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Antiviral Activity and Therapeutic Potential of Medicinal Plants and their Bioactive Constituents: A Review of Experimental Evidence, Mechanistic Insights, and Molecular Docking Studies

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Abstract

This review estimated the antiviral potential of plant-derived natural products, focusing on phenolic compounds (flavonoids, phenolic acids), alkaloids, essential oils and terpenoids, based on a comprehensive literature analysis including molecular docking, molecular dynamics, and pharmacokinetic studies including absorption, distribution, metabolism, excretion, and toxicity studies. Our theoretical results show that plants synthesize and accumulate a wide range of secondary metabolites that interact with key viral targets such as the main protease, papain-like protease, RNA-dependent RNA polymerase, spike glycoprotein and host ACE2 receptor. Phenolic acids (caffeic acid, gallic acid, ellagic acid), flavonoids (quercetin, kaempferol, naringenin, epigallocatechin gallate), alkaloids (emetine, lycorine, michellamine B) and essential oil constituents (eucalyptol, thymol, carvacrol) all showed strong binding affinities and stable interactions with conserved viral proteins, preventing viral entry, replication, and assembly while regulating inflammatory reactions. The majority of natural antivirals have pharmacokinetic constraints, such as low oral bioavailability, rapid phase II metabolism and high polarity, despite their positive drug-likeness. These drawbacks may be addressed by sophisticated formulation techniques. In summary, this work demonstrates that aromatic and medicinal plants are abundant sources of broad-spectrum antiviral secondary metabolites and offers a theoretical foundation for their logical selection and development as reasonably priced antiviral treatments.

Keywords

natural antivirals, secondary metabolites, molecular docking, pharmacokinetics, drug-likeness, viral infections

1 Introduction

Viruses were ascertained at the end of the 19th century as filterable agents triggering infectious diseases of humans, plants and animals [1]. Consequently, their pathogenicity and capacity to undergo swift evolutionary modification [2] has sparked huge scientific works related to the so-called "microevolution" of relatively closely related viruses [3]. Actual frequent worldwide, viral infections and pandemic ailments have menaced humanity historically and inflict a great economic burden. Viruses are known to cause grave infectious diseases such as human immunodeficiency virus (HIV), hepatitis B and C (HBV and HCV), coronaviruses comprising Middle Eastern respiratory syndrome (MERS) and extreme acute respiratory syndrome (SARS), influenza, Ebola, and chikungunya virus [4, 5]. The propagation of novel and dangerous viruses mainly HIV, Ebola, and coronaviruses and the possible risk of their utilization as an arsenal for bioterrorism has improved our urgency to discover new and powerful antivirals rapidly. Among the different types of viruses, respiratory infections (RI) provoke the most frequent illnesses [6], conducting to morbidity and death in humans worldwide, trigging a crucial problem in public health, particularly for infants, mature and immune-arranged individuals [7]. Viruses epitomize the prevailing pathogens existing in the respiratory tract.

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In fact, it is assessed that about 200 various viruses such as influenza viruses, coronaviruses, rhinoviruses, metapneumoviruses, adenoviruses, as well as orthopneumoviruses, can contaminate the human airway. Aging people and children characterize more sensitive populations, in which viruses provoke 40 and 95% of all respiratory illnesses, respectively [8, 9]. Among the innumerable respiratory viruses (RV), some are obstinately circulating every year in human population worldwide, where they cause a plethora of symptoms, from popular colds to more dangerous difficulties compiling hospitalization [10]. Additionally, to the countless permanent viruses that circulate and contaminate lots of persons each year, new RV agents materialize sometimes, provoking viral epidemics or pandemics related to very grave symptoms [11], like neurologic troubles. These atypical events frequently take place when RNA viruses such as influenza A, human coronaviruses, like MERS-CoV and SARS-CoV, or henipaviruses, attending in an animal reservoir, traverse the species barrier as an expedient strategy to adapt to novel environments and hosts. These zoonoses may have dreadful impacts in humans [12, 13], and the burden is even higher if they have neurological consequences. Therefore, currently available treatment based on synthetic drugs such as neuraminidase inhibitors, channel blockers, viral polymerase inhibitors (VPI), ribavirin, lopinavir-ritonavir, interferon, corticosteroids have been approved for treating viral diseases [14]. Their low efficiency and the progress of viral resistance led to the escalating interest of natural products as a potential source of antiviral and inhibitory activities. To combat many human viruses, diverse strategies have been developed to research on phytochemicals, which can be used as therapeutic agents with great potential as complementary with several anti-viral therapies. Natural bioactive compounds are in huge utilization randomly as anti-viral drugs and immune promoters [15], which could complement our quotidian nutrition, with positive impacts on prevention and diminution of the harshness of COVID-19 signs. Nature still provides the majority of natural products with biological and chemical diversity [15]. Some medicinal plants offer a solution as a source of natural antiviral compounds by the accumulation of secondary metabolites able to alleviate antiviral symptoms, decreasing the inflammatory response and by acting as a platform to express viral immunogenic proteins. The demand of treatment against antiviral infections is increasing, indeed, vaccine progress *versus* several viruses, is an uncontrollable approach, and there is no definitive vaccine *versus* a number of prevalent viral contagions including most respiratory area viruses. Several natural molecules extracted from different parts of plants (root, bark, flowers, or essential oils) are considered an effective alternative *versus* numerous illnesses.

Suggestion of innovative drugs and approaches for efficacy treatment of the new coronavirus is an inevitability after the rapid propagation of the illness. Among these compounds, sulfated polysaccharides are considered as a potential source of pharmacological capacities for medication development [16, 17]. These molecules exhibited a variety of biological properties such as antioxidant, antitumor, antiviral, antimicrobial, anticoagulant, and immune inflammatory actions [18, 19]. Countless screening research have been carried out in recent years to reveal the antiviral potentiality of herbal medicinal products using *in vitro* and *in vivo* tests. Indeed, selecting of Colombian herbal medicines proved antiviral activity against respiratory syncytial virus (RSV), coronavirus, influenza virus, and herpes simplex virus (HSV) that spirulina kelp has an antimutagenic effect on immunomodulatory and has shown antiviral activities [20]. In the same line, a phytochemical metabolite (cyanovirin) extracted from blue-green algae protein, deactivates HIV-1 by binding to its glycoprotein [21], whereas the sulfated algae and algae polysaccharides have proven anti-HIV and anti-HSV actions [20]. Ferulic acid and isoferulinic acid inhibited the production of murine interleukin-8 in reply to influenza virus contamination [20]. A direct inhibitory effect of steam distillate made from fresh *Houttuynia cordata* (*Saururaceae*) plants rich in aporphine alkaloids was active against HSV-1, influenza and HIV-1 viruses, but not against polio and coxsackie viruses (enterovirus family) [16].

The flavonoids isolated from *Chamaesyce thymifolia* (*Euphorbiaceae*) proved a great cytotoxicity on HEp-2 cells and modest inhibitory ability *versus* HSV-1 [20]. Sclerocarpic acid isolated from *Glyptopetalum sclerocarpum* stem bark showed antiviral capacity *versus* HSV types (1 and 2) [22]. In another work, isolated gallic acid (GA) and epigallocatechin gallate from Tunisian *Limonium densiflorum* have remarkable ability *versus* HSV-1 [23]. Rhamnansulfat, a natural sulfated polysaccharide identified in *Monostroma latissimum*, showed strong inhibitory action on the virus replication of HSV-1, HCMV and HIV-1 *in vitro* [24]. Moreover, Schnitzler et al. [24] displayed that lemon balm oil repressed plague formation of HSV-1 and HSV-2 viruses in a dose-dependent manner. Besides, at increased concentrations it stopped

the viral infection practically totally. Docherty et al. [25] showed that resveratrol, a phytoalexin, repressed the replication of HSV-1 and HSV-2 in a reversible dose-dependent way. Sahli et al. [26] displayed that the rhizome extract of Tunisian *Juncus maritimus* showed a significant antiviral activity against hepatitis C virus (HCV). In a recent study, dehydrojuncusol, a natural phenanthrene molecule extracted from the *J. maritimus*, is a powerful inhibitor of hepatitis C virus RNA replication [27]. Natural phenolic compounds, abundant in various plant species, have garnered significant attention for their antiviral properties.

Recent computational studies have employed molecular docking techniques to elucidate the interactions between natural bioactive compounds and viral proteins, providing insights into their mechanisms of action in line with the direct inhibition strategy shown in Fig. 1. For instance, gingerderived phenolic compounds such as gingerol, shogaol, and paradol have demonstrated strong binding affinities to the SARS-CoV-2 main protease (Mpro), suggesting their potential as inhibitors of viral replication. Similarly, flavonoids and phenolic acids from *Ruellia* species have shown inhibitory effects against HSV-2 proteases, highlighting their antiviral potential [28]. In addition to docking studies, pharmacokinetic evaluations have assessed the bioavailability and safety profiles of these compounds. For example, *in silico* absorption, distribution, metabolism, excretion (ADME) analyses and toxicity predictions have indicated favorable pharmacokinetic properties and low toxicity for gingerderived phenolics, supporting their candidacy as therapeutic agents. Moreover, as predicted in Fig. 1, multiligand docking studies suggest that combining multiple phenolic compounds may enhance antiviral efficacy through synergistic effects [29].

Thus, this review aims to assess the antiviral potential of natural products, especially plant-derived compounds, by focusing on molecular docking studies that elucidate their interactions with viral targets and mechanisms of inhibition. In addition, it highlights pharmacokinetic and drug-likeness evaluations, including ADME and toxicity predictions, to determine the suitability of these natural antivirals as candidates for drug development.

