response triggers the activation of specific receptors that cause the release of many pro-inflammatory cytokines [27]. Interestingly, Brazilian researchers investigated possible mechanisms responsible for the SARS-CoV-2 infection since the patient may develop psychiatric disorders, such as depression, and neurodegenerative diseases [28]. These data reinforce the urgent need for drugs capable of modulating the main substances (cytokines and chemokines) of the inflammatory process associated with COVID-19. Therefore, the aforementioned compounds could contribute to the development of antiviral therapies for RNA virus infections not only by inhibiting viral replication but also minimize secondary conditions related to the pathophysiology of viral infections. In previous studies, compounds 31 and 38 (Table 1) were observed to inhibit HCV RdRp. The authors suggested that either one of them may have multiple binding sites on NS5B and reported that these chemical compounds do not act as competitive inhibitors. All these data are extremely important because they indicate compounds...
Fig. 1 Structures of isolated compounds that inhibited RdRp

(3β)-3-(acetylxy)-urs-12-en-28-oic acid (1)

(3β)-3,23-dihydroxy-12,20 (29)-dien-28-oic acid (2)

3-hydroxystigmast-5-en-7-one (3)

3β-O-cis-p-coumaroylalphitolic acid (4)

3β-O-trans-p-coumaroylalphitolic acid (5)

6-hydroxystigmast-4-en-3-one (6)

Apigenin (8)

Amentoflavone (7)

Betulin (9)

Betulinic acid (10)

Betulinic aldehyde (11)

Carneic acids C (12)

Carneic acids E (14)

Carneic acids F (15)

Carneic acids D (13)

Carneic acids O (16)
Fig. 1 (continued)
Fig. 1 (continued)
with high inhibitory capacity that directly interfere with replication processes and may be good low-toxicity alternatives [30]. In the literature, several natural compounds have also been mentioned, capable of interfering with HCV replication and/or blocking the entry of HCV by binding to structural and nonstructural proteins [4].

