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EDITED BY
Arif Nur Muhammad Ansori,
Universitas Airlangga, Indonesia

REVIEWED BY
Saikat De,
The Scripps Research Institute, United States
Arli Aditya Parikesit,
Indonesia International Institute for Life-Sciences (i3L), Indonesia
Ali Jaber,
Lebanese American University, Lebanon

*CORRESPONDENCE
Carsten Wrenger
cwrenger@icb.usp.br

†These authors have contributed equally to this work

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Plant-derived extracts and natural products with antiviral activity

Giovane de Jesus Gomes Ribeiro[1†], Edmarcia Elisa de Souza[1†], Giuseppe Palmisano[1], Edison Luiz Durigon[2,3], Eva Liebau[4] and Carsten Wrenger[1,3*]

[1]Department of Parasitology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil, [2]Department of Microbiology, Institute of Biomedical Sciences, University of São Paulo, São Paulo, Brazil, [3]Institut Pasteur de São Paulo, São Paulo, Brazil, [4]Institute of Integrated Cell Biology and Physiology, University of Münster, Münster, Germany

In recent years, several viral epidemics and pandemics have emerged, leading to significant increases in both morbidity and mortality rates. This highlights the urgent need for the discovery of effective antiviral agents. A promising alternative approach to treating viral infections is the use of medicinal plants and their secondary metabolites. Plant-derived natural products have long been a valuable source for discovering novel therapeutic agents, owing to their chemical and structural diversity. This mini-review focuses on the antiviral activity of various enriched extracts and phytoconstituents isolated from medicinal plants, which have demonstrated efficacy against viral infections caused by the influenza virus, coronaviruses, arboviruses such as dengue, chikungunya, Zika, and Mayaro, as well as the human immunodeficiency virus (HIV).

KEYWORDS

medicinal plants, antiviral and pharmacological targets, SARS-CoV-2, ZIKV, CHIKV, MAYV, DENV, Influenza

Introduction

In recent years, viral infections have emerged as major global public health concerns, with increasing incidence and geographic spread. These infections significantly impact global health and economies due to their epidemic and pandemic potential (1). RNA viruses, in particular, are leading causes of human infectious diseases. Their high mutation rates contribute to the emergence of new viral subtypes and genotypes resistant to existing therapies, posing persistent threats of new outbreaks (2). For instance, Influenza A virus (H1N1), an enveloped, single-stranded RNA virus of the Orthomyxoviridae family, is responsible for most seasonal influenza epidemics (3). Highly pathogenic avian influenza A (H5N1) has also caused recent outbreaks involving zoonotic transmission (4). Similarly, SARS-CoV-2, a member of the Coronaviridae family with a single-stranded RNA genome encoding approximately 29 proteins, caused the COVID-19 pandemic, resulting in over seven million deaths worldwide (5). Although licensed antiviral therapies exist, RNA

viruses can rapidly evolve through reassortment and point mutations, leading to resistance against conventional treatments such as neuraminidase inhibitors for Influenza (6) and protease inhibitors targeting SARS-CoV-2 main protease (M^{pro}) (7).

In addition, four arboviruses Dengue (DENV) and Zika (ZIKV) (Flaviridae family), as well as Chikungunya (CHIKV) and Mayaro (MAYV) (Togaviridae family) primarily transmitted by the mosquito *Aedes aegypti* or *Haemagogus janthinomys* (MAYV), are single-stranded RNA representing a significant global public health concern, particularly due to their increasing geographic distribution and potential to cause a wide spectrum of neurological complications in recent years (8). Dengue virus, with its four major serotypes (DEN-1 to DEN-4), infects up to 400 million people annually (9, 10). Although vaccines and therapeutics are available, their efficacy varies widely across serotypes (11). No effective treatments or vaccines currently exist for Zika virus, Chikungunya virus, or Mayaro virus, highlighting the urgent need for new antiviral agents. Therefore, identifying new inhibitors for these arboviruses is imperative. With over 42.3 million deaths reported over the past four decades, HIV continues to affect global populations. Its single-stranded RNA genome encodes 15 proteins essential for viral replication and immune evasion. While antiretroviral therapies have significantly reduced viral loads, they are not curative and often cause adverse side effects. A prophylactic vaccine is still lacking (12).

This scenario raises an intensified focus on medicinal plants since they hold an immense reservoir of bioactive compounds that could lead to the discovering novel antiviral drugs (6, 13). Such compounds include mainly diverse secondary metabolites, isolated, purified, and identified from the crude extracts of various plant parts, harboring rich structural and chemical diversity which allows them to interact with different biological and viral targets (7). These characteristics led to wide functionality of these phytochemicals, favoring a sustained safety and effectiveness blocking multiples viral infections (14, 15). This review presents recent advances in plant-derived extracts and phytochemicals that inhibit various stages of the viral life cycle of Influenza, Dengue, Zika, Chikungunya, Mayaro, Coronavirus, and HIV (Figure 1), underscoring their potential for antiviral drug development.

Family of Orthomyxoviridae

Here we analyze 17 extracts and 16 isolated compounds from species across 12 plant families that exhibit anti-influenza activity, as listed in Table 1.

Extracts of medicinal plants with anti-Influenza activity

For instance, dry extracts from the aerial parts of *Spiraea* species have demonstrated a pronounced antioxidant effect against Influenza A, as well as cytoprotective activity by reducing the viral cytopathic effect in infected cells (41). Accordingly, the hydroethanolic extract of *Caesalpinia mimosoides*, primarily containing flavonoids and glycosylated derivatives, showed strong antioxidant and antiviral properties against H1N1. In this context, computational molecular docking studies revealed that multiple derivative metabolites preferentially interacted with viral neuraminidase and the PB2 subunit of RNA polymerase, suggesting potential mechanisms of anti-influenza activity. Molecular dynamics simulations and further *in vitro* assays are needed to support its therapeutic potential (32). Similarly, Melk (2024) (16) reported that hydroethanolic extracts of *Ruellia tuberosa* and *Ruellia patula*, both rich in flavonoids, exhibited antiviral activity against H1N1 by reducing infectious viral particles, likely through molecular interactions between the bioactive compounds quercetin, hesperetin, and rutin with viral neuraminidase (NA), as determined by molecular docking and dynamics simulations. In addition, aqueous extracts of raw *Nepeta cataria* and *Glechoma hederacea* showed strong inhibitory effects on H5N1 virus replication. Specifically, the aerial parts of *N. cataria* were rich in catechin flavonoids, suggesting that this group of phenolic compounds may be responsible for the observed antiviral effects (30).