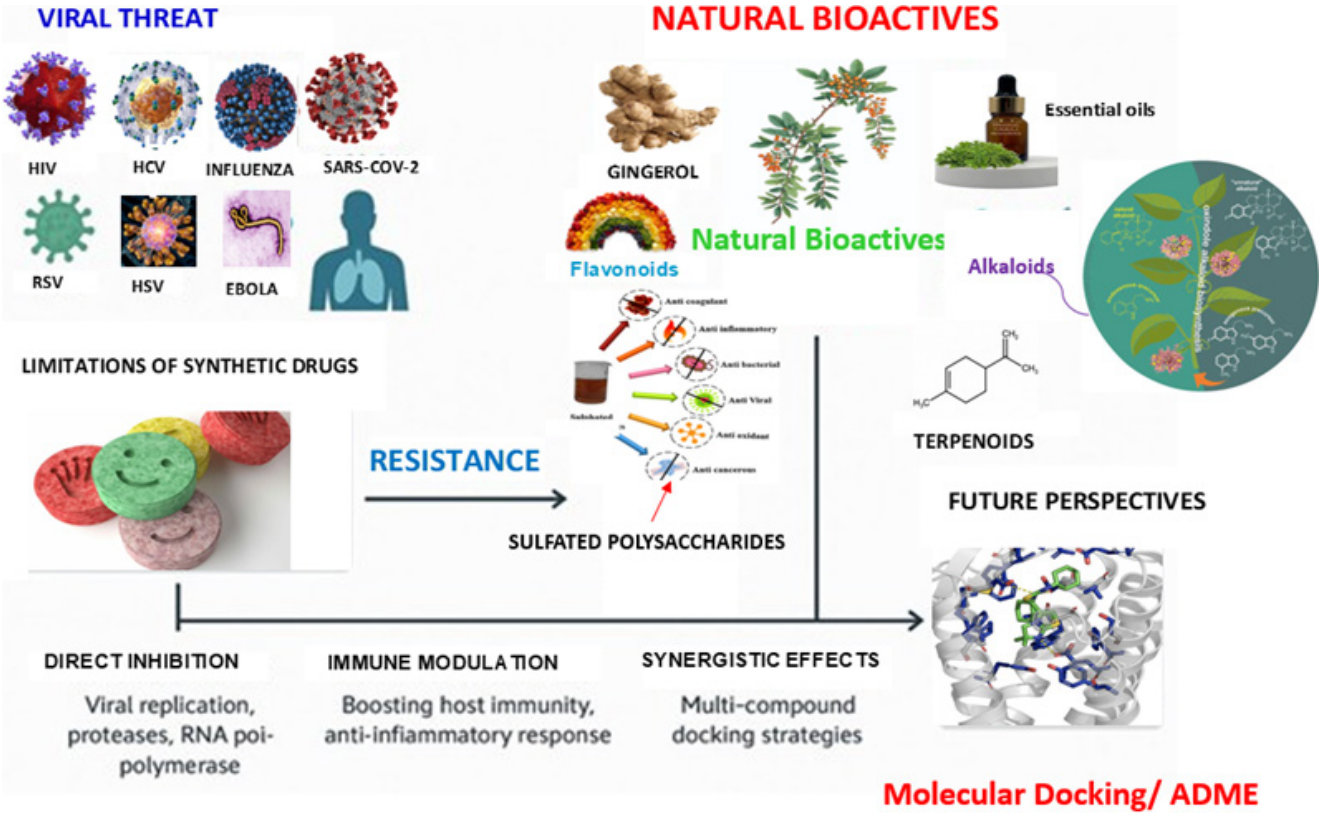


Fig. 1 Schematic overview of major viral threats (HIV, HCV, influenza, SARS-CoV-2, RSV, HSV, Ebola), limitations of synthetic antivirals (toxicity, cost, resistance), classes of natural bioactive compounds (essential oils, gingerol, flavonoids, sulfated polysaccharides, terpenoids, *Houttuynia* alkaloids), and future therapeutic perspectives (direct inhibition, immune modulation, synergistic effects, and *in silico* ADME/toxicity docking)

2 Materials and methods

The current review provides precise and comprehensive information on secondary metabolites and their possible contribution in the prevention and treatment of viral infections. All available information was collected via an electronic search of different scientific sources including PubMed [30], ScienceDirect [31], Google Scholar [32], Scientifc Electronic Library Online (SciELO) [33], Cochrane Library [34] and ClinicalTrials.gov database [35]. The authors opted the following keywords to find relevant studies: "phenolic compounds", "alkaloids", "essential oils", "antiviral", "immunomodulatory", "anti-infammatory", "corona virus", "molecular docking", "pharmacokinetics", "drug-likeness". These terms were used alone or in combination using Boolean operators ("and", "or", "not").

3 Results and discussion

3.1 Phenolic compounds as potent antiviral agents

Plant-based natural products are currently garnering significant attention from researchers in the search for novel antiviral agents to treat and prevent infectious diseases. Polyphenols are powerful bioactive molecules from vegetables and about 8000 various phenolic molecules have been identified [36]. These molecules have an aromatic ring bearing one or more hydroxyl groups and their structures can reach from a simple phenolic compound to a complex high-molecular weight polymer. In this sense, the structural diversity of polyphenols was used as motivation for the medications under progress to be used for the prevention and treatment of some viruses. Antiviral abilities of these molecules and their impact on immune system modulation could help as interesting basis for emerging polyphenol-based natural approaches for preventing and treating viral diseases. Furthermore, to their well-known antioxidative, anti-inflammatory, and immunomodulatory properties, tend to influence viral infection outcomes by regulating the body's immune system [37]. Phenolics in diet provide significant protection against chronic diseases and promote numerous physiological processes, such as cellular redox potential, enzymatic ability, cell proliferation, and modulate multiple cellular signaling pathways. Nonetheless, phenolics are poorly absorbed and/or extensively bio-transformed in enterocytes and liver by phase I and phase II reactions but by gut microbiota. Despite this low bioavailability, most polyphenols carried important pharmacological activities. During these last years, polyphenols have attracted more attention as many of them showed similar or higher intrinsic biological actions when compared to the chemical drugs. Thus, this review highlighted the effectiveness of the most important phenolic compounds against viruses (Table 1 [38–53]) and their mechanisms of action and their complementary impacts in virus disease prevention [42]. In general, phenolic compounds exert antiviral capacity *versus* the virus by several processes like direct interaction with viral membrane proteins and/or host cell receptors, disruption of the viral envelope, inhibition of viral proteases, and replication in the host cell via their phenol rings and modulating host factors and pathways (Fig. 2).

In addition, *in vitro* and *in viv*o studies have confirmed the antiviral action of phenolics *versus* numerous viruses (HIV, HCV, HBV, H1N1, and SARS-CoV); it is tempting to speculate that these secondary bioactive compounds may also attenuate the virus infectivity by mechanisms as shown in Fig. 2.

3.2 Caffeic acid and compounds with caffeoyl functional group

Caffeic acid (3,4-dihydroxycinnamic acid, CA) is the principal hydroxycinnamic acid plentifully existing in blueberries, coffee, kiwis, cherries, apples, tea and oils [54]. CA and molecules with caffeoyl functional groups (chicoric acid, chlorogenic acid, caffeic acid phenethyl ester (CAPE)) have been recognized to be antiviral against HSV1 [55], influenza A [55], canine distemper [56] and HIV. Such molecules attended by satisfactory care characteristics, makes them appropriate candidates for clinical trials. A relationship between reactive oxygen species (ROS) and HCV infection has been proved in numerous studies linked to best alternative for HCV treatment [57].

Heme oxygenase-1 (HO-1) is an important enzyme involved in the antioxidant pathways, responsible for cleaving heme to form biliverdin. This later is demonstrated to have anti-HCV action by eliciting IFNα antiviral response and impairing HCV NS3/4A proteinase action. In turn, caffeic compounds could stop HCV replication, which was mediated by the stimulation of HO-1 through Keap1/Nrf2 signaling pathway. The augmented expression of HO-1 lead to the stimulation of IFNα antiviral reaction which inhibiting HCV replication. Other studies displayed that the antiviral actions of CA were not due to the virucidal effect. Indeed, caffeic groups seemed to have its effect before the completion of viral DNA synthesis, but no earlier times were measured [55]. Concerning influenza A, the principal target of action seems to be in the early stages of contamination [55].

Table 1 Main sources of phenolic compounds and their effectiveness on viruses (SARS-CoV-2, H1N1, HIV, HCV, HBV, HSV)

Compound and its derivatives	Main source	Effectiveness against virus	References
	Phenolic acids		
Hydroxybenzoic acids:			
Gallic acid and its dimers ellagic acid, tergallic acid, and gallic acid	Persimmons, tea, red fruits, black radish, and onions, strawberries, raspberries, and pomegranates	H1N1, HCV, HSV-1, RNA virus, parainfluenza (type-3)	[38–40]
Hydroxycinnamic acids:			
caffeic acid, chicoric acid, chlorogenic acid, caffeic acid phenethyl ester	Coffee, apples, artichoke, berries, olives, and pears Propolis	HSV-1, H1N1, Canine distemper, HIV	[41]
	Flavonoids		
Quercetin		SARS-CoV-2	[42]
Quercetin-3*ß*-O-glucoside		Makona, EBOV	[43]
Quercetin 7-rhamnoside	Buckwheat, onions, capers, apples, and berries, citrus, blueberries and cranberries	HSV-2, PEDV	[41]
Quercetin 3-rhamnoside		Influenza virus strain-A/WS/33	[44]
Quercetagetin		CHIKV, ZIKV	
Isoquercitrin			
Catechin			
Epicatechin		HSV-1	[41]
(-) Gallocatechin gallate	Green, black and oolong tea, apples, blueberries, gooseberries, grape seeds, kiwi, strawberries	Strain:2 MA-EBOV, HSV-1	[45]
Epigallocatechingallate		HSV-1	[46]
Epigallocatechingallate		Influenza A&B	[47]
Epigallocatechingallate		ACE2 receptor, NF-*κ*B, epigenetic regulation inhibits hepatitis B virus, influenza A, and CHIKV	[46, 47]
Theasinensin A		SARS-CoV-2 inactivation. Inhibited significantly the interaction between recombinant ACE2 and RBD of S protein.	[48]
Theaflavin 3,3′-di-O-gallate		SARS-CoV-2 inactivation. Inhibited significantly the interaction between recombinant ACE2 and RBD of S protein.	[48]
Kaempherol	Capers, saffron, brassicaceae		[49]
Silibilin and dihydromyricetin		SARS-CoV-2 protease, glycoproteins, RBO-spike, NF-*κ*B	
Naringin	Citrus fruits, tomatoes,	3CLpro	
Hesperetin, and hesperidin	Citrus fruits	ACE2 receptor, NF-κB, 3CLpro	[50]
Isorhamentin and its derivatives	Sea buckthorn and *Ginkgo biloba* L		
Apigenin	Parsley, onions, oranges, tea, chamomile, wheat sprouts,	HCV	[51]

Table 1 Main sources of phenolic compounds and their effectiveness on viruses (SARS-CoV-2, H1N1, HIV, HCV, HBV, HSV) (continued)