Table 1  Bioactive compounds that showed RdRp inhibitory activity

| Natural source     | Bioactive compound (No) | IC_{50} (µM) | Enzyme                  | Reference |
|--------------------|-------------------------|--------------|-------------------------|-----------|
| Cryptocarya chartacea | Chartaceone E (20)      | 2.9          | RdRp-DENV*               | [21]      |
| Cryptocarya chartacea | Chartaceone C (18)      | 4.2          | RdRp-DENV*               | [21]      |
| Cryptocarya chartacea | Chartaceone D (19)      | 1.8          | RdRp-DENV*               | [21]      |
| Cryptocarya chartacea | Chartaceone F (21)      | 2.4          | RdRp-DENV*               | [21]      |
| Dacrydium balansae  | Hinokiflavone (28)      | 0.26         | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | Podocarpusflavone a (36)| 0.75         | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | Amentoflavone (7)       | 1.40         | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | Isoginkgetin (29)       | 3.12         | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | 3-hydroxystigmast-5-en-7-one (3) | 7.9 | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | Trans-3,5,4′-trimethoxystilbene (37) | 14.4 | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | Cis-3,5,4′-trimethoxystilbene (22) | 18.5 | RdRp-DENV*               | [18]      |
| Dacrydium balansae  | 6-hydroxystigmast-4-en-3-one (6) | 28.0 | RdRp-DENV*               | [18]      |
| Diospyros glans    | Usnic acid (39)         | 4.7          | RdRp-DENV*               | [31]      |
| Diospyros glans    | (3β)-3,23-dihydroxylup-12.20(29)-dien-28-oic acid (2) | 5.3 | RdRp-DENV*               | [31]      |
| Diospyros glans    | Betulinic aldehyde (11) | 6.1          | RdRp-DENV*               | [31]      |
| Diospyros glans    | Betulinic acid (10)     | 6.6          | RdRp-DENV*               | [31]      |
| Diospyros glans    | (3β)-3-(acetyloxy)-urs-12-en-28-oic acid (1) | 7.0 | RdRp-DENV*               | [31]      |
| Diospyros carbonaria | 3β-O-cis-p-coumaroylalphtolic acid (4) | 3.0 | RdRp-DENV*               | [15]      |
| Diospyros carbonaria | Betulin (9)             | 4.1          | RdRp-DENV*               | [15]      |
| Diospyros carbonaria | Betulinic aldehyde (11) | 7.5          | RdRp-DENV*               | [15]      |
| Diospyros carbonaria | 3β-O-trans-p-coumaroyl-alphtolic acid (5) | 2.2 | RdRp-DENV*               | [15]      |
| Diospyros carbonaria | Eucalyptus acid (27)   | 2.3          | RdRp-DENV*               | [15]      |
| Diospyros carbonaria | Betulinic acid (10)     | 4.3          | RdRp-DENV*               | [15]      |
| Eclipta alba        | Wedelolactone (40)      | 7.7          | RdRp-HCV*                | [18]      |
| Eclipta alba        | Luteolin (30)           | 11.3         | RdRp-HCV*                | [18]      |
| Eclipta alba        | Apigenin (8)            | 175.5        | RdRp-HCV*                | [18]      |
| Ligustrum lucidum   | Ursolic acid (38)       | 3.1          | RdRp-HCV*                | [30]      |
| Ligustrum lucidum   | Ursolic acid (38)       | 6.4          | RdRp-HCV*                | [30]      |
| Ligustrum lucidum   | Oleanolic acid (31)     | 0.8          | RdRp-HCV*                | [30]      |
| Ligustrum lucidum   | Oleanolic acid (31)     | 1.0          | RdRp-HCV*                | [30]      |
| Phomopsis sp.      | Carneic acids E (14)    | 15.5         | RdRp-DENV*               | [22]      |
| Phomopsis sp.      | Carneic acids C (12)    | 19.0         | RdRp-DENV*               | [22]      |
| Phomopsis sp.      | Carneic acids D (13)    | 19.0         | RdRp-DENV*               | [22]      |
| Phomopsis sp.      | Carneic acids F (15)    | 11.8         | RdRp-DENV*               | [22]      |
| Phomopsis sp.      | Carneic acids O (16)    | 13.6         | RdRp-DENV*               | [22]      |
| Phyllanthus amarus  | Corilagin (23)          | 20.0         | RdRp-HCV*                | [33]      |
| Platycodon grandiflorum | Platycodon D (33)    | 5.0          | RdRp-HCV*                | [34]      |
| Platycodon grandiflorum | Platycodon D2 (35)    | 6.0          | RdRp-HCV*                | [34]      |
| Platycodon grandiflorum | Deapioplatycodon D (24) | 7.0 | RdRp-HCV*                | [34]      |
| Platycodon grandiflorum | Platycodon D3 (34)    | 8.0          | RdRp-HCV*                | [34]      |
| Platycodon grandiflorum | Deapioplatycodon D2 (25) | 10.0 | RdRp-HCV*                | [34]      |
| Platycodon grandiflorum | Platycopon acid A (32) | 15.0         | RdRp-HCV*                | [34]      |
| Tetramomum hypoglauccum | Celastrol (17)         | 36.4         | RdRp-HCV*                | [6]       |
| Tripterygium hypoglauccum | Demethylzeylasteral (26) | 7.4 | RdRp-HCV*                | [6]       |

*Half-maximum inhibitory concentration
bRNA-dependent RNA polymerase of the dengue virus
cRNA-dependent RNA polymerase of the hepatitis C virus, genotype 1a
dRNA-dependent RNA polymerase of the hepatitis C virus, genotype 2a JFH1
eRNA-dependent RNA polymerase of the hepatitis C virus
fEndophyte isolated from the leaves of Diospyros carbonaria Benoist
In 2016, a phytochemical analysis of the *Diospyros glans* species disclosed the presence of compound 39, lupane- and ursane-type triterpenoids (Table 1) [31]. This finding marked the beginning of the discovery of an array of compounds capable of inhibiting the dengue virus replication. Later, in another study, compounds 5, 27, 4, 9, 10, and 11 (known lupane-type triterpenoids) (Table 1) were isolated from the crude extract of *Dyospyros carbonaria* bark. The results were promising for both the crude extract of *D. carbonaria* and the 6 isolated compounds. Therefore, the researchers also analyzed the 38 endophytic fungi that were colonizing this species and, for the first time, compound 10 was isolated from an endophyte (*Phomopsis* sp. SNB-LAP1-7-32) [15]. The preliminary analysis of the endophyte *Phomopsis* sp. (SNB-LAP1-7-32) prompted further investigation of the extract and, this time, a total of 13 new carneic acids were obtained, among which, compounds 15, 16, 14, 18, and 13 showed significant activity (Table 1) [22]. Data from the literature show that several natural compounds such as curcumin, baicalein, delphinidin, naringenin, quercetin, and quinine were already related to DENV inhibitory activity, but few showed the potential to inhibit RdRp according to the IC$_{50}$ value [32].