The butanolic extract of *Davallia mariesii*, a species used in traditional Chinese medicine for treating osteoporosis and inflammatory conditions, impaired the neuraminidase activity of H1N1 (26). Similarly, butanol extracts of *S. glycycarpa* and *S. sarmentosa* inhibited the replication of Influenza H1N1 (42).

A phytochemical investigation revealed that various extracts and fractions of *Tilia platyphyllos*, *Camellia sinensis*, and *Myrtus communis* exhibited *in vitro* hemagglutination inhibition after H1N1 treatment, possibly due to reduced physical interaction between the extracts and fractions and the virus surface hemagglutinin glycoprotein (36). Finally, *Lonicera japonica* has been studied for its antiviral properties against H1N1, using extracts from its dry buds and flowers, which are rich in acidic flavonoids. *In vivo* studies showed that mice treated with 600 mg/kg/day of the acidic extracts for 8 days were protected from influenza-induced death (22).

Isolated natural compounds with anti-Influenza activity

In a bio-guided assay of the ethanolic extract of *Angelica dahurica*, four isolated furanocoumarin compounds, isoimperatorin, oxypeucedanin, oxypeucedanin hydrate, and imperatorin, exhibited activity against both H1N1 and H9N2 viruses by inhibiting infection and replication. Notably, oxypeucedanin strongly inhibited H1N1 neuraminidase activity, suppressed the synthesis of NA and nucleoprotein (NP), and exerted an anti-apoptotic effect on virus-infected cells, suggesting multiple roles in preventing H1N1 infection and replication (63).

From the roots of *Isatis indigotica*, several glucosinolate compounds, epiprogoitrin, progoitrin, epigoitrin, and goitrin,

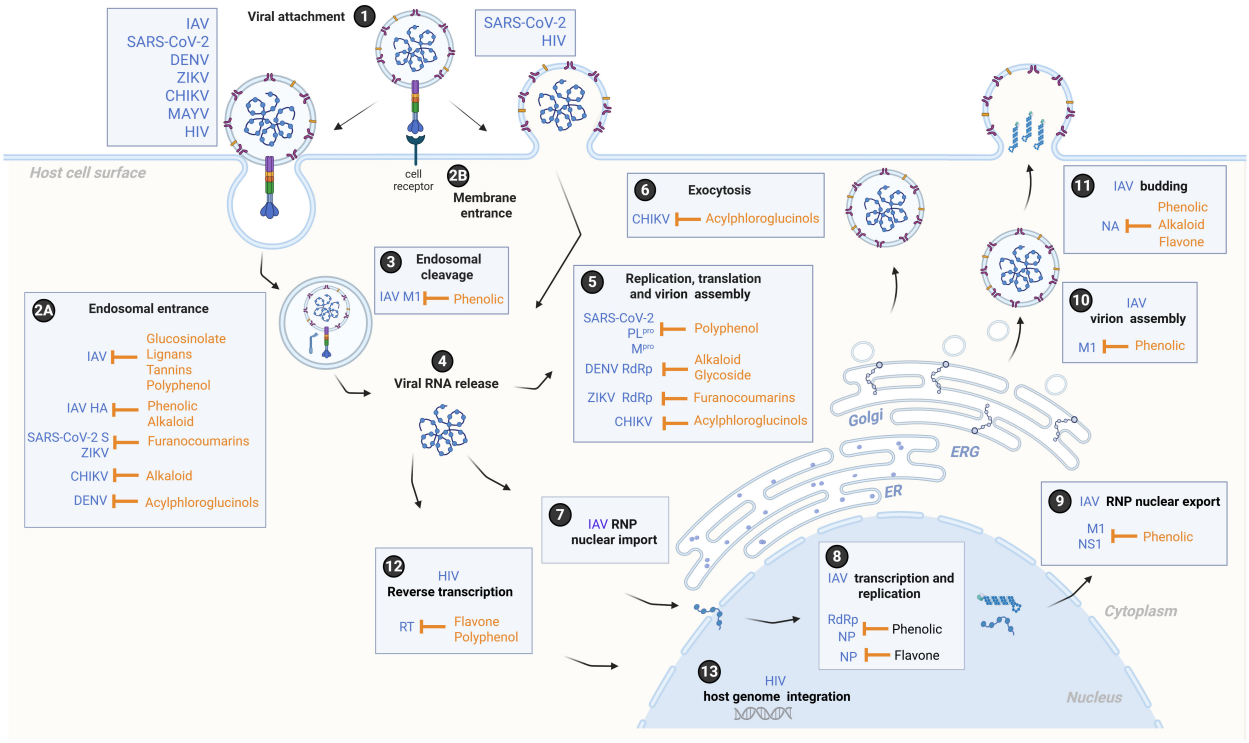

FIGURE 1
A schematic overview of the life cycle of Influenza A virus (IAV), SARS-CoV-2, Dengue virus (DENV), Zika virus (ZIKV), Chikungunya virus (CHIKV), Mayaro virus (MAYV), and the human immunodeficiency virus (HIV), depicting potential mechanisms of action and targets of phytocompounds. Viruses attach to a host cell (1), and entry is mediated by host receptor binding and fusion at the endosomal membrane (2A) or the cellular membrane (2B). The virions within endosomal compartments undergo viral uncoating (3), resulting in the release of the viral RNA genome into the cytoplasm (4). At the endoplasmic reticulum (ER), the viral RNA genomes of SARS-CoV-2, DENV, ZIKV, CHIKV, and MAYV are translated into viral polyproteins, which are subsequently cleaved by host and viral proteases into non-structural proteins forming the viral replication and transcription complex, and structural proteins that transit through the ER-to-Golgi intermediate compartment (ERGIC) for virion maturation (5). Finally, virions are secreted from the host cell by exocytosis (6). For IAV, viral ribonucleoproteins (RNPs) are transported into the nucleus (7), where viral mRNAs are transcribed by RNA-dependent RNA polymerase (RdRp) and replicated by the viral polymerase along with nucleoprotein (NP) (8). The nuclear export of RNPs is facilitated by matrix protein 1 (M1), which provides structural support and regulates the trafficking of viral RNA segments within the cell, and by nonstructural protein 1 (NS1), which modulates the host nuclear export response and viral mRNA processing (9). Subsequently, RNPs are translated at the ER membrane, trafficked to the Golgi for further processing, and virions are assembled in the cytoplasm (10). Lastly, the expression of viral transmembrane glycoproteins, including neuraminidase (NA), induces lipid raft formation at the host plasma membrane, from which progeny virions bud (11). Regarding HIV, the viral RNA genome is reverse transcribed into DNA by viral reverse transcriptase (RT) to form the provirus (12), which transits through the cytoplasm and nucleus to stably integrate into the host cell genome (13). Subsequent steps involve replication and viral gene expression, followed by the assembly and egress of nascent viral particles (not shown). The figure was created with the help of BioRender.com (2025) (License #2364–1,511, Toronto, ON, Canada).