Compound and its derivatives	Main source	Effectiveness against virus	References
	Other aromatic compounds		
Curcumin	Tumeric	3CLpro, glycoproteins RBO-spike, ACE2 receptor, HCV and HIV	[41, 52]
Resveratrol	Grapes	SARS-CoV-2	[53]

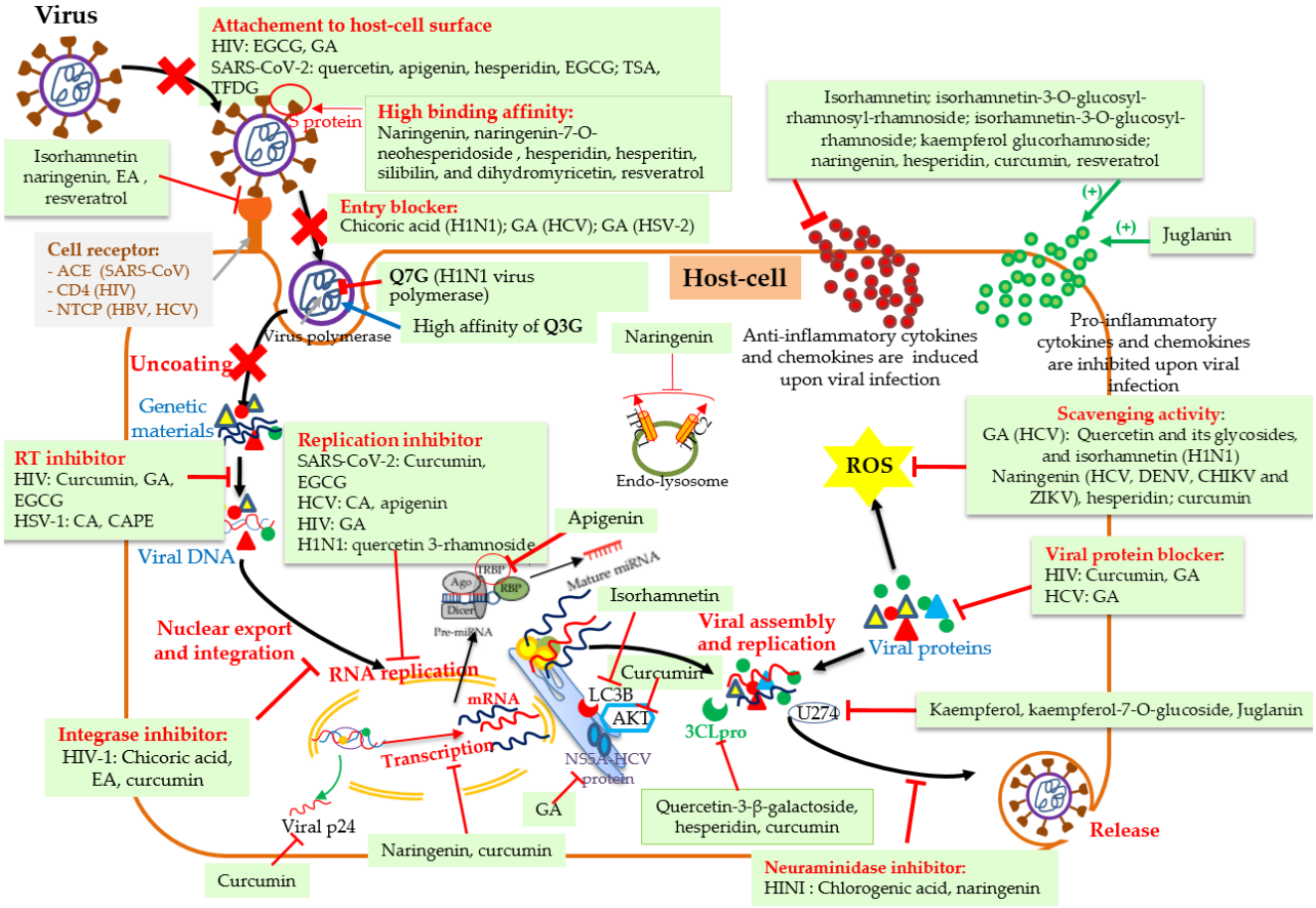


Fig. 2 Impact of phenolic compounds on molecular targets during various stages of the viral multiplication process (SARS-CoV-2, H1N1, HIV, HCV, HBV, and HSV). Abbreviations: GA: gallic acid; EA: ellagic acid; CA: caffeic acid; EGC: epigallocatechin-3-gallate; Q3G: quercetin 3'-glucuronide; Q7G: quercetin 7-glucoside; 3CLpro: SARS-CoV 3CLpro inhibitor; LC3B: microtubule-associated protein 1 light chain 3B; Akt: protein kinase B signaling; U274: protein 3a of coronavirus; TPC1 and TPC2: endo-lysosomal two-pore channels; RT: reverse transcriptase.

On the other hand, phenolic compounds with caffeoyl functional groups displayed several mechanisms of action against viruses. Chicoric acid has been reported to affect the intracellular mechanism of action of HIV-1 integrase. Antiviral activity of chlorogenic acid against influenza A occurs late in the infectious cycle and seems to neutralize neuraminidase. Chlorogenic acid actions on influenza A differs with those of CA, which acts in the first stages of infection [55]. Kishimoto et al. [58] showed that CAPE decreased the development of Type A and B influenza viruses (at 8.8 μM), respectively by 95 and 92%. In the other report, cells treatment by an anti-IL-6 receptor antibody and CAPE decreased the detached cell number, viral titers, and ameliorate cell viability after infection with the pandemic virus of influenza A [59]. To characterize new beneficial phenolics as an anti-COVID-19 agent, ethanolic extract effect from stem of *Sambucus formosana* Nakai (elderberry) from a human coronavirus variant HCoVNL63 was determined [38]. Among *S. formosana Nakai* compounds, phenolic acid such as CA, chlorogenic acid, and GA sustained the anti-HCoV-NL63 activity that was ranked in the succeeding order of virus yield decrease: CA (half-maximal inhibitory concentration (IC_{50}) = 3.54 μM) > chlorogenic acid (IC_{50} = 43.45 μM) > coumaric acid (IC_{50} = 71.48 μM). CA considerably repressed the replication of virus in a cell-type independent manner, and precisely blocked virus attachment (IC_{50} = 8.1 μM).

3.3 Hydroxybenzoic acid derivatives

Hydroxybenzoic acid derivatives (HBAs) can be perceived as free acids in many fruits (e.g., gallic acid in persimmons) or after being released through fruit and vegetable processing, these bioactive phenolics are present as conjugates. GA may be conjugated as such, or as its dimer (ellagic acid), trimer (tergallic acid), and tetramer (gallagic acid). GA is the principal phenolic acid in tea and reported in several plants. This compound possesses multiple pharmacological actions, comprising the antioxidant, anti-inflammatory, antibiotic, anticancer, antiviral, and cardiovascular properties. Antiviral *in vitro* effect of GA has

been reported *versus* HIV-1 with a therapeutic index (TI) value of >32.84 [40]. GA from *Lagerstroemia speciosa* L. can reduce HIV-1 by inhibiting the activity of reverse transcriptase and HIV protease respectively [60]. The anti-HSV-2 activity of GA was attributed to its virucidal action on virus particles, a change that was likely accompanied by restricted inhibition of the virus attachment to cells and its subsequent cell-to-cell feast activity [61]. In addition, GA has the capacity to block HIV-1 integrase, HIV-1 protease dimerization, HIV-1 transcriptase, HCV replication, attachment and diffusion of HCV, HSV-1, HCV serine protease and attachment and diffusion of HSV-2 [11]. A study conducted by Govea-Salas et al. [39], displayed that GA reduced the expression levels of NS5A-HCV protein (~55%) and HCV-RNA (~50%) in a time-dependent manner as compared with the levels in untreated cells. Particularly, GA treatment declined the production of ROS at the first time points of exposure in cells expressing HCV protein. Comparable data were found upon pyrrolidine dithiocarbamate exposure. These results showed that the antioxidant activity of GA may be implicated in the down regulation of HCV replication in hepatoma cells. Khalil and Tazeddinova [40] showed that CA and GA are potential candidates in the treatment of COVID-19 and its associated symptoms. GA and CA were also shown to apply sustainable anti-viral activity against human coronavirus NL63 (HCoV-NL63), one of the main circulating corona viruses worldwide that causes respiratory tract diseases like runny nose, cough, bronchiolitis and pneumonia [38]. More recently, Nagy et al. [62] evaluated the activities of GA as serious respiratory syndrome coronavirus 2 (SARS-CoV-2) RNA-dependent RNA polymerase (PDB ID 6M71) inhibitor. GA exhibited high binding affinity against the SARS-CoV-2 polymerase and expressed worthy drug-likeness and pharmacokinetic properties.

Ellagic acid (EA) is also a significant molecule of many fruits like raspberries (*Rubus idaeus*), strawberries (*Fragaria ananassa*), and blackberries (*Rubus fruticosus*). EA displayed antiviral activity toward both groups of Human rhinoviruses (group A: HRV-2; group B: HRV-3 and HRV-4). IC_{50} of EA was between 95.9 and 125.8 μM toward three HRVs and a higher antiviral activity than ribavirin toward three HRVs and high selectivity [60]. These authors reported that EA does not interact with the HRV-4 particles, as pre-exposure of the virus to the constituent did not alter the infectivity of HRV-4 particles. Based on time-of-addition experiments, this compound significantly suppressed HRV-4 infection only when added just after virus inoculation (0 h), but not before −1 h or after 1 h or later. This result suggests that EA may directly interact with human cells in the first stage of HRV infection. A study conducted by Park et al. [63] showed that EA extracted from Banaba leaves inhibited the HIV-1 protease activity. However, in one of the previous studies, EA has HIV integrase inhibitory activity [64]. Recent docking simulation studies showed that EA has a high affinity to the ACE-2-receptors, which makes it a strong candidate for the prevention and treatment of SARS-CoV-2 infection. EA could be a promising agent to prevent and ameliorate the damaging effects in infected persons [64].

3.4 Flavonoids and their antiviral mode of action

Flavonoids are the main phenolic class, subdivised into diverse sub-classes: anthocyanins, flavanols, dihydroflavonols, flavanones, flavones, flavonols, isoflavonoids, chalcones, and dihydrocalcones [65]. Current studies highlighted the important role of flavonoids against viral infections, pneumonia [66], cancer and cardiovascular diseases [67]. In addition, for its antimicrobial [68], antioxidant and anti-inflammatory potentialities [45]. As antiviral action, flavonoids have been tested since 1951 [69].