This review lists isolated compounds reported in the literature that showed the potential to inhibit the RdRp enzyme. Further details about these inhibitors are presented in Table 1.

The isolated compounds that showed lower concentrations when inhibiting the RdRp enzyme were grouped in Fig. 2.

### Isolated compounds and groups of plant metabolites

Classes of secondary metabolites such as flavonoids, coumarins, terpenoids, essential oils, polysaccharides, and proteins are currently under testing for a wide range of antiviral activities [35].

A study reports that several natural compounds of the flavonoid class showed antiviral activities not only against SARS-CoV-2, but also against other RNA viruses such as influenza A and B, human immunodeficiency 1 (HIV-1), and hepatitis C viruses [27]. Most of the isolated compounds included in this review with IC$_{50}$ values below 5.0 μM belonged to the flavonoid and triterpenoid classes (Fig. 3), such as compounds 19, 21, 20, 18 (designated mono- and dialkylated flavanones), which showed an IC$_{50}$ between 1.8 and 4.2 μM (Table 1) [21]. The biflavonoids isolated from *D. balansae* exhibited specific inhibitory activity against RdRp-DENV [8].

![](Fig_2.png)

**Fig. 2** Bioactive compounds that showed significant polymerase inhibitory activity with IC$_{50}$ values $<$5.0 μM

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1 In fact, the inhibition of replication and transcription processes is a mechanism of action common to molecules capable of interfering with the activity of RdRp, present in RNA viruses. Flavonoids such as kaempferol, fisetin, hyperoside, afzelin, biorobin, myricitrin, astragalin, quercetin, quercetin-3-O-glycoside and quercitin showed high affinity for RdRp using molecular docking.
Compounds 29, 36, and 7 were isolated from the *D. balansae* species and, according to the literature, compounds 36 and 7 were also found in *Garcinia subelliptica*, described as an important source of polyphenols [36]. Compound 29, which is also present in *Ginkgo biloba* leaves, has shown anti-inflammatory effects [37] and the ability to change pre-mRNA splicing in vitro and *in cellulo*, biological effects that were also reported for compound 1 [38].

Triterpenoids comprise the largest class of secondary metabolites, with over 20,000 identified structures found in various medicinal plants. This is directly related to the fact that these secondary metabolites have a wide range of pharmacological activities, including antiviral effects [39]. Compound 31 is a known example of a triterpenoid used in several countries to treat liver-related diseases and diabetes, and also as a wound-healing agent [39]. Studies report that plants such as *Lantana camara* and *Ligustrum lucidum*, like others from the Oleaceae family, are rich sources of compound 31 and are used as alternative therapies. The traditional indication for this natural compound also includes alternative treatment for various chronic diseases [37]. Thus, this compound may be a valuable alternative to prevent viral infection, since it showed a significant IC₅₀, and to ameliorate the complications or onset of chronic diseases associated with the initial viral infection. Another triterpenoid cited in this review is compound 10, which is isolated from birch (*Betula* sp.) and also found in many other species. This compound has a high potential to inhibit RdRp activity and is known mainly for its antiviral and antitumor effects [40]. Figure 3 shows the isolated compounds with IC₅₀ values below 5.0 µM and the group of metabolites to which they belong.

**Extracts and fractions with the potential to inhibit RdRp**

Research shows that several plant species have anti-HCV potential, such as methanolic extracts from *Ajuba parviflora*, *Ajuba bracteosa*, *Barberis lycium*, and *Citrus lemon* [31]. One of the species included in this review was *E. Alba*, a plant used in traditional African medicine whose extract inhibited the enzymatic activity of RdRp in vitro (Table 2). From its extracts, researchers isolated phenolic compounds, alkaloids, and terpenoids [41]. Using the Western Blotting and RT-PCR techniques, researchers confirmed a decrease in NS5B and NS5A protein expression. They verified over 95% inhibition when the cells were incubated with the extract at a concentration of 130 µg/mL for 48 h [18].