were isolated, showing potent anti-H1N1 activity by interfering with viral adsorption or budding from host cells. However, mechanistic studies indicated that these glucosinolates have limited inhibitory effects on hemagglutinin and neuraminidase (53).

Other studies have shown that berberine, an isoquinoline alkaloid from *Berberis vulgaris*, blocks the host mitogen-activated protein kinase/extracellular signal-related kinase (MAPK/ERK) signaling pathway, which is essential for the transport of viral ribonucleoproteins into the cytoplasm, thereby inhibiting H1N1 replication (52).

From *Elaeocarpus sylvestris* (Lour.), distributed in the subtropical regions of Jeju Island (Korea), Japan, and southern China, two polyphenol compounds, 1,2,3,4,6-penta-O-galloyl-β-D-glucose and geraniin, were isolated from the butanol fraction. These compounds significantly inhibited the production of H1N1 RNAs, non-structural proteins, and infectious viral particles *in vitro*. They also reduced pulmonary viral load and inflammatory cytokines (IFN-γ, TNF-α, and IL-6) *in vivo*, which are associated with disease severity in influenza infection (57).

Additionally, *Camellia sinensis* is a promising medicinal source, as its isolated polyphenolic compounds, theaflavins, inhibited both hemagglutinin and neuraminidase of H1N1, exhibiting a virucidal action and indicating a direct effect on the viral particle (62).

Family Coronaviridae

In this study, we investigated 15 species from 12 plant families, along with 9 extracts (Table 1), exhibiting promising medicinal properties against Coronavirus and SARS-CoV-2.

TABLE 1 Profile of the promising medicinal plant extracts and compounds with antiviral activity.

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Acanthaceae	*Ruellia tuberosa* L.	Tropical and subtropical areas Malaysia, Africa, Pakistan, Brazil, Indonesia	Hydroethanolic extracts of Flowering aerial	H1N1; neuraminidase (NA); viral infection	IC_{50} 13.13 μg/mL	(16)
Acanthaceae	*Ruellia patula L.*	Tropical and subtropical areas Malaysia, Africa, Pakistan, Brazil, Indonesia	Hydroethanolic extracts of Flowering aerial	H1N1; neuraminidase (NA); viral infection	IC_{50} 23.03 μg/mL	(16)
Acanthaceae	*Strobilanthes cusia (Nees) Kuntze*	Northeast India, Bangladesh, southern China, the Himalayan region, Myanmar, and Taiwan	Methanolic of the leaves	Human coronavirus (HCoV)-NL63; viral infection and replication	EC_{50} 0.64 μg/mL	(17)
Anacardiaceae	*Ancitrocladus heyeanu Wall.*	India	Chloroform of the bark	Dengue; viral replication	EC_{50} 1.95 μg/mL	(18)
Anacardiaceae	*Ancitrocladus heyeanu Wall.*	India	Chloroform of the bark	Chikungunya; viral replication	EC_{50} 2.5 μg/mL	(18)
Apocynaceae	*Plumeria alba L.*	India	Chloroform of the bark	Dengue; viral replication	EC_{50} 7.8 μg/mL	(18)
Asteraceae	*Campuloclinium macrocephalum (Less.)*	Argentina	Dichloromethane of the leaves	Dengue; viral replication	EC_{50} 0.11 μg/mL	(19)
Asteraceae	*Campuloclinium macrocephalum (Less.)*	Argentina	Methanolic of the leaves	Dengue; viral replication	EC_{50} 1.8 μg/mL	(19)
Asteraceae	*Helenium radiatum (Less.)*	Argentina	Dichloromethane of leaves	Dengue; viral replication	EC_{50} 0.15 μg/mL	(19)
Asteraceae	*Grindelia pulchella Dunal.*	Argentina	Methanolic of the leaves	Dengue; viral replication	EC_{50} 3.85 μg/mL	(19)
Bignonaceae	*Fridericia formosa (Bureau) LG Lohmann*	South America	Ethanolic of the leaves	Mayaro; viral infection	EC_{50} 36.1 μg/mL	(20)
Bignoniaceae	*Fridericia chica (Bonpl.)*	Latin American countries	Ethanolic of the leaves	Zika; viral infection	EC_{50} 40.9 μg/mL	(21)
Bignoniaceae	*Fridericia chica (Bonpl.)*	Latin American countries	Ethanolic of the leaves	Mayaro; viral infection	EC_{50} 30.1 μg/mL	(21)
Caprifoliaceae	*Lonicera japonica Thumb.*	China	Acid extract of dried bud or flower	H1N1 and H3N2; NA, viral infection and replication	EC_{50} 3.8 μg/mL	(22)
Celastraceae	*Maytenus quadrangulata (Schrad.) Loes*	Brazil	Ethyl acetate of the leaves	Mayaro; adsorption and internalization	EC_{50} 12.0 μg/mL	(23)

(Continued)