They have been stated to inhibit the targets of different types of corona-viruses (SARS and MERS) in several ways. Namely, it can block the enzymatic activities of viral proteases (3CLpro and PLpro), interfered with spike glycoproteins or suppressed the activity of ACE2 receptors [70]. Flavonoids can inhibit viruses from being released to attack other healthy host cells [71]. They rely on the metabolism of the host and its surroundings to reproduce and continue to survive. Roschek et al. [45] described that flavonoids can attach itself to the surface proteins of viruses, prohibiting the virus from entering the host cells. Different researches have mainly focused on the interference of these compounds with the most important viral proteases of SARS and MERS coronaviruses by using tools such as common enzymatic activity measurement fluorescence resonance energy transfer (FRET) based methods and molecular docking. In addition, there are several mechanisms by which flavonoids inhibit and act on viruses. They can block the attachment and entrance of viruses into the cells, obstruct with several phases of viral DNA replication, protein translation, and poly-protein processing. Some flavonoids act as a transcription blocker and affect the replication process, while others hinder the late stages of viral assembly, packaging, and release (Fig. 2). Flavonoids can also modulate the immune system and reduce viral load [45]. In fact, numerous works have recently advised kaempferol, quercetin, naringenin, curcumin, catechin,

and epicatechin-gallate as acclaimed bioactive molecules from vegetables that may act against COVID-19 proteases.

3.5 Antiviral action of flavonols

Quercetin compounds and its derivatives: Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is one of the most important flavonoids and belongs to the class of flavonols (Fig. 3). The quercetin and quercetin glycosides are found in a variety of plants such as onions, apples, berries, tomatoes, brassica vegetables, various edible flowers, grapes, nuts, teas, and plant barks [72]. Quercetin is the aglycone form of several glycoside flavonoids. It is acting as antiviral, antioxidant, antiulcer, antidiabetic, antihypertensive, anti-inflammatory, and anticancer [73].

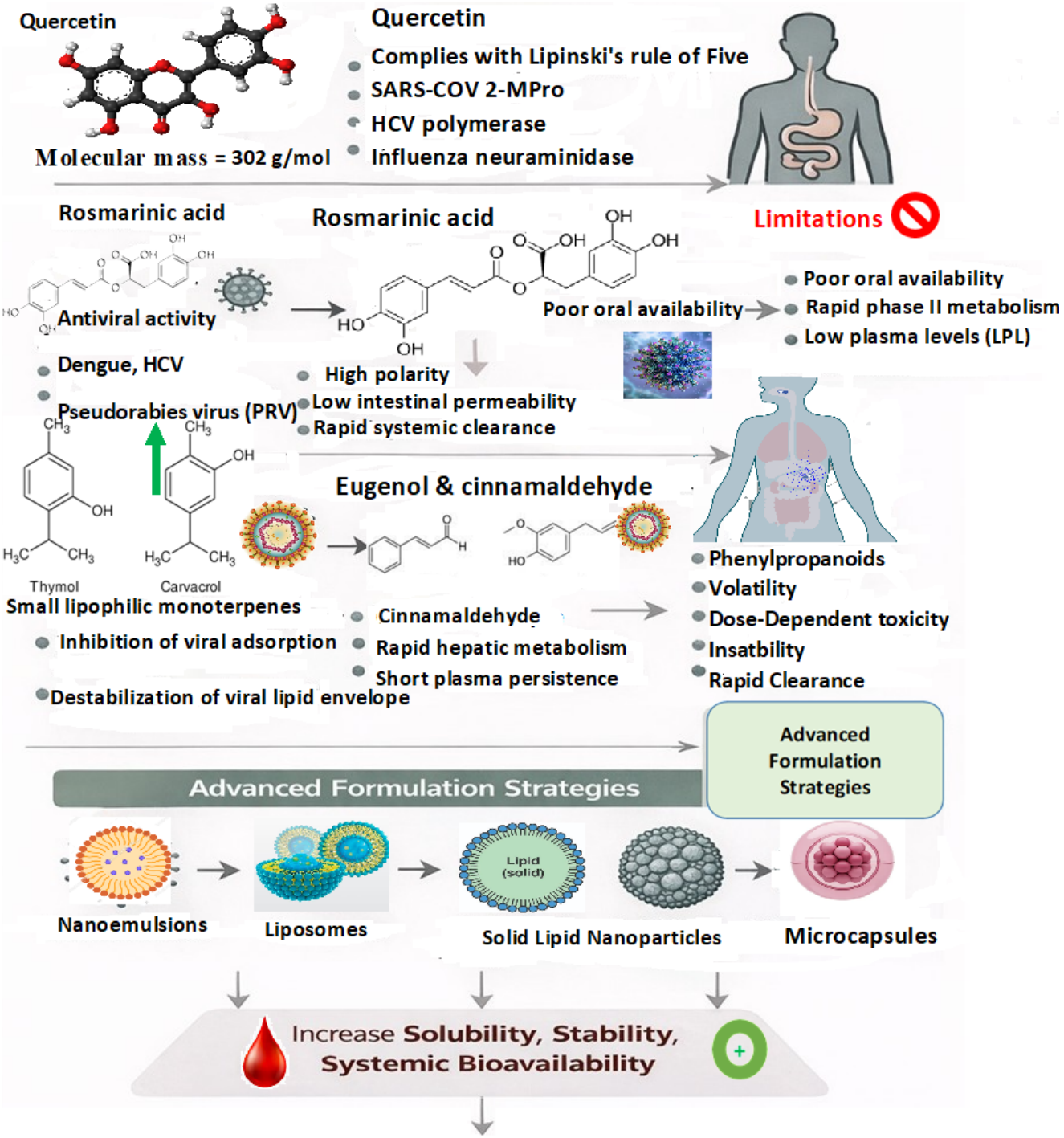


Fig. 3 Pharmacokinetic and drug-likeness evaluation of natural antivirals SARS-CoV-2, main protease (MPro), hepatitis C virus (HCV), pseudorabies virus (PRV), low plasma levels (LPL)

Several reports on quercetin glycosides have been proved that these compounds act as a potent drug candidate towards inhibition of influenza virus infection through inferring the viral cellular immune system inhibition of viral cellular targets, interfering viral replication and inhibiting the viral growth phase [74].

The quercetin 3-rhamnoside showed stronger inhibitory effect on influenza viral mRNA synthesis with promising inhibition for influenza viral infections. In addition, it was found that the quercetin 7-O-glucoside rhamnoside showed stronger inhibitory effect on influenza viral mRNA synthesis with promising inhibition for blocked significantly H1N1 virus polymerase through binding of 7-O-methylated GTP on PB2 subunit of RNA polymerase causing effective inhibition [43]. Gansukh et al. [43] screened 410 quercetin derivatives using molecular docking (affinity: ≤9.0 kcal) for their drug-likeness and *in vitro* cytopathic effect by Sulforhodamine B (SRB) assay. Among all quercetin derivatives, quercetin 3′-glucuronide (Q3G) exerted the strongest binding affinity towards cap-binding site of the PB2 subunit with −9.6 kcal of binding affinity and 0.00054 mM of the inhibitory constant (*Ki*) value, while quercetine 3′-glucuronide (Q7G) was presented highest anti-influenza A/PR/8/34 virus activity ($IC_{50} \approx 2.10$) and non-cytotoxic effect as CC_{50} (50% cytotoxic concentration) >100 μg/mL. In the other studies, isoquercetin administration at 10 mg/kg/day (i.p.) in mice infected by influenza virus significantly reduced the levels of lung viral titers compared to those of untreated mice. The isoquercetin treatment significantly lowered the levels of IFN-*γ*, iNOS, and RANTES in the lungs, compared to those of the untreated group [74]. Quercetin and its glucoside forms such as isoquercetin are reported to scavenge free radicals and interfere with NOS activity to play a protective role in ischemic tissue damage [70]. Furthermore, different flavonols possess antiviral activity against coronaviruses (such as SARS-CoV and MERS-CoV) through the inhibition of 3CL and PLpro proteases. In this context, Solnier and Fladerer [42] have proposed quercetin as a good anti-SARS-CoV-2 candidate. Rashed et al. [75] used quercetin flavonoid to inhibit HCV by targeting the NS3 protease. They used the Huh-7 cells and transfected it with a Plasmid EGFP-NS5A/B-DsRed-NLSX3, which has the NS3 protease gene. Quercetin showed no cytotoxicity towards the Huh-7 cells at a concentration of 10 μg/mL and can reduced the expression of NS3 protease by up to 90%. Indeed, this flavonoid displayed antiviral effects against influenza A virus, HSV1, and respiratory syncytial virus (RSV and other viruses) [75]. Furthermore, the screening of a library of 150 phytochemicals allowed the identification of quercetin as a potent inhibitor of SARS-CoV-2 3CLpro [44]. In fact, since the former SARS-CoV and the new SARS-CoV-2 show high sequence similarity to spike glycoproteins, several flavonols showed antiviral activity against coronaviruses (such as SARS-CoV and MERSCoV) through the inhibition of 3CL and PLpro proteases and hamper the entry of SARS-CoV-2 into host cells. Moreover, it has been demonstrated that the spike protein of the novel virus binds the ACE2 receptor with higher affinity compared to SARS-CoV [72]. Therefore, the inhibition of ACE2 through a competing binding appears to be a good approach to prevent SARS-CoV-2 infection. In this framework, experimental results have demonstrated that quercetin exerts strong inhibitory effects on ACE2 *in vitro* and *in vivo* when tested in rats [76, 77]. Based on the docking study, Quercetin-3-*β*-galactoside revealed that this compound was SARS-CoV 3CLpro inhibitor. The residue Gln189 (Q189) and OH-groups on the quercetin moiety are critical keys in the binding interaction [78].