*Phyllanthus amarus* is described in the literature as a valuable natural source and is used in different countries around the world; in South America, it is known as “stone breaker” or “shatter stone”. This plant has several pharmacological activities, including antiviral properties, and is used in traditional medicine for hepatitis A and B [42]. Looking at the traditional use of this plant, the literature has explored and found evidence of the anti-HCV effect of *P. amarus*, according to the IC₅₀ values (between 5-10 µg/mL) of its extracts and fractions [20]. The same study compared extracts from different parts of *P. amarus* and found that the leaf extract (commonly used in homemade preparations) had the lowest concentration, capable of inhibiting only 50% of the target in question.

Regarding species popularly used in Yunnan, China, *Polygonum cymosum* showed a promising result, being able to inhibit 50% of the RdRp-mediated RNA synthesis at a concentration of 5.2 µg/mL (IC₅₀) for the aqueous fraction (Table 2). Favorable results were also reported for the *Ceratostigma willmottianum* (methanolic extract), *Dioscorea cirrhosa* (methanolic extract), and *Daucus maritimus* (butanolic fraction) extracts, which showed IC₅₀ at concentrations of 3.1, 0.6, and 1.0 µg/mL, respectively (Table 2) [6]. The butanolic fraction of *D. maritimus* was most effective in inhibiting the RdRp of West Nile virus (WNV), but it was also effective in inhibiting the HCV protein (Table 2). In assays with the aqueous extract of *D. cirrhosa* (IC₅₀ = 0.6 µg/mL), researchers found that this extract was able to increase cell viability (myocardial H9c2 cells) and decrease the content of reactive oxygen species when exposed to hydrogen peroxide. This result demonstrated the potential of this extract to protect the cell during oxidative stress [43], which is high during long-term viral infections. Restoring the balance depends on endogenous (albumin, urea, reduced glutathione) and exogenous (polyphenols, carotenoids, etc.) antioxidant compounds. Natural compounds with antioxidant properties may help reduce endothelial damage caused by oxidative stress. These compounds with antioxidant activity may be used to treat other diseases, such as COVID-19, since they act in the modulation of the immune system, a key spot to decrease complications caused by viral infections [44].
| Species | Part used | Solvent | Extract type | IC<sub>50</sub><sup>a</sup> (µg/mL) | Enzyme | Reference |
|---------|-----------|---------|--------------|----------------|--------|-----------|
| Akebia trifoliata var. australis | Branch | Water | Crude extract | 19.4 | RdRp-HCV<sup>b</sup> | [6] |
| Anemone rivularis | Branch | Water | Crude extract | 14.0 | RdRp-HCV<sup>b</sup> | [6] |
| Artemisia annua | Whole plant | Water | Crude extract | 16.0 | RdRp-HCV<sup>b</sup> | [6] |
| Bergenia purpurascens | Root | Methanol | Crude extract | 14.7 | RdRp-HCV<sup>b</sup> | [6] |
| Ceratostigma willmottianum | Branch | Water/methanol | Crude extract | 6.0/3.1 | RdRp-HCV<sup>b</sup> | [6] |
| Cryptocarya chartacea | Bark | Methanol and methyl cyanide | Fraction<sup>c</sup> | | RdRp-DENV<sup>d</sup> | [21] |
| Dactrydium balansae | Leaves | Dichloromethane/hexanes and acetonitrile residues | Fraction<sup>c</sup> | | RdRp-DENV<sup>d</sup> | [8] |