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TABLE 1 Continued

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Cistaceae	*Cistus ladanifer L.*	Morocco	Ethyl acetate extract of the leaves	SARS-CoV-2; viral replication and entry	EC_{50} 3.75 μg/mL	(24)
Cistaceae	*Cistus ladanifer L.*	Morocco	Dichloromethane extract of the leaves	SARS-CoV-2; viral replication and viral entry	EC_{50} 1.8 μg/mL	(24)
Compositae	*Gynura bicolor (Roxb. exWilld.)DC.*	Peninsular Malaysia (Perak, Kelantan, Pahang, Selangor, and Johor)	Ethyl acetate of the leaves	Chikungunya; viral replication	EC_{50} 1.91 μg/mL	(25)
Cucurbitaceae	*Sechium edule (Jacq.) Sw.*	Peninsular Malaysia (Perak, Kelantan, Pahang, Selangor, and Johor)	Ethyl acetate of the leaves	Chikungunya; viral replication	EC_{50} 2.71 μg/mL	(25)
Davalliaceae	*Davallia mariesii H.J.Veitch*	China	Butanolic extract of the whole plant	H1N1; NA, viral adsorption, infection, replication,	EC_{50} 24.32 μg/mL	(26)
Euphorbiaceae	*Croton dichogamus Pax*	Africa	Methanol of the branches	HIV; viral infection	IC_{50} 0.06 μg/mL	(27)
Euphorbiaceae	*Macaranga hurifolia Beille*	Cameroon	Hydroethanolic extract of Leaves	Chikungunya;viral infection and replication	EC_{50} 26.89 μg/mL	(28)
Lamiaceae	*Melissa officinalis L*	Mediterranean and Western Asia	Methanolic extract of the whole herb	SARS-CoV-2; spike, viral infection	IC_{50} 10.83 μg/mL	(29)
Lamiaceae	*Nepeta cataria L.*	Russia	Aqueous extract of the leaves	H5N1; viral replication	EC_{50} 3.75 μg/mL	(30)
Lamiaceae	*Glechoma hederacea L.*	Russia	Aqueous extract of the leaves	H5N1; viral replication	EC_{50} 3.75 μg/mL	(30)
Lamiaceae	*Ocimum sanctum (L.)*	India	Aqueous of the leaves	Dengue; Dengue; non-structural dengue proteins NS1 and NS5, viral replication	EC_{50} 31.25 μg/mL	(31)
Lamiaceae	*Ocimum americanum L.*	Peninsular Malaysia (Perak, Kelantan, Pahang, Selangor, and Johor)	Ethanol of the leaves	Chikungunya; viral infection and replication	EC_{50} 1.33 μg/mL	(25)
Leguminosae	*Caesalpinia mimosoides Lamk*	Khon Kaen province, Thailand	Aqueous-ethanolic extract	H1N1; NA, PB2 subunit of RNA polymerase, viral infection	IC_{50} 2.33 μg/mL	(32)
Leguminosae	*Glycyrrhiza glabra L.*	Western Asia	Aqueous of the roots	Dengue; viral adsorption	EC_{50} 10 μg/mL	(33)
Loganiaceae	*Strychnos mattogrossensis S. Moore*	Africa	Methanolic of the leaves	SARS-CoV-2; viral infection	EC_{50} 2.05 μg/mL	(34)
Malpighiaceae	*Byrsonima coccolobifolia Kunth*	North and Northeast of Brazil	Methanolic of the leaves	SARS-CoV-2; viral infection	EC_{50} 7 μg/mL	(35)

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TABLE 1 Continued

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Malvaceae	*Tilia platyphyllos Scop.*	Iran	Ethanolic of the flower	H1N1; HA, viral infection	EC_{50} 9.56 μg/mL	(36)
Meliaceae	*Azadirachta indica L.*	India	Methanolic of the leaves	SARS-CoV-2; viral infection	IC_{50} 8.45 μg/mL	(37)
Meliaceae	*Melia azedarach L.*	India	Methanolic of the leaves	SARS-CoV-2; viral infection	IC_{50} 6.92 μg/mL	(37)
Meliaceae	*Khaya grandifoliola C.DC Sapindales*	Cameroon	Hydroethanolic extract of Stem bark	Chikungunya;viral infection and replication	EC_{50} 12.81μg/mL	(28)
Meliaceae	*Entandrophragma cylindricum Sprague*	Cameroon	Hydroethanolic extract of Stem bark	Chikungunya;viral infection and replication	EC_{50} 8.14 μg/mL	(28)
Mimosaceae	*Entada africana Guill & Pers*	Cameroon	Hydroethanolic extract of Stem bark	Chikungunya;viral infection and replication	EC_{50} 8.29 μg/mL	(28)
Moraceae	*Ficus rubiginosa Desf. ex Vent.*	Madagascar, Africa, Asia, and South America	Methanolic of the leaves	Human coronavirus (HCoV)-229E; viral infection,	EC_{50} 1.25 μg/mL	(38)
Moringaceae	*Moringa oleifera Lam. LC*	India anda Africa	Ethanolic of the leaves	(HCoV)-229E, viral infection	EC_{50} 21 μg/mL	(39)
Myrtaceae	*Myrtus communis L.*	Iran	Chloroform of the leaves	H1N1; HA, viral infection	EC_{50} 0.65 μg/mL	(36)
Phyllanthaceae	*Phyllanthus brasiliensis (Aubl.) Poir*	Brazilian Amazon	Methanolic of the leaves	Zika; viral infection	EC_{50} 0.84 μg/mL	(40)
Phyllanthaceae	*Phyllanthus brasiliensis (Aubl.) Poir*	Brazilian Amazon	Hydroalcoholic of the leaves	Zika; viral infection	EC_{50} 1.36 μg/mL	(40)
Phyllanthaceae	*Phyllanthus brasiliensis (Aubl.) Poir*	Brazilian Amazon	Methanolic of the bark	Zika; viral infection	EC_{50} 0.80 μg/mL	(40)
Plantaginaceae	*Bacopa monnieri L.*	India	Hydroalcoholic of the whole herb	Dengue; viral infection	EC_{50} 15.62 μg/mL	(18)
Rosaceae	*Spiraea media Schmidt*	Europe, Asia and North America	Ethanol 70% of the aerial parts	H1N1; viral infection and replication	IC_{50} 5.8 μg/mL	(41)
Rosaceae	*Spiraea salicifolia L.*	Europe, Asia and North America	Ethanol 70% of the aerial parts	H1N1; viral infection and replication	IC_{50} 3.7 μg/mL	(41)
Siparunaceae	*Siparuna glycycarpa (Ducke)*	Brazil	Butanolic of the leaves	H1N1; viral infection and replication	EC_{50} 25 μM	(42)