Isorhamnetin (3′-methoxyquercetin) is a methylated flavonol that possesses a OH-group on the C ring and a 3′-methyl group on the B ring. A common food source of this 3′-methoxylated derivative of quercetin and its glucoside conjugates are pungent yellow or red onions, in which it is a minor pigment. Isorhamnetin was found abundantly in herbal plants such as sea buckthorn and *Ginkgo biloba* L. have beneficial effects in the treatment of cardiovascular diseases, antioxidant activity, and protective effects against ischemic heart disease [79]. Dayem et al. [80] showed that co-treatment and pre-treatment with isorhamnetin produced a strong antiviral effect against influenza virus A/PR/08/34 (H1N1). Isorhamnetin treatment reduced virus-induced ROS generation and blocked cytoplasmic lysosome acidification and lipidation of microtubule associated protein1 light chain 3-B (LC3B). Oral administration of isorhamnetin in mice infected with influenza A virus significantly decreased lung virus titer by twofold, increased the survival rate which ranged from 70–80%, and decreased body weight loss by 25%. Furthermore, this compound decreased the virus titer in *ovo* using embryonated chicken eggs. The structure-activity relationship (SAR) of isorhamnetin could explain its strong anti-influenza virus potency; the methyl group located on the B ring of isorhamnetin may contribute to its strong antiviral potency against influenza virus in comparison with other flavonoids. Isorhamnetin contributes

also to the inhibition of acute inflammatory response by the inhibition of JNK and Akt/IKKα/β pathway activation, which leads to NF-κB inactivation [81]. This metabolite inhibits the ROS production induced by LPS and acts as a natural COX-2 inhibitor [82]. Isorhamnetin and its sulfate derivative persicarin displayed antithrombotic and anticoagulant activities [79]. Isorhamnetin-3-O-glucosyl-rhamnosyl-rhamnoside and iso-rhamnetin-3-O-glucosyl-rhamnoside showed significant anti-inflammatory actions by numerous mechanisms of action including the regulation of cytokine secretion, suppression of cellular infiltration, and the reduction of nitric oxide production and COX-2 activity. Nevertheless, isorhamnetin-3-O-glucosyl-rhamnosyl-rhamnoside is less active than isorhamnet-in-3-O-glucosyl-rhamnoside, suggesting that the glycosylation profile affects the bioactivity [83]. More recently, Wu et al. [56] showed that isorhamnetin were shown strong retention of ACE2 expression HEK293 (ACE2h) cells by CMC analysis.

Based on drug receptor interaction analysis and viral entry studies *in vitro*, authors researched the interaction of these flavonoids and ACE2 as well as the inhibitory effect of these compounds on viral entry. Surface Plasmon resonance assay proved the effect that isorhamnetin bound to ACE2 with an affinity value K_D equal to 2.51 ± 0.68 μM. Viral entry studies *in vitro* reported that iso-rhamnetin inhibited SARS-CoV-2 spike pseudo-typed virus entering ACE2h cells.

Kaempferol and its derivatives: kaempferol is another important flavonol found in a widespread variety of edible plants and food derived products (Fig. 3) [83]. The highest level of this compound was found in caper and saffron (259 and 205 mg/100 g, respectively). Based on several *in vitro* studies, kaempferol showed a strong activity against hepatitis B virus [84] and two influenza viruses H1N1 and H9N2 with EC_{50} values of 30.2 and 18.5 μM [49]. The potency of kaempferol (100 μmol/L) to inhibit completely BoHV-1 replication at the post-entry stage in Madin-Darby bovine kidney (MDBK) cells has been shown *in vitro*. The inhibition of Akt signaling is a potential mechanism underlying the antiviral effect of kaempferol molecules. This later showed potent antiviral properties due to inhibition of protein kinase B (Akt) signaling in response to BoHV-1 infection in a dose dependent manner, suggesting that the interruption of Akt signaling is a potential mechanism for the antiviral effect of kaempferol against BoHV-1 infection.

Astragalin is the glycoside form of kaempferol is well-known for its multiple therapeutic properties [50] such as antioxidant, anti-inflammatory, anticancer, neuroprotective, and antiviral. The anti-HIV-1 activities of kaempferol and kaempferol-7-O-glucoside (10–100 μg/mL) have been studied [47]. Protein 3a (U274) which is the most important accessory viral channel forming protein and contains 274 amino acids plays an important role in corona viral particles release phase. In addition, 3a protein plays a crucial role in caspase-1 activation and its consequent stimulatory effect on NLRP3 inflammasome, which are important in IL-1β secretion and pyroptotic death in lung cells, respectively [47]. Therefore, using Xenopus oocyte, Schwarz et al. [85] showed a significant inhibition of kaempferol on 3a protein and stronger inhibition of kaempferol glycosides. Efficacy of all tested molecules was measured by Ba+2-sensitive assay. Juglanin, a glycoside of kaempferol with an arabinose moiety, inhibited potently the activity of 3a protein with an IC_{50} value equal to 2.3 μM. Furthermore, the presence of 72% of similarity in ORF3a protein sequence between to SARS3a protein in SARS-CoV, with the conservation of all functional domains. The presence of mutations and the detection of polyproline regions in ORF3a of SARS-CoV-2 could be driving the evasion of the host immune response thus favoring viral spread [46]. These authors showed that the rapid mutations in ORF3a should be carefully scrutinized throughout the COVID-19 pandemic. Restoring the deficient immune status of COVID-19 patients by anti-inflammatory agents is an optimal choice to treat severe cases. Immunomodulatory effects of kaempferol investigations revealed that kaempferol glucorhamnoside could inhibit NF-κB and MAP kinase phosphorylation. Indeed, a strong reduction in IL-1β, IL-6, and TNF-α levels were also observed in an *in vivo* study [46].

3.6 Antiviral action of flavanols

Catechin and its derivates: catechins are polyphenolic compounds belonging to the flavan-3-ol group and were abundant in green tea and present in a few quantities in onions, apple skin and plums. This group of compounds contributes to several biological effects including virus inactivation [46, 47]. (-)-Epigallocatechin gallate (EGCG) is regarded as a representative tea cate-chin with the highest activity. EGCG is a strong antioxidant and antitumor molecule and has the potential to prevent and counteract several human diseases with chronic metabolic and inflammatory components, such as obesity, Parkinson's and Alzheimer's diseases, diabetes and stroke [86]. It may be due to its capacity to interact with DNA methyltransferases (DNMT), ACE-2 and helicase. EGCG is also an

efficient antiviral molecule which counteracts diseases caused by a large panel of viruses: HIV, HSV, adenovirus, hepatitis B and C viruses, human papillonavirus, Dengue virus (DENV), Ebola virus (EBOV), Zika virus (ZIKV), West Nile viruses (WNV), influenza virus and Chikungunya virus (CHIKV) [39]. Recently, Ohgitani et al. [48] demonstrated that green tea and black tea, as well as their constituents, EGCG, theasinensin A (TSA), and theaflavin 3,3′-di-O-gallate (TFDG), significantly inactivated SARS-CoV-2. The infectivity of SARS-CoV-2 was decreased to 1/100 to undetectable levels after treatment with black tea, green tea, roasted green tea, or oolong tea for 1 min. An addition of EGCG significantly inactivated SARS-CoV-2, while the same concentration of TSA and TFDG had more remarkable anti-viral activities. EGCG (1 mM), TSA (40 μM), and TFDG (60 μM), respectively, which are comparable to the concentrations of these metabolites in tea beverages, significantly lowered SARS-CoV-2 infectivity, viral RNA replication in cells, and secondary virus multiplication from the cells. EGCG, TSA, and TFDG significantly reduced the interaction between recombinant ACE2 and RBD of S protein. Other studies indicates that the oral administration or gargling of tea, along with its isolated catechin components – EGCG, TSA, and TFDG – could offer a protective effect. This is proposed to occur through the direct inactivation of SARS-CoV-2 in the oral cavity and pharynx, thereby preventing viral entry at the mucosal surface. Indeed, ingestion/gargling with tea may reduce person-to-person virus transmission, since EGCG/TSA/TFDG may make inactive virions in saliva of infected people [48, 50].

3.7 Antiviral action of flavanones

Naringenin is an important flavonoid compound that belongs to the flavanone class, is widely present in a variety of fruits and vegetables either in the Free State or as glycosides or acyl glycosides. The highest amounts are reported in grapefruit, tangerines, oranges, and tomatoes. Like other flavonoids, naringenin was found to be capable of demonstrating strong antioxidant, anti-inflammatory, and antiviral properties [87, 88]. In particular, the antioxidant role of naringenin was shown to be carried out by eliminating free radicals and preventing DNA oxidative damage [89], while the strong anti-inflammatory activity is due to the inhibition of the nuclear factor kappa B (NF-*κ*B) signaling pathway [90] since NF-*κ*B promotes the expression of many important inflammatory proteins [91]. The antiviral activity of NAR was tested against some viruses: HCV, DENV, CHIKV, and ZIKV [92]. Naringenin has been recommended as a therapeutic adjunct to nucleoside-reverse-transcriptase-inhibitors for antiretroviral therapy [92].

The *in silico* docking approaches have shown blocking of the neuraminidase site by naringenin in Influenza A virus [93]. Thus, naringenin exhibits a broad-spectrum antiviral activity which involves inhibiting a variety of viruses. In this context, the beneficial properties of naringenin and its possible therapeutic effects, pointing out that it may exert therapeutic effects against COVID-19 through the inhibition of the main protease 3CLpro, and the reduction of ACE2 activity. Moreover, one additional mechanism by which this flavanone can counteract the effects of corona virus infection can be attributed to the reduction of inflammatory responses. In another study, among the 10 flavonoid compounds docked into S protein, naringenin-7-O-neohesperidoside displayed the highest binding affinity (−9.8 kcal/mol), even higher than that of the standard drug dexamethasone (−7.9 kcal/mol). By using molecular dynamics simulation method, naringin possessed a conformational stability within the active site of S protein [94], and decreased viral load and related cytopathic effects in Vero E6 cells [95]. Some pharmacokinetic studies proved that NAR denotes promising drug-likeness properties. This flavanone showed low GI absorption and a high volume of distribution, and, therefore, it should attain therapeutic effects upon oral administration [81]. In a study by Nguyen et al. [96] related to the inhibitory effects of plant polyphenols on SARS-CoV-2 Mpro, it was found that NAR displayed 50% inhibition and an IC_{50} of 150 μM [92]. Interestingly, naringenin can inhibit the activity of endo-lysosomal two-pore channels (TPC1 and TPC2), both in humans and plants [97]. NAR is a hydrophilic molecule with high affinity to the cytoplasmic membrane, causing intracellular accumulation of this compound. It has recently been demonstrated that the activity of human TPC channels can be blocked by naringenin [98].

Hesperidin and its aglycone (hesperitin): hesperidin is a flavanone glycoside containing hesperitin (the aglycone form) and sucrose is abundant in citric fruits such as lemons, grapefruits, etc.. This flavonoid denotes a potent anti-inflammatory, anti-fungal, antibacterial, antiviral, antioxidant and immunomodulatory properties, and free radical scavenger's capacity [50].