| Daucus maritimus | Seeds | Ethyl acetate | Crude extract | 8.0 | RdRp-WNV<sup>e</sup> | [46] |
| Daucus maritimus | Seeds | Butanol | Fraction | 1.0 | RdRp-WNV<sup>e</sup> | [46] |
| Dioscorea cirrhosa | Root | Water/methanol | Crude extract | 9.5/0.6 | RdRp-HCV<sup>b</sup> | [6] |
| Diospyros glans | Bark | Water and acetonitrile | Fraction<sup>c</sup> | | RdRp-DENV<sup>d</sup> | [31] |
| Diospyros carbonaria | Leaves and bark | Ethyl acetate | Crude extract | c | RdRp-DENV<sup>d</sup> | [15] |
| Eclipta alba | Whole plant | Water | Crude extract | 11.0 | RdRp-HCV<sup>b</sup> | [18] |
| Eleutherine Americana | Bulb | Water/methanol | Crude extract | 16.8/17.8 | RdRp-HCV<sup>b</sup> | [6] |
| Euchema gelatine | Whole plant | Methanol | Crude extract | 17.0 | RdRp-HCV<sup>b</sup> | [6] |
| Kadsura longipedunculata | Branch | Water | Crude extract | 14.4 | RdRp-HCV<sup>b</sup> | [6] |
| Ligustrum lucidum | Fruit | Ethyl acetate | Fraction 1 | 5.5 | RdRp-HCV<sup>f</sup> | [30] |
| Maytenus fookerii | Leaf | Water/methanol | Crude extract | 8.9/4.6 | RdRp-HCV<sup>b</sup> | [6] |
| Maytenus fookerii | Branch | Water | Crude extract | 13.7 | RdRp-HCV<sup>b</sup> | [6] |
| Periploca calophylla | Branch and leaf | Methanol | Crude extract | 15.9 | RdRp-HCV<sup>b</sup> | [6] |
| Phomopsis sp.<sup>g</sup> | Fungal endophyte | Ethyl acetate | Fraction<sup>c</sup> | | RdRp-DENV<sup>d</sup> | [22] |
| Phyllanthus amarus | Whole plant | Methanol | Crude extract | 6.0 | RdRp-HCV<sup>b</sup> | [20] |
| Phyllanthus amarus | Root | Methanol | Crude extract | 10.0 | RdRp-HCV<sup>b</sup> | [20] |
| Phyllanthus amarus | Leaf | Methanol | Crude extract | 5.0 | RdRp-HCV<sup>b</sup> | [20] |
| Phyllanthus amarus | Leaf | n-hexane | Fraction<sup>c</sup> | | RdRp-HCV<sup>b</sup> | [33] |
| Phyllanthus amarus | Leaf | Chloroform | Fraction | 10.0 | RdRp-HCV<sup>b</sup> | [33] |
| Phyllanthus amarus | Leaf | Ethyl acetate | Fraction | 10.0 | RdRp-HCV<sup>b</sup> | [33] |
| Piper hancei | Whole plant | Water | Crude extract | 13.6 | RdRp-HCV<sup>b</sup> | [6] |
| Platycodon grandiflorum | Roots | Methanol | Fraction<sup>c</sup> | 5.0 | RdRp-HCV<sup>b</sup> | [34] |
| Polygonum cynosum | Root | Water/methanol | Crude extract | 7.7/5.2 | RdRp-HCV<sup>b</sup> | [6] |
| Potentilla griffithii | Whole plant | Water/methanol | Crude extract | 8.7/11.0 | RdRp-HCV<sup>b</sup> | [6] |
| Pueraria phaseoloides | Root | Water/methanol | Crude extract | 16.5/17.4 | RdRp-HCV<sup>b</sup> | [6] |
| Rheum tanguticum | Rhizome | Water/methanol | Crude extract | 6.9/10.5 | RdRp-HCV<sup>b</sup> | [6] |
| Rhodobryum giganteum | Whole plant | Water | Crude extract | 19.0 | RdRp-HCV<sup>b</sup> | [6] |
| Rumex nepalensis | Rhizome and root | Water/methanol | Crude extract | 18.3/15.0 | RdRp-HCV<sup>b</sup> | [6] |
| Salvia yunnanensis | Underground part | Water/methanol | Crude extract | 7.4/16.8 | RdRp-HCV<sup>b</sup> | [6] |
| Sargentodoxa cuneata | Wood | Methanol | Crude extract | 14.2 | RdRp-HCV<sup>b</sup> | [6] |
| Schisandra henryi var. marginalis | Branch | Methanol | Crude extract | 19.6 | RdRp-HCV<sup>b</sup> | [6] |
| Swertia mussotii | Whole plant | Methanol | Crude extract | 10.6 | RdRp-HCV<sup>b</sup> | [6] |
Table 2  (continued)