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TABLE 1 Continued

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Siparunaceae	*Siparuna sarmentosa Perkins*	Brazil	Butanolic of the leaves	H1N1; viral infection and replication	EC_{50} 37 μM	(42)
Solanacea	*Withania somnifera L*	India	Hydroalcoholic of the roots	HIV; reverse transcriptase (RT), protease, p24 protein, viral replication	EC_{50} 17 μg/mL	(12)
Solanacea	*Withania somnifera L*	India	Aqueous of the roots	HIV; RT, protease, p24 protein, viral replication	EC50 59 μg/mL	(12)
Theaceae	*Camélia sinensis L. Kuntze*	Iran	Chloroform of the leaves	H1N1; HA, viral infection	EC50 1.62 μg/mL	(36)
Verbenaceae	*Vitex negundo L.*	India	Chloroform extract of leaves	Dengue; viral infection and replication	EC_{50} 7.8 μg/mL	(18)
Verbenaceae	*Lantana camara L.*	Brazil, India, Kenya, Thailand, Mexico, Nigeria, Australia and Southeast Asia	Ethanolic of the leaves	SARS-CoV-2; RNA-dependent RNA polymerase (RdRp), envelope (E) protein	IC_{50} 3.18 μg/mL	(43)
Verbenaceae	*Lantana camara L.*	Brazil, India, Kenya, Thailand, Mexico, Nigeria, Australia and Southeast Asia	Ethanol of the flowers	SARS-CoV-2; RdRp, E protein, viral replication and assembly	IC_{50} 3.67 μg/mL	(43)
Vitaceae	*Vitis vinifera L.*	Naples, Italy	Methanolic of the leaves	SARS-CoV-2; S protein, viral infection and replication	EC_{50} 10 μg/mL	(44)
Zingiberaceae	*Kaempferia parviflora L.*	Thailand	Hexane extract of the rhizomes	SARS-CoV-2; protease $3CL^{pro}$, viral replication	EC_{50} 39.28 μg/mL	(45)
Acanthaceae	*Justicia adhatoda L.*	India	Alkaloid, anisotine	SARS CoV-2; main protease (M^{pro})	ND	(46)
Amaryllidaceae	*Crinum jagus (J.Thomps.)*	China and Africa	Alkaloid, cherylline	Dengue; viral replication	EC_{50} 8.8 μM	(47)
Amaryllidaceae	*Crinum jagus (J.Thomps.)*	China and Africa	Alkaloid, cherylline, lycorine	Zika; RdRp, viral replication	EC_{50} 20.3 μM	(47, 48)
Apocynaceae	*Nerium oleander L.*	ND	Glycoside, oleandrin	SARS-CoV-2; viral infection	EC_{50} 0.05 μg/mL	(49)
Asteraceae	*Urolepis hecatantha* (DC) R.	Argentina	Phenolic, euparin	Dengue; viral infection	EC_{50} 6.8 μM	(19)
Asteraceae	*Stevia alpina* Griseb	Argentina	Phenolic, 2-oxo-8-deoxyligustrin	Dengue; viral infection	$EC5_{50}$3.7 μM	(19)
Asteraceae	*Stevia satureiifolia* (Lam.)	Argentina	Phenolic, santhemoidine	Dengue; viral infection	$EC5_{50}$3.1 μM	(19)
Asteraceae	*Carpesium abrotanoides L.*	China, Korea, Japan, and other Southeast Asian countries	Flavone, 1β-hydroxy-8-epi-inuviscolide	SARS-CoV-2; M^{pro}	IC_{50} 16.58 μM	(50)
Asteraceae	*Tagetes patula L.*	Karachi, Pakistan	Polyphenol, 4-hydroxybenzaldehyde	SARS-CoV-2; papain-like protease (PL^{pro})	IC_{50} 3.99 μM	(51)

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TABLE 1 Continued

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Berberidaceae	*Berberis vulgaris L*	ND*	Alkaloid, berberine	H1N1; mitogen-activated protein kinase (MAPK), extracellular signal-regulated kinase (ERK)	IC_{50} 4 μM to 16 μM	(52)
Brassicaceae	*Isatis indigotica Fortune ex Lindl.*	China	Glucosinolate, epiprogoitrin	H1N1; exert low inhibition rates on HA and NA	IC_{50} 0.44 μM	(53)
Brassicaceae	*Isatis indigotica Fortune ex Lindl.*	China	Glucosinolate, progoitrin	H1N1; exert low inhibition rates on HA and NA	IC_{50} 0.19 μM	(53)
Brassicaceae	*Isatis indigotica Fortune ex Lindl.*	China	Glucosinolate, epigoitrin	H1N1; exert low inhibition rates on HA and NA	IC_{50} 0.36 μM	(53)
Brassicaceae	*Isatis indigotica Fortune ex Lindl.*	China	Glucosinolate, goitrin	H1N1; exert low inhibition rates on HA and NA	IC_{50} 0.19 μM	(53)
Cannabaceae	*Humulus lupulus*	China, India, Europe, South, North America	Acylphloroglucinols, β-acids	Chikungunya; viral entry, infection and replication, virion assembly and release	EC_{50} 15.21 μg/mL	(54)
Combretaceae	*Anogeissus acuminate (Roxb.ExDC.) Wall.*	Asia and Bangladesh	Lignans, anolignan A	HIV; HIV-1 reverse transcriptase (HIV-1 RT)	ND	(55)
Combretaceae	*Anogeissus acuminate (Roxb.ExDC.) Wall.*	Asia and Bangladesh	Lignans, anolignan B	HIV; HIV-1 RT	ND	(55)
Elaeagnaceae	*Shepherdia argentea (Pursh) Nutt.*	Central and Western North America	Tannins, shephagenin A	HIV; HIV-1 RT	ND	(56)
Elaeagnaceae	*Shepherdia argentea (Pursh) Nutt.*	Central and Western North America	Tannins, shephagenin B	HIV; HIV-1 RT	ND	(56)
Elaeocarpaceae	*Elaeocarpus sylvestris (Lour.)*	Subtropical zones, Jeju Island in Korea, Japan, and southern China	Polyphenol, 1,2,3,4,6-penta-O-galloyl-β-d-glucose	H1N1; matrix protein 1 (M1), nucleoprotein (NP), non-structural proteins 1 (NS1), HA, NA, RdRp	EC_{50} 5.51 μg/mL	(57)
Elaeocarpaceae	*Elaeocarpus sylvestris (Lour.)*	Subtropical zones, Jeju Island in Korea, Japan, and southern China	Polyphenol, geraniin	H1N1; M1, NP, NS1, HA, NA, RdRp	EC_{50} 5,30 μg/mL	(57)
Euphorbiaceae	*Acalypha torta hort. ex Pax & K.Hoffm.*	Karachi, Pakistan	Polyphenol, 3, 4-dihydroxybenzoate	SARS-CoV-2; papain-like protease (PL^{pro})	IC_{50} 3.76 μM	(51)
Lythraceae	*Lawsonia alba L.*	Karachi, Pakistan	Polyphenol, 4-(2-hydroxyethyl)phenol	SARS-CoV-2; papain-like protease (PL^{pro})	IC_{50} 6.68 μM	(51)