The antiviral activity of hesperidin against influenza virus involves its implication in the activation of the mitogen-activated protein kinase (MAPK) pathway. The MAPK host defense cascade contributes to efficiently restraining

viral replication, spread, and reducing tissue damage [99]. Hesperidin with its high anti-inflammatory activity inhibited the secretion of pro-inflammatory cytokines such as IFN-γ and IL-2 [100] and inhibited IL-1β-stimulated inflammatory responses by inhibiting the activation of the NF-κB signaling cascade [101]. Indeed, these reports suggest an effective antiviral action of hesperidin because it is low binding energy to the spike glycoprotein and to the protease 3CLpro. In addition, hesperidin is considered an important antioxidant compound, able to counteract the damaging effects of oxygen free radicals, triggered by infection and inflammation [102]. Recently Riaz et al. [50] denoted that hesperidin and its analogs showed an effective effect in the control SARS-CoV-2; the entire drug bank database was screened for strong analogous remedy like compounds as hesperidin. Virtual screening and docking studies were envisioned for these substances against spike protein with auto dock virtual screening to land the auto dock vena. The docking outcome showed that hesperitin, silibilin, and dihydromyricetin compounds having the highest binding energies, like −8 and −6.2 Kcal/mol. Hesperidin can obstruct coronavirus from entering host cells through ACE2 receptors, which can prevent the infection. Anti-viral activity of hesperidin might constitute a treatment option for COVID-19 through improving host cellular immunity against infection and its good anti-inflammatory activity may help in controlling cytokine storm [56]. Hesperidin mixture with diosmin co-administrated with heparin can protect against venous thrombo-embolism which may prevent disease progression.

3.8 Antiviral action of flavones

Apigenin (4′,5,7-trihydroxyflavone), found in many fruits and vegetables (parsley, celery, celeriac, and chamomile flowers), is the aglycone of several naturally occurring glycosides.

A study conducted by Shibata et al. [51] studied the antiviral activity of apigenin in Huh7-cells infected with HCV. This flavonoid inhibited the activity of HCV by targeting its replication process. It was found that Apigenin targeted the transactivation response element RNA-binding protein (TRBP) of mature MicroRNA (miRNA122) and decreased the expression of mature miRNA122 at 5 μM by down-regulation of its miRNA 122 RNA gene levels without considerably upsetting the cell growth. In addition, apigenin inhibited the HCV life cycle [103]. This effect is attributed to putting off viral genome replication and affecting infectious particles' morphogenesis.

3.9 Other interesting phenolic compounds

Curcumin (diarylheptanoid) belongs to the group of curcuminoids, which are phenolic pigments responsible for the yellow color of turmeric *Curcuma longa* L. In India and Southeast Asia, curcuma powder is widely used in traditional medicine to treat various disorders. In Europe, it is used as a food dye for its yellow color and it is classified as a food additive. Curcumin is characterized by numerous valuable properties, acting as anti-inflammatory, antineoplastic, antiangiogenic, and as antiviral (influenza virus, HCV, HIV) natural agent [52]. Indeed, it is well-known that different compounds like piperine (major active component of black pepper) can increase curcumin bioavailability. as much as 20-fold [104].

One of the bio-functions of curcumin is revoking the infection of viruses, by targeting the viral entry, or solely attacking the viral components essential for viral replication. Chen et al. [78] reported that curcumin incubated directly with viruses abrogates the function of viral envelope proteins, i.e., hemagglutinin-neuraminidase (HN) protein of Newcastle disease virus and hemagglutinin (HA) protein of influenza A virus (IAV). In a more recent study, two arthropod-borne viruses, CHIKV and ZIKV infections, were inhibited by this molecule by obstructing the attachment of viruses to the cell surface [105]. Wen et al. [41] used cytopathic effects of SARS-CoV in Vero 6 cells as a cell-based assay to screen the antiviral action of curcumin. They reported that this molecule (at 20 μM and 40 μM) showed strong anti-SARS-CoV activity and reduced the activity of SARS-CoV 3CL protease, which is vital for viral replication. In addition, several observations denoted that curcumin induced perturbation of the fluidity of viral envelop. The effect of this compound at a very early stage of viral infection was also observed in human norovirus (HuNoV), a non-enveloped type of virus [81]. Since viral entry implicates an initial engagement between the viral surface protein and the receptor on the host membrane, curcumin might affect the viral entry into HuNov (without the targets of lipid bilayer envelop structure) by preventing the function of viral surface proteins. Based on its effect on the viral envelope of surface proteins, curcumin was proposed as a virucidal agent. It affects membrane integrity in the liposome models and curcumin pretreatment significantly abrogates plaque formation of various enveloped viruses, including influenza A virus, pseudorabies virus [60], and RSV [29].

Propagation of HIV evolved various viral enzymes such as reverse transcriptase, integrase, and proteases, as well as

Tat, a trans-activator of transcription. It was shown that curcumin inhibited HIV-integrase and protease by direct intermolecular binding. The activity of curcumin was enhanced by coordinating the central keto-enol groups of two curcumins with a boron atom on HIV-1 and HIV-2 proteases due to the simultaneous occupation of two binding sites in the viral protease [87]. In addition to the direct targeting of the viral replication machinery, curcumin also affects viral replication via modulating cellular factors. Curcumin treatment reduced trans-activator of transcription (Tat) protein levels, Tat-mediated long terminal repeat (LTR) promoter transactivation, as well as reduced production of the HIV-1 virus [106]. Accumulated evidence indicates curcumin mediates antiviral actions partly by modulating multiple cells signaling pathways and cellular essential processing. A large number of viruses rely on PI3K/Akt pathway by activating them for their replication. HCV requires Akt pathway for their growth and replication. Therefore, curcumin strongly inhibited the replication of HCV by suppressing the Akt pathway, in turn, suppressing a transcriptional factor sterol regulatory element binding protein-1 (SREBP-1) essential for HCV replicon expression [107]. In addition, HO-1, an enzyme involved in the degradation of heme, plays a vital role in maintaining cellular homeostasis, coupled with anti-inflammatory and antioxidant effects [87]. A stimulation of HO-1 was perceived in curcumin-treated HCV infected Huh7.5 cells, eventually reducing intracellular HCV RNA expression in a dose-dependent manner [75], suppressing HCV replication and targeting PI3K-AKT signaling pathway. Cytokines, especially IL-1β and IL-6, were markedly expressed in severely ill COVID patients admitted to intensive care units compared to stable COVID-19 patients. These observations have implicated inflammasome activation in driving CRS. Several studies have found the potency of curcumin to block inflammasome activation through Nod-like receptor family, pyrin domain-containing 3 (NLRP3), and inhibit the secretion of mature IL-1β [108] and abrogate pulmonary inflammation [109].

Resveratrol (3, 5, 4′-trihydroxystilbene) is a stilbenoid, a type of natural phenol, and a phytoalexin (Fig. 3). It was mainly present in some plant sources such as grapes, apples, blueberries, plums, and peanuts. Resveratrol is another aromatic compound, which protects against multiple viruses [110]. The antiviral mechanism of resveratrol against influenza A virus was described to be associated with the inhibition of cellular signaling pathway (PKC/MAPK pathway) leading to retention of viral ribonuclea protein in the nucleus, thereby reduction of virus replication [111]. Resveratrol stably binds to the viral protein/ACE2 receptor complex of SARS-CoV-2, indicating it to be a promising agent against COVID-19 by disrupting the virus S protein [87]. In addition, stilbene diminished the expression of N protein in SARS-CoV-2 and reduced the apoptosis of Vero E6 cells. Moreover, resveratrol alleviated the Vero E6 cell death induced by MERS-CoV, most likely due to an antiviral effect because the MERS-CoV RNA and virus titer levels were lower in resveratrol-treated cells (150–250 μM). Additional compounds are under research for their beneficial properties on human health, which may be interesting under the antiviral activity aspect. Several researchers applied network pharmacology to analyze Qingfei Paidu, a traditional Chinese herbal decoction, and found that quercetin, kaempferol, luteolin, β-sitosterol, naringenin, isorhamnetin, baicalein, and tussilagone could be the major active ingredients in treating epidemic diseases and in the management of COVID-19 [53]. Ren et al. [112] showed that kaempferol, naringenin, and wogonin in Jinhua Qinggan granules docked well with specific target proteins of SARS-CoV-2.

3.10 Antiviral action alkaloids

Alkaloids are nitrogen-containing organic compounds present in plants, animals, and microbes, existing as esters (cocaine), amides (piperine), or glycosides (solanine), and classified into heterocyclic or non-heterocyclic forms [56, 113]. Several alkaloids exhibit potent antiviral activities by interfering with viral entry, replication, or host–virus interactions. Michellamine B inhibits HIV fusion and syncytium formation [114], while lycorine from *Lycoris radiata* shows strong activity against SARS-CoV (half maximal effective concentration (EC_{50}): 15.7 nM), HCoV-OC43, MERS-CoV, and HCoV-NL63, and protects mice from HCoV-OC43 lethality [115, 116]. Emetine from *Carapichea ipecacuanha* blocks coronavirus entry and replication, as well as ZIKV and EBOV by impairing lysosomal function and polymerase activity [117, 118]. It also suppresses HIV reverse transcriptase, viral RNA synthesis, and replication of DENV, BPXV, BHV-1, and NDV without resistance emergence [119, 120] (Table 2). Tylophorine and its analogs from *Tylophora indica* inhibit coronavirus RNA replication at nanomolar levels through JAK2/NF-κB modulation [116, 121]. Alkaloids from *Stephania tetrandra* (tetrandrine, fangchinoline, cepharanthine) reduce HCoV-OC43 replication [122], while homoharringtonine from *Cephalotaxus hainanensis* exhibits broad anti-CoV activity (IC_{50}: 12 nM) [107]. Moreover, isatin derivatives inhibit rhinovirus and

SARS-CoV 3CLpro, highlighting potential for COVID-19 therapy [107] (Table 2).