| Species                  | Part used | Solvent       | Extract type | IC_{50}^{a} (µg/mL) | Enzyme                  | Reference |
|--------------------------|-----------|---------------|--------------|----------------------|--------------------------|-----------|
| Tripterygium forrestii   | Branch    | Methanol      | Crude extract | 11.4                 | RdRp-HCV^{b}             | [6]       |
| Tripterygium hypoglaucom | Stem      | Water/methanol| Crude extract | 12.0/9.2             | RdRp-HCV^{b}             | [6]       |
| Valerian jatamansi      | Root      | Water         | Crude extract | 19.7                 | RdRp-HCV^{b}             | [6]       |

\(^{a}\text{Half-maximum inhibitory concentration}\)

\(^{b}\text{RNA-dependent RNA polymerase of the hepatitis C virus}\)

\(^{c}\text{The IC}_{50}^{c} \text{ value was not determined or shown for the extract or fraction, only for the isolated compound. See the isolated compound corresponding to the species in Table 3}\)

\(^{d}\text{RNA-dependent RNA polymerase of the dengue virus}\)

\(^{e}\text{RNA-dependent RNA polymerase of the West Nile virus}\)

\(^{f}\text{RNA-dependent RNA polymerase of the hepatitis C virus, genotype 1a}\)

\(^{g}\text{Endophyte isolated from the leaves of Diospyros carbonaria Benoist}\)

Table 3  Extracts that exhibited significant polymerase inhibition activity with IC_{50} values >20.0 µg/mL.

| Species                        | Part used | Solvent       | Extract type | IC_{50}^{a} (µg/mL) | Enzyme                  | Reference |
|--------------------------------|-----------|---------------|--------------|----------------------|--------------------------|-----------|
| Acorus calamus                 | Rhizome   | Methanol      | Crude extract | 36.9                 | RdRp-HCV^{b}             | [6]       |
| Acorus calamus                 | Rhizome   | Water         | Crude extract | 31.0                 | RdRp-HCV^{b}             | [6]       |
| Aucklandia lappa               | Root      | Water         | Crude extract | 40.7                 | RdRp-HCV^{b}             | [6]       |
| Bergeinia purpurascens         | Root      | Water         | Crude extract | 28.9                 | RdRp-HCV^{b}             | [6]       |
| Brandisia caulis               | Branch, leaf | Water       | Crude extract | 40.9                 | RdRp-HCV^{b}             | [6]       |
| Dioscorea nipponica            | Rhizome   | Methanol      | Crude extract | 37.2                 | RdRp-HCV^{b}             | [6]       |
| Euchema gelatinae              | Alga      | Water         | Crude extract | 32.3                 | RdRp-HCV^{b}             | [6]       |
| Heracleum scabridum            | Root      | Water         | Crude extract | 30.6                 | RdRp-HCV^{b}             | [6]       |
| Kadsura longipedunculata       | Branch    | Methanol      | Crude extract | 20.2                 | RdRp-HCV^{b}             | [6]       |
| Ligustrum lucidum              | Fruit     | Ethyl acetate | Fraction 2    | 33.8                 | RdRp-HCV^{f}             | [30]      |
| Lobaria retigera               | Fungus    | Water         | Crude extract | 21.7                 | RdRp-HCV^{b}             | [6]       |
| Malus yunnanensis              | Fruit     | Water         | Crude extract | 35.7                 | RdRp-HCV^{b}             | [6]       |
| Menispermum dauricum           | Root      | Water         | Crude extract | 26.0                 | RdRp-HCV^{b}             | [6]       |
| Phellodendron chinense         | Branch, stem | Water       | Crude extract | 36.2                 | RdRp-HCV^{b}             | [6]       |
| Sargentodoxa cuneata           | Wood      | Water         | Crude extract | 20.1                 | RdRp-HCV^{b}             | [6]       |
| Sauurea lanceps                | Whole plant | Water      | Crude extract | 35.0                 | RdRp-HCV^{b}             | [6]       |
| Sauurea namikawae              | Whole plant | Water      | Crude extract | 28.8                 | RdRp-HCV^{b}             | [6]       |
| Schisandra henri var. marginalis| Branch    | Water         | Crude extract | 30.4                 | RdRp-HCV^{b}             | [6]       |
| Scutellaria amoena             | Root      | Water/methanol| Crude extract | 24.9/29.1            | RdRp-HCV^{b}             | [6]       |
| Scutellaria barbata            | Whole plant | Water      | Crude extract | 20.7                 | RdRp-HCV^{b}             | [6]       |
| Scutellaria barbata            | Whole plant | Methanol    | Crude extract | 41.6                 | RdRp-HCV^{b}             | [6]       |
| Smilax ferox                   | Rhizome   | Methanol      | Crude extract | 23.5                 | RdRp-HCV^{b}             | [6]       |
| Strobilomyces floccopus        | Fungus    | Water/methanol| Crude extract | 22.8/21.8            | RdRp-HCV^{b}             | [6]       |
| Swertia mussotii               | Whole plant | Water      | Crude extract | 31.9                 | RdRp-HCV^{b}             | [6]       |
| Thalictrum glandulosissimum    | Underground part | Water/methanol | Crude extract | 29.5/24.9            | RdRp-HCV^{b}             | [6]       |
| Thamnolia vermicularis         | Whole plant | Water      | Crude extract | 30.6                 | RdRp-HCV^{b}             | [6]       |
| Tripterygium forrestii         | Branch    | Water         | Crude extract | 23.9                 | RdRp-HCV^{b}             | [6]       |
| Tripterygium hypoglaucom       | Root bark  | Water/methanol| Crude extract | 32.0/29.4            | RdRp-HCV^{b}             | [6]       |
| Valerian jatamansi             | Root      | Methanol      | Crude extract | 34.2                 | RdRp-HCV^{b}             | [6]       |
| Verbena officinalis            | Whole plant | Water      | Crude extract | 40.0                 | RdRp-HCV^{b}             | [6]       |