(Continued)

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TABLE 1 Continued

Plant family	Plant species[1]	Country or continent where the plant species are traditionally found and medicinally used	[2]Extract solvent/plant part or [3]compound/ metabolite class	Virus, potential inhibition mechanism and molecular target	[4]IC_{50} or [5]EC_{50} concentration (μg/mL or μM)	Reference
Moraceae	*Morus alba L*	China, Japan and Korea	Flavone, kuwanon C	SARS-CoV-2; Spike protein (S)	0.019 μg/mL	(58)
Nelumbonaceae	*Nelumbo nucifera L.*	China	Alkaloid, neferine salt	SARS-CoV-2; viral infection	EC_{50} 4.78 μM	(45)
Phyllanthaceae	*Phyllanthus phillyreifolius Poir.*	Reunion Island	Polyphenol, geraniin	Zika; viral infection and entry	EC_{50} 22 μg/mL	(59)
Sapindaceae	*Aesculus hippocastanum L. (AH)*	ND	Saponin, β-escin	SARS-CoV-2; viral infection	EC_{50} 1.3 μg/mL	(60)
Simaroubaceae	*Brucea javanica L. Merr.*	Malaysia	Alkaloid, 1-hydroxy-11-methoxycanthin-6-one	Dengue; RdRp, NS5 protease	EC_{50} 1.8 μM	(61)
Theaceae	*Camellia sinensis (L.) Kuntze*	China and Southeast Asia	Polyphenol, theaflavins	H1N1; NA, HA	EC_{50} 1.33 μg/mL	(62)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, isoimperatorin	H1N1; viral infection	EC_{50} 7.67 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, isoimperatorin	H9N2; viral infection	EC_{50} 6.72 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, oxypeucedanin	H1N1; NA, nucleoprotein (NP)	EC_{50} 5.98 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, oxypeucedanin	H9N2; viral infection	EC_{50} 4.52 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, oxypeucedanin hydrate	H1N1; viral infection	EC_{50} 10.50 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, oxypeucedanin hydrate	H9N2; viral infection	EC_{50} 10.50 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, imperatorin	H1N1; viral infection	EC_{50} 11.31 μM	(63)
Umbelliferae	*Angelica dahurica (Hoffm.)*	Northern and eastern Asia	Furanocoumarins, imperatorin	H9N2; viral infection	EC_{50} 8.10 μM	(63)

[1]Extracted from https://www.worldfloraonline.org/taxon/; [2] Blue color is designed for plant extracts. Only extracts from plants of traditional use and that presented inhibitory effect are listed; [3]Gray color is designed for isolated compounds. Only compounds isolated from plants of traditional use and that presented well validated inhibitory effect are listed. [4]IC_{50}, 50% inhibitory concentration; [5]EC_{50}, 50% effective concentration; *ND, not determined.

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Extracts from medicinal plants with anti-Coronavirus and anti-SARS-CoV-2 activity

Using UPLC-MS/MS coupled with *in vitro* studies and chemometric analysis, Darwish (2022) (43) demonstrated that ethanol extracts from the flowers and leaves of *Lantana camara*, native to the tropical regions of the Americas (cultivar Chelsea Gem), and flower extracts from the cultivars Spreading Sunset and Drap d'Or, exhibited robust selectivity indices by inhibiting the expression levels of the viral RNA-dependent RNA polymerase (RdRp) gene. These findings indicate high safety, efficacy, and promising anti-COVID-19 properties. Additionally, *in vitro* tests were conducted to assess the crude methanolic leaf extract of *Byrsonima coccolobifolia* against SARS-CoV-2. The extract demonstrated excellent *in vitro* activity with no cytotoxicity under the tested conditions, confirming its efficacy and safety against SARS-CoV-2 (35).

In a study by Giugliano (2024) (39), ethanolic extracts of *Moringa oleifera* leaves obtained via microwave-assisted extraction showed significant inhibition of coronavirus HCoV-229E infection, without cytotoxic effects in either of the two cell models used.

Likewise, the methanolic extract of *Strobilanthes cusia* leaves, traditionally used in Chinese medicine for respiratory viral infections, potently inhibited the cytopathic effect (CPE) and viral RNA yield of human coronavirus NL63 (HCoV-NL63), indicating potential to block viral infection and replication (17). Similarly, antiviral activity was observed with the methanolic extract of *Ficus rubiginosa* leaves against coronavirus HCoV-229E by impairing viral replication (38).

Azadirachta indica and *Melia azedarach*, both long used in traditional Indian folk medicine, had total methanolic extracts enriched with phenolic and flavonoid compounds evaluated against SARS-CoV-2. These showed strong antiviral activity and robust safety indices by restraining infectious viral particles (37). Likewise, the methanolic extract of *Strychnos mattogrossensis* was reported for the first time to have biological activity against SARS-CoV-2, protecting cells from the virus's cytopathic effects (34). Additionally, methanolic leaf extracts of *Vitis vinifera* significantly reduced SARS-CoV-2 replication at early stages of infection by directly blocking expression of the spike protein, as confirmed by Real-Time PCR (44). Similarly, *Cistus ladanifer*, a traditional Moroccan medicinal plant, was shown by Bouothmany (2025) (24) to interfere with both replication and viral entry into SARS-CoV-2-infected host cells. Ethyl acetate and dichloromethane extracts of its leaves were particularly effective against the Omicron variant.