3.11 Antiviral action of essential oils

Essential oils are complex volatile mixtures of terpenes (mono-, sesqui-, di-terpenes) and phenylpropanoids that display multiple pharmacological activities, including immunomodulatory, anti-inflammatory, and antiviral effects [123]. Their antiviral potential has been confirmed against influenza viruses, herpes viruses, flaviviruses, and coronaviruses. For influenza, *Cinnamomum zeylanicum*, *Citrus bergamia*, and *Thymus vulgaris* essential oils completely inhibited H1N1, while *Lavandula angustifolia* and tea tree oil (*Melaleuca alternifolia*) also showed strong activity [124, 125]. Oils rich in limonene, sabinene, linalool, and terpinen-4-ol, such as those from *Citrus reshni* and *Fortunella margarita*, inhibited H5N1, while *Lippia citrodora* and *L. alba* oils rich in geranial, neral, and carvone suppressed Yellow fever virus at low IC_{50} values [61, 126, 127]. *Melissa officinalis* essential oil displayed potent inhibition of HSV-1 and HSV-2 [25], and rosemary essential oil (1,8-cineole, α-and β-pinene, rosmarinic acid) inhibited both herpes and hepatitis A viruses.

Essential oils have also gained attention against coronaviruses. *Laurus nobilis*, *Thymus orientalis*, *Juniperus oxycedrus*, and *Rosmarinus officinalis* EOs inhibited SARS-CoV and SARS-CoV-2, while *Origanum vulgare* compounds (carvacrol, thymol) were effective against RSV and COVID-19 (Table 3) [124–132]. Mechanistically, essential oil lipophilic components can integrate into viral envelopes, disrupting membrane fluidity, or directly bind viral proteins.

Molecular docking confirmed that eucalyptol (*Eucalyptus spp.*, *Mentha piperita*) can inhibit SARS-CoV-2 proteases while modulating inflammatory mediators (IL-6, TNF-α, IL-8) *via* epigenetic regulation [129, 133]. Similarly, trans-anethole (fennel), cinnamaldehyde (cinnamon), and garlic essential oil constituents interact with viral Mpro and host ACE2 receptor, suggesting therapeutic potential against COVID-19 [131, 134] (Table 3). Overall, the chemical diversity and multitargeted mechanisms of essential oils highlight them as promising natural antivirals, though further pharmacokinetic and clinical investigations remain essential.

3.12 Antiviral potential of terpenoids

Terpenoids have shown significant antiviral activity against various viral infections, including influenza, SARS-CoV-2, hepatitis, and rotavirus. Influenza viruses, responsible for seasonal epidemics, have been targeted by compounds such as glycyrrhizin (1) and its derivatives, which exhibit broad-spectrum antiviral effects [15, 135]. Additionally, terpenoids like hollongdione, lup-12,20(29)-diene, and β-amyrin acetate from *Euphorbia leucocephala* display strong anti-influenza potential. For SARS-CoV-2, terpenoids like artemisinins (arteannuin B, artesunate) and essential oils from *Origanum vulgare* and *Cannabis sativa* have shown promise in reducing infectivity [128, 129]. Terpenoids also exhibit efficacy against HBV and HCV, with compounds like astragaloside IV and oleanolic acid demonstrating antiviral effects by inhibiting viral replication and enhancing immune responses [136]. Lastly, terpenoids such as 2α-hydroxyursolic acid and ursolic acid have been shown to inhibit rotavirus replication and stimulate immune responses, providing potential therapeutic options for viral enteritis [29, 137]. These findings underline the diverse and potent antiviral properties of terpenoids, highlighting their therapeutic potential in combating viral infections. Terpenoids process strong antiviral activity against a broad range of human and animal viruses. Their varied structural and chemical characteristics present promising avenues for the development of new antiviral agents. Different classes of terpenoids, such as monoterpenes, sesquiterpenes, diterpenes, and triterpenes, show significant inhibitory effects on viral replication and entry processes.

3.13 Natural metabolites as broad-spectrum antiviral agents: A review of computational and mechanistic approaches

Natural bioactive metabolites, such as flavonoids, terpenoids, alkaloids, and polyphenols, have been shown through molecular docking and molecular dynamics (MD) studies to have conserved mechanistic patterns that can inhibit viral replication across a broad range of pathogenic viruses. Flavonoids like rutin, quercetin, myricetin, and baicalein bind to the main protease (Mpro/3CLpro) catalytic dyad (Cys145, His41) and other residues (Gly143, Ser144, Glu166, Met165). MD trajectories show that π–π stacking and hydrophobic contacts stabilize the complex, preventing polyprotein processing and decreasing loop flexibility [136, 137]. EGCG and baicalin also target the SARS-CoV-2 papain-like protease (PLpro), which interacts with hydrophobic pockets and the catalytic triad (Cys111, His272, Asp286) to suppress immune evasion and deubiquitination [138].

To stop viral RNA elongation, RNA-dependent RNA polymerase (RdRp) inhibitors like luteolin, hesperidin, and curcumin create hydrogen bonds with active site residues (Asp618, Asp623, Asp760, Asp761) [137].

Table 2 Antiviral activity of alkaloids

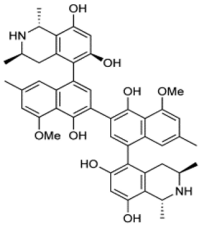
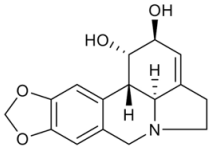
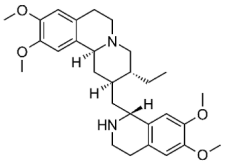
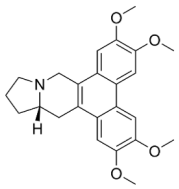
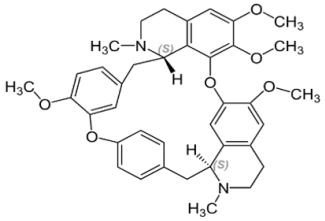
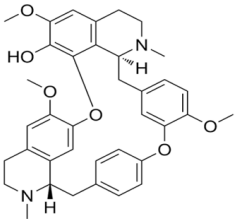
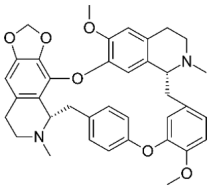
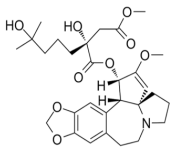
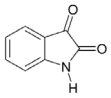
Alkaloid		Occurrence (Plant source)	Anti-viral activity/Target	References
Michellamine B		*Ancistrocladus korupensis*	HIV (Inhibits fusion & syncytium formation)	[115]
Lycorine		*Lycoris radiata*	SARS-CoV, HCoV-OC43, MERS-CoV, HCoV-NL63	[117]
Emetine		*Carapichea ipecacuanha*	Broad-spectrum: SARS-CoV, HCoV-OC43, MERS-CoV, HCoV-NL63, ZIKV, Ebola, DENV, BPXV, BHV-1, NDV	[118–120]
Tylophorine		*Tylophora indica*	SARS-CoV (Inhibits RNA replication *via* JAK2/NF-κB)	[116, 121]
Tetrandrine		*Stephania tetrandra*	HCoV-OC43 replication	[122]
Fangchinoline		*Stephania tetrandra*	HCoV-OC43 replication	[122]
Cepharanthine		*Stephania tetrandra*	HCoV-OC43 replication	[122]
Homoharringtonine		*Cephalotaxus hainanensis*	Human and animal coronaviruses	[106, 118]
Isatin		*Strobilanthes cusia*, *Isatis tinctoria*, *Couroupita guianensis*, *Calanthe discolor*	SARS-CoV 3CLpro, rhinovirus	[106]

Table 3 Antiviral activity of essential oils

Plant species	Main essential oil compound	Effectiveness against virus	References
Cinnamomum zeylanicum	Eugenol (75–85%), linalool (1.6–8.5%), (E)−cinnamaldehyde (0.6–1.5%), (E)−cinnamyl acetate (0.7–2.6%), benzyl benzoate (0.1–8.3%) and *β*-caryophyllene (0.5–6.7%)	(H1N1)	[124, 125]
Lavandula angustifolia Mill.	Linalyl acetate (37–43.6%), linalool (19.7–39%), geraniol (≤ 9%), *β*-caryophyllene (≤ 5%), terpinene−4−ol (≤ 15%), lavandulol (up to 1.5%), lavandulyl acetate (≤ 5%), 1,8-cineole (≤ 4%), and borneol (≤ 6%)	(H1N1)	[127]
Citrus bergamia	Limonene (37.2%), linalyl acetate (30.1%), linalool (8.8%), *γ*-terpinene (6.8%) and *β*-pinene (2.8%)	H1N1 SARS-CoV19	[124, 125]
Thymus vulgaris L.	Thymol (40.5%), *p*-cymene (23.6%), carvacol (3.2%), linalool (5.4%), *β*-caryophyllene (2.6%) and terpinen-4-ol (0.7%)	(H1N1)	[124, 125]
Melaleuca alternifolia	Terpinen-4-ol (30–48%), *γ*-terpinene (10–28%), *α*-terpinene (5–13%), 1,8-cineole (≤ 15%), terpinolene (1.5–5%), *p*-cymene (0.5–12%), *α*-pinene (1–6%), and *α*-terpineol (1.5–8%)	(H1N1)	[124, 125]
Fortunella margarita (Lour.)	*α*-terpineol (55.5%), carvone (5.7%), carveol (5.5%), *γ*-muurolene (5.5%), and citronellal (5.0%)	H5N1	[126, 127]
Citrus reshni Hort ex Tan. (leaf essential oil)	Sabinene (40.5%), linalool (23.3%), and terpinen-4-ol (8.3%)	H5N1	[128]
Lippia citriodora Kunth (syn. *Aloysia citriodora* Palau)	Geranial (19%), neral (15.6%), limonene (10.7%), and 1,8-cineole (5 %)	Yellow fever (YFV)	[129]
*Lippia alb*a (Mill.)	Carvone (≈ 40%), limonene (30.6%), and bicyclosesquiphellandrene (8.9%)	Yellow fever (YFV)	[129]
Juniperus oxycedrus	*α*-pinene (27.4%) and *β*-myrcene (≈ 19%). Other recognized compounds were *α*-phellandrene (7%), limonene (≈ 7%), epibicyclosesquiphellandren (≈ 2%) and *δ*-cadinene (≈ 2%).	SARS-CoV19	[130]
Laurus nobilis	*β*-ocimene,1,8-cineole, *α*- and *β*-pinene	SARS-CoV19	[131]
Eucalyptus spp.	Eucalyptol, 1, 8-Cineole (55%), Spathulenol (≈ 7%) and *α*-Terpineol (5.5%)	Inhibited HSV by about >80%, SARS-CoV19	[131]
Foeniculum vulgare Mill.	Trans-anethole, estragole, limonene, fenchone, *α*-pinene, *y*-terpinene, and myrcene	SARS-CoV19	[129, 131]
Mentha piperita	Menthol (7–48%), menthone (20–46%), menthyl acetate (3–10%), menthofuran (1–17%) and 1, 8-cineol (3–6%)	Antiviral effects against HSV1 at 0.025–0.8 µg/m	[132]
Syzygium aromaticum	Eugenol (69.4%), Eugenol acetate (10.8%), Tyranton (7.8%) Caryophyllene (≈ 7%),	SARS-COV19	[130]
Rosmarinus officinalis L.	1,8-cineol (33–38%), camphor (13.6–18%), *α*-pinene (≈ 9%), *α*-terpineol (6.8–8.8 %), camphene (5–5.6%), borneol (4–5.5%), limonene (3.2–3%) and *p*-cymene (2.4–3%)	HSV-1 SARC-CoV-2.	[130]

Meanwhile, limonoids and terpenoids such as limonin, deacetylnomilin, β-sitosterol, and silibinin interact with residues Tyr453, Arg403, Gln493, Gly496, and Asn501 to engage the spike receptor-binding domain (RBD) and obstruct ACE2 binding and conformational changes necessary for viral entry [139].