\(^{a}\text{Half-maximum inhibitory concentration}\)

\(^{b}\text{RNA-dependent RNA polymerase of the hepatitis C virus}\)
The Diospyros genus encompasses some species, out of a total of 350, that are known to have antiviral properties against the human immunodeficiency virus, human norovirus, H3N2, H5N3 influenza virus, and herpes simplex-1 virus. Several studies were conducted with different species of this genus. A phylogenetic analysis from a dendrogram curiously showed that extracts from different species but from the same geographical area had phytochemical similarities [31]. Research on the D. carbonaria species in 2016 and 2020 has resulted in several promising studies. Extracts from both D. carbonaria bark (44% inhibition at 5 µg/mL) [15] and Phomopsis sp. culture (60% inhibition at 10 µg/mL) [22] were able to inhibit the replication of the dengue virus. Several studies on medicinal plant extracts with antiviral potential against DENV appeared in the literature, but few of them focused specifically on the RdRp enzyme. The acetone extracts of Pavetta tomentosa and Asian Tarenna demonstrated pupicidal potency against Aedes aegypti, and P. tomentosa also had an effect against dengue viral cell line [45].

This review lists natural extracts, including one from the fungal endophyte Phomopsis sp. SNB-LAP1-7-32, which showed the potential to inhibit the RdRp enzyme as per the determined IC50 values. The extracts in a concentration up to 20 µg/mL are presented in Table 2; Table 3 lists the remaining extracts (>20 µg/mL).

The species that showed the lowest concentrations of the extract when inhibiting the RdRp enzyme are presented in Fig. 4.

**Conclusions**

The lack of specific pharmacological agents is a limitation in the treatment of viral diseases. This review compiles natural compounds that can be tested as alternative therapies or used as prototypes to develop synthetic drugs that prevent viral replication. The data shows the potential these compounds from natural products have against several diseases, either by directly acting to inhibit the RdRp enzyme or by reducing secondary conditions related to the pathophysiology of viral infections. By gathering these data, we intend for this study to contribute with new insights about the structure-activity relationship of these molecules.

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analysis, acquisition of financing. EdBS: Formal analysis, acquisition of financing. FBM: Software, visualization, acquisition of financing. DPM: Conceptualization, acquisition of financing. JdFGD: Conceptualization, acquisition of financing. OGM: Conceptualization, acquisition of financing. MDM: Conceptualization, supervision, acquisition of financing.

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**Compliance with ethical standards**

**Conflict of interest** The authors declare no competing interests.

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