Melissa officinalis, with a long history of use in Mediterranean and Western Asia, showed strong virucidal and antiviral activity in its methanolic extract by inhibiting SARS-CoV-2 infection, with a robust safety profile (selectivity index of 230). The inhibition mechanisms of five key compounds from *M. officinalis* were investigated via molecular docking, revealing strong binding affinities with the spike receptor-binding domain (RBD) of SARS-CoV-2, indicating promising anti-infective action (29).

Isolated natural compounds with anti-SARS-CoV-2 activity

Numerous studies have evaluated the ability of isolated natural compounds to inhibit viral replication by targeting M^{pro} and PL^{pro} of SARS-CoV-2. For example, the alkaloids vasicoline, vasicolinone, vasicinone, vasicine, adhatodine, and anisotine, particularly enriched in the leaves of *Justicia adhatoda*, were examined using molecular docking, dynamics simulations, and molecular mechanics with Generalized Born surface area (MMGBSA) calculations. Notably, anisotine was more effective at inhibiting M^{pro} than the approved antiviral drugs darunavir and lopinavir, suggesting its potential to block SARS-CoV-2 replication by inhibiting M^{pro} enzymatic activity (46). Sesquiterpene metabolites claroguaiane A, claroguaianes B and C, and claroeudesmane A, derived from *Carpesium abrotanoides* (native to Europe, Japan, and the Himalayas), were tested via bio-guided inhibitory activity assay against SARS-CoV-2 M^{pro}. Claroeudesmane A showed moderate activity, while 1β-hydroxy-8-epi-inuviscolide demonstrated stronger activity. Other compounds showed no noticeable effect (50). Srinivasan (2022) (51) evaluated phenolic compounds for PL^{pro} inhibition. *In vitro* and structural assays showed that 4-hydroxybenzaldehyde (from *Tagetes patula*), 3,4-dihydroxybenzoate (from *Acalypha torta*), and 4-(2-hydroxyethyl)phenol (from *Lawsonia alba*) effectively inhibited PL^{pro} under non-cytotoxic conditions.

Natural compounds may also prevent SARS-CoV-2 infection. Kuwanon C, a flavone from *Morus alba*, was shown by Kim et al. (2022) (58) to suppress SARS-CoV-2 cell entry. ELISA and *in vitro* kinetic binding analysis confirmed that kuwanon C effectively blocked spike S1 RBD-ACE2 interaction. *In silico* docking simulations supported this, making kuwanon C a promising lead compound. Yang (2025) (45) reported that crude extracts from seed embryos of *Nelumbo nucifera*, as well as the isolated alkaloid neferine, significantly reduced SARS-CoV-2 infectious particles and showed improved virucidal activity and safety when combined with organic salts. The virucidal effect of β-escin, a bioactive constituent in *Aesculus hippocastanum* seed extract, was also tested. β-escin limited virus infection *in vitro* and reduced SARS-CoV-2 spike protein expression as seen via immunofluorescence microscopy (60).

Finally, oleandrin, a cardiac glycoside from *Nerium oleander*, was tested *in vitro* against SARS-CoV-2, significantly reducing viral replication, likely by blocking ATP binding sites on Na/K-ATPase. *In vivo* tests on golden Syrian hamsters treated with up to 130 μg/mL oleandrin for 7 days provided preliminary evidence of efficacy (49).

Family Flaviviridae

The potential therapeutic properties of plant extracts from 22 species across 17 families are explored in this section, as outlined in Table 1.

Extracts of medicinal plants with anti-Dengue, anti-Zika, anti-Chikungunya, and anti-Mayaro activity

Alagarasu (2022) (18) reported *in vitro* anti-Dengue and anti-Chikungunya activities of extracts from several plant species, including *Plumeria alba*, *Ancistrocladus heyneanus*, *Bacopa monnieri*, and *Vitex negundo*, commonly used in traditional medicine in Belagavi, India. Specifically, chloroform extracts of the bark of *P. alba* and *A. heyneanus*, and the hydroalcoholic extract of the whole *B. monnieri* plant, reduced replication or infection of Dengue and Chikungunya viruses, while the chloroform extract of *V. negundo* leaves showed activity only against Dengue. In addition, *Ocimum sanctum*, a traditional Ayurvedic herb known as Vishnu-Priya or Tulsi, containing the isolated compound eugenol (1-hydroxy-2-methoxy-4-allylbenzene), exhibited potent inhibition of Dengue-2 replication, achieving complete inhibition in *in vitro* assays. Docking analysis showed that eugenol interacts with Dengue non-structural proteins NS1 and NS5 with binding energies of 5.33 and 5.75 kcal/mol, respectively, suggesting potential pharmacological use in Dengue treatment (31). Jayasekara (2024) (33) investigated the antiviral potential of aqueous extracts from the roots of *Glycyrrhiza glabra* (Leguminosae) against Dengue and found that subfractions of the extract significantly suppressed viral adsorption to cells.

Carvalho (2023) (40) reported that methanolic and hydroalcoholic leaf extracts, as well as a methanolic bark extract from *Phyllanthus brasiliensis*, showed potent *in vitro* activity against Zika virus infection. Similarly, Chan (2021) (25) reported *in vitro* activity of ethyl acetate extracts of *Gynura bicolor* and *Sechium edule* against Chikungunya virus replication, and the activity of *Ocimum americanum* against both infection and replication of this virus.

The ethanolic leaf extract of *Fridericia formosa*, a Bignoniaceae species rich in xanthones and found in the Brazilian Cerrado biome, exhibited effective activity against Mayaro virus infection (20). In turn, *Fridericia chica*, rich in flavonoids and traditionally used in Latin American countries to treat infections, showed activity against Dengue-2, Zika, and Mayaro viruses in *in vitro* assays (21). Lastly (23), reported that ethyl acetate extracts of *Maytenus quadrangulata* leaves had a virucidal effect against Mayaro virus by acting on viral adsorption and internalization.

Isolated natural compounds with anti-Dengue, anti-Zika, and anti-Chikungunya activity

In this respect, pure phenolic compounds, euparin, 2-oxo-8-deoxyligustrin, and santhemoidine, isolated from *Urolepis hecatantha*, *Stevia alpina*, and *Stevia satureiifolia*, respectively, were able to inhibit Dengue virus infections (19). Furthermore, two major alkaloid compounds, canthin-6-one and 1-hydroxy-11-methoxycanthin-6-one, abundant in the roots of *Brucea javanica*, a traditional medicinal plant used in Malaysia for treating fever, showed potential binding interactions with the active sites of the NS5 protease and RNA-dependent RNA polymerase (RdRp) by molecular docking analysis using DENV-2. Notably, 1-hydroxy-11-methoxycanthin-6-one reduced viral RNA load in *in vitro* assays (61).

Phytochemical investigations of *Crinum jagus* revealed the presence of lycorine and several alkaloids from the cherylline, crinine, and galanthamine groups, which efficiently inhibited both Dengue and Zika viruses. Specifically, cherylline effectively hindered RNA synthesis in both viruses, indicating RNA replication as its main target (47). In turn, lycorine inhibited Zika RNA synthesis by binding to RdRp *in vitro* and protected against Zika-induced lethality by reducing viral load *in vivo* (48). Additionally, *Phyllanthus phillyreifolius*, endemic to Réunion Island and traditionally used to treat fever, venereal diseases, and kidney stones, contains the polyphenol-rich compound geraniin, which prevented RNA production in Zika-infected human cell assays (59). For Chikungunya, fractions of *Humulus lupulus* containing α-acids, β-acids, cohumulon, canthohumol, and flavonoids were found to affect the entire viral cycle, from entry to the egress of newly formed viral particles, without cytotoxic effects. Notably, the acylphloroglucinol β-acid fraction exhibited the strongest virucidal effect *in vitro* and caused a significant reduction in viral replication in drug-addition cell experiments (54).

Family Retroviridae

Two species of medicinal plants and four promising isolated compounds (Table 1) with anti-HIV activity are discussed in this section.

Active plant extracts with anti-HIV activity

The hydroalcoholic and aqueous extracts from the roots of *Withania somnifera*, commonly used in traditional Indian medicine, were investigated for their bioactive potential against HIV-1 replication. *In vitro* enzymatic analysis revealed that the hydroalcoholic extract inhibited HIV-1 integrase activity by 86.18%, while the aqueous extract achieved 93.98% inhibition. For HIV-1 protease activity, the hydroalcoholic and aqueous extracts showed inhibition rates of 91.77% and 84.84%, respectively. Regarding HIV-1 reverse transcriptase (RT) activity, the hydroalcoholic extract exhibited 76.82% inhibition, whereas the aqueous extract demonstrated a lower inhibition rate of 58.53%. All results were obtained within the sub-cytotoxic concentration range.

Confirmatory cell-based assays showed that both hydroalcoholic and aqueous extracts effectively inhibited infectious virus release, as indicated by HIV-1 p24 detection, even at lower dosages, with EC_{50} values of 17 μg/mL and 59 μg/mL, respectively. Additionally, *in silico* molecular docking studies revealed the highest binding affinity against HIV-1 integrase by the compounds 12-deoxywithastramonolide and 27-hydroxywithanone; against HIV-1 protease by ashwagandhanolide

and withacoagin; and against HIV-1 reverse transcriptase by ashwagandhanolide and withanolide B. These findings suggest potential mechanisms for the inhibition of HIV-1 replication (12). Another species, *Croton dichogamus*, traditionally used in African medicine, exhibited significant anti-HIV activity in its methanolic extract. This extract inhibited more than 90% of infectious viral particles in cell lines (IC_{50} value of 0.06 μg/mL) and demonstrated a high safety profile, with a selectivity index (SI) of 318.5 (27).

Isolated natural compounds with anti-HIV activity

Anogeissus acuminata, an Asian species found in the Bandarban, Chattogram, Cox's Bazar, Khagrachari, and Rangamati regions of Bangladesh, produces two dibenzylbutadiene lignans: anolignan A and anolignan B. Both compounds showed significant inhibitory activity against the HIV-1-RT. Furthermore, the two phytocompounds exhibited a synergistic effect against this enzyme (55). Similarly, from the leaf extract of *Shepherdia argentea*, the tannins shephagenin A and B were isolated and also demonstrated inhibitory activity against the HIV-1-RT, highlighting the importance of these compounds as potential HIV-1 reverse transcription inhibitors (56).

Future perspectives

The ongoing discovery of bioactive compounds in plants represents a valuable source for identifying new, potent antiviral agents and selective compounds. These compounds not only offer potential as standalone treatments but can also complement or enhance existing therapies, especially when they exhibit synergistic interactions with other drugs. This can increase the overall effectiveness and potentially reduce adverse side effects. However, the connection between traditional knowledge and future research on plant-derived products with potential pharmacological properties should be further strengthened.

This mini-review provides an overview of recent literature (from the last five years) on medicinal plant extracts and isolated natural compounds with potential antiviral effects. A major limitation in exploring the bioactivity of plant-derived products lies in the absence of standardized methodologies for extraction, fractionation, and characterization. This is due to the immense diversity of extracts and phytochemicals found in nature, which ultimately affects the development of new antiviral agents (64). For instance, isolating alkaloid phytocompounds presents several challenges, such as solvent use, low extraction efficiency, and variations in plant genotype, all of which complicate the process of obtaining consistent yields. Moreover, the current understanding of the antiviral activity of plant-derived extracts and compounds is mainly based on *in vitro* studies, limiting their clinical applicability.

In this context, emerging technologies such as artificial intelligence (AI) have proven effective in predicting and optimizing the chemical, physical, and biological properties of phytocompounds. AI contributes to accelerating the identification of bioactive molecules that can target viral pathogens. Similarly, CRISPR-Cas technologies are increasingly being employed in plants to speed up the screening of phytocompounds and their targets through functional characterization. Additionally, these strategies enhance and optimize the biosynthesis of compounds in plants, offering a scalable production (65).

By applying these advanced techniques, well-characterized plant-derived compounds can be incorporated into modern medicinal chemistry. This approach could potentially alter their activity and selectivity, enabling them to target both emerging and established viral threats.

Author contributions

GR: Writing – review & editing, Writing – original draft, Investigation, Visualization, Validation. EES: Conceptualization, Writing – original draft, Validation, Writing – review & editing. GP: Validation, Supervision, Writing – review & editing. ED: Writing – review & editing, Conceptualization. EL: Writing – review & editing, Writing – original draft. CW: Supervision, Writing – review & editing, Conceptualization, Writing – original draft, Funding acquisition, Resources.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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