Comparable mechanisms are observed in Influenza A virus, where flavonoids such as quercetin, baicalein, catechin, and chlorogenic acid interact with neuraminidase residues (Glu119, Asp151, Arg371, Tyr406) and hemagglutinin (Tyr98, His183, Glu190, Gln226), impairing both viral release and entry, while quercetin-3-rhamnoside (Q3R) binds the M2 ion channel via hydrophobic interactions and π–π stacking with His37, inhibiting proton transport necessary for uncoating [93, 140].

In HIV-1, biflavonoids such as amentoflavone and flavonols like quercetin interact with the reverse transcriptase NNRTI pocket (Lys101, Tyr181, Tyr188, Trp229) to block polymerase activity, whereas alkaloids such as berberine and lycorine engage the protease catalytic dyad (Asp25–Asp25′) and flap residues Gly27, Thr26, preventing polyprotein cleavage. Additionally, EGCG binds the gp120 envelope glycoprotein (Asn276, Asp368, Lys421), blocking CD4 receptor engagement and viral entry [141] (Table 4). For Hepatitis C virus (HCV), silibinin and luteolin inhibit NS3/4A protease (His57, Asp81, Ser139) and NS5B polymerase (Asp225, Asp318, Asp319, Cys366), disrupting polyprotein cleavage and RNA polymerization [142], whereas in HBV, rutin and quercetin interact with polymerase residues (Tyr63, Lys65, Asp205) to block reverse transcription [143] (Table 4). In Dengue virus, flavonoids including naringenin, hesperetin, and luteolin target the NS2B-NS3 protease catalytic triad (His51, Asp75, Ser135) and NS5 polymerase (Lys46, Asp146, Asp533, Lys741) to inhibit polyprotein processing and RNA synthesis [144] (Table 4, Fig. 4). Similarly, in Chikungunya virus, luteolin and kaempferol bind nsP2 protease residues (Cys478, His548) to reduce replication, while in ZIKV, EGCG and curcumin interact with NS5 polymerase (Asp540, Asp668, Asn612) and the envelope protein (Glu393, Lys394, Gly395) to block RNA elongation and host-cell fusion [144] (Table 4, Fig. 4).

In HSV-1 and HSV-2, kaempferol, luteolin, and EGCG target DNA polymerase (Asp715, Asp886) and thymidine kinase (Glu83, Asp162, Arg163), inhibiting DNA synthesis and nucleoside phosphorylation, thereby impeding viral replication [145] (Table 4).

Across all these viral systems, recurring mechanistic patterns emerge, including hydrogen bonding to catalytic or conserved residues, π–π stacking and hydrophobic stabilization, steric blockade of active sites or receptor interfaces, and ligand-induced modulation of protein flexibility or oligomerization. Computational free-energy calculations (MM-GBSA/MM-PBSA) and ADMET predictions further prioritize compounds with strong binding, favorable pharmacokinetics, and low toxicity, highlighting natural metabolites as promising broad-spectrum antiviral scaffolds (Fig. 4).

3.14 Pharmacokinetic and drug-likeness evaluation of natural antivirals

Since they can target viral entry, replication, and host immune modulation, natural phenolic compounds and constituents of essential oils are becoming more widely acknowledged as broad-spectrum antiviral agents. But their pharmacokinetic characteristics frequently restrict systemic efficacy, necessitating a thorough assessment for drug-likeness and bioavailability.

With molar mass M ~302 g/mol, quercetin is a flavonol that conforms to Lipinski's rule of five and exhibits a high binding affinity for viral enzymes such as influenza neuraminidase, HCV polymerase, and SARS-CoV-2 Mpro, which inhibits viral entry and replication [146, 147]. Notwithstanding these encouraging properties, quercetin has a poor oral bioavailability, rapid phase II metabolism (glucuronidation, sulfation), and plasma concentrations that are frequently insufficient to produce antiviral effects [148].

By preventing viral replication and strengthening antioxidant defenses, rosmarinic acid, a caffeic acid ester, has antiviral properties against the dengue, chikungunya, and pseudorabies viruses [149, 150]. However, due to its large topological polar surface area and high polarity, it has a low intestinal permeability and is cleared quickly, which limits its systemic distribution [151]. In contrast, essential oil constituents are typically small and lipophilic, allowing for favorable drug-likeness profiles and good gastrointestinal absorption. Structurally related monoterpenes, thymol and carvacrol (M ~150 g/mol), exhibit antiviral properties against respiratory pathogens and herpesviruses mainly by inhibiting adsorption and disrupting the viral lipid envelope [152, 153]. Persistence in plasma is decreased by the glucuronide/sulfate conjugates produced by their quick liver metabolism (phase I oxidation, phase II conjugation) [9]. Due to its short half-life, dose-dependent toxicity, and volatility, eugenol, a phenylpropanoid, exhibits strong

Table 4 Natural bioactive compounds targeting viral proteins: Binding interactions and mechanistic insights from molecular docking studies

Virus	Target protein(s)	Representative natural compound(s)	Key interacting residues / Binding features	Mechanistic effect	References
SARS-CoV-2	Main protease (Mpro/3CLpro)	Rutin, Quercetin, Myricetin, Baicalein	H-bonds with Cys145, His41; additional contacts with Gly143, Ser144, Glu166, Met165; π–π stacking with His41	Blocks polyprotein cleavage; stabilizes loops; reduces catalytic flexibility	[136, 137]
	Papain-like protease (PLpro)	EGCG, Baicalin	H-bonds with Cys111, His272, Asp286; hydrophobic contacts	Inhibits deubiquitinating activity; reduces replication and immune evasion	[138]
	RdRp	Luteolin, Hesperidin, Curcumin	Active site residues Asp618, Asp623, Asp760, Asp761	Blocks RNA elongation; inhibits viral genome replication	[137]
	Spike RBD	Limonin, Deacetylnomilin, β-Sitosterol, Silibinin	H-bonds with Tyr453, Arg403, Gln493, Gly496, Asn501; hydrophobic contacts with Leu455, Phe486	Blocks ACE2 binding; impairs conformational changes required for entry	[139]
Influenza A	Neuraminidase (NA)	Quercetin, Baicalein, Catechin, Chlorogenic acid	H-bonds with Glu119, Asp151, Arg371, Tyr406; stacking with Trp178	Prevents sialic acid cleavage; blocks viral release	[140]
	Hemagglutinin (HA)	Quercetin, Luteolin	Residues Tyr98, His183, Glu190, Gln226	Blocks HA–sialic acid interaction; prevents viral entry	[140]
	M2 Ion Channel	Quercetin-3-rhamnoside (Q3R)	Hydrophobic and π–π stacking with His37	Inhibits proton transport → blocks uncoating	[93]
HIV-1	Reverse Transcriptase (NNRTI pocket)	Amentoflavone, Quercetin, Resveratrol	H-bonds with Lys101, Tyr181, Tyr188, Trp229	Blocks polymerase activity	[142]
	Protease	Berberine, Lycorine	Catalytic dyad Asp25– Asp25′; flap residues Gly27, Thr26	Prevents polyprotein cleavage	[141]
	gp120	EGCG	Asn276, Asp368, Lys421	Blocks CD4 binding → inhibits entry	[141]
HCV	NS3/4A Protease	Silibinin, Quercetin, Baicalein	Catalytic triad His57, Asp81, Ser139	Inhibits polyprotein cleavage	[142]
	NS5B Polymerase	Silymarin derivatives, Luteolin	Active site residues Asp225, Asp318, Asp319, Cys366	Blocks RNA synthesis	[142]
HBV	Polymerase	Rutin, Quercetin	Tyr63, Lys65, Asp205	Inhibits reverse transcription	[143]
Dengue	NS2B-NS3 Protease	Naringenin, Hesperetin, Luteolin	Catalytic triad His51, Asp75, Ser135	Blocks polyprotein processing	[143]
	NS5 Polymerase	Baicalein, Curcumin	Lys46, Asp146, Asp533, Lys741	Inhibits RNA polymerization	[143]
Chikungunya	nsP2 Protease	Luteolin, Kaempferol	Cys478, His548	Inhibits protease activity → reduces replication	[144]
Zika	NS5 Polymerase	EGCG, Curcumin	Asp540, Asp668, Asn612	Blocks RNA elongation	[144]
	Envelope Protein (E)	Baicalein, Apigenin	Glu393, Lys394, Gly395	Prevents host-cell fusion	[144]
HSV-1/ HSV- 2	DNA Polymerase	Luteolin, Kaempferol, EGCG	Asp715, Asp886	Inhibits DNA synthesis	[145]
	Thymidine Kinase	Quercetin, Morin	Glu83, Asp162, Arg163	Blocks nucleoside phosphorylation	[145]

antiviral activity against influenza and other respiratory viruses by binding to viral proteins and destabilizing viral envelopes [154]. A key component of cinnamon oil, cinnamonaldehyde, disrupts the structural protein integrity and viral replication of influenza and coronaviruses, but its instability and quick clearance jeopardize systemic delivery; it has been demonstrated that nanoemulsions and microcapsules greatly increase its stability and antiviral efficacy [127] (Table 5, Fig. 3).

Although limonene and linalool work together in essential oil mixtures to destabilize membranes and exert antiviral activity against enveloped respiratory viruses, their rapid cytochrome P450 enzymes (CYP)-mediated metabolism and low aqueous solubility limit their bioavailability [154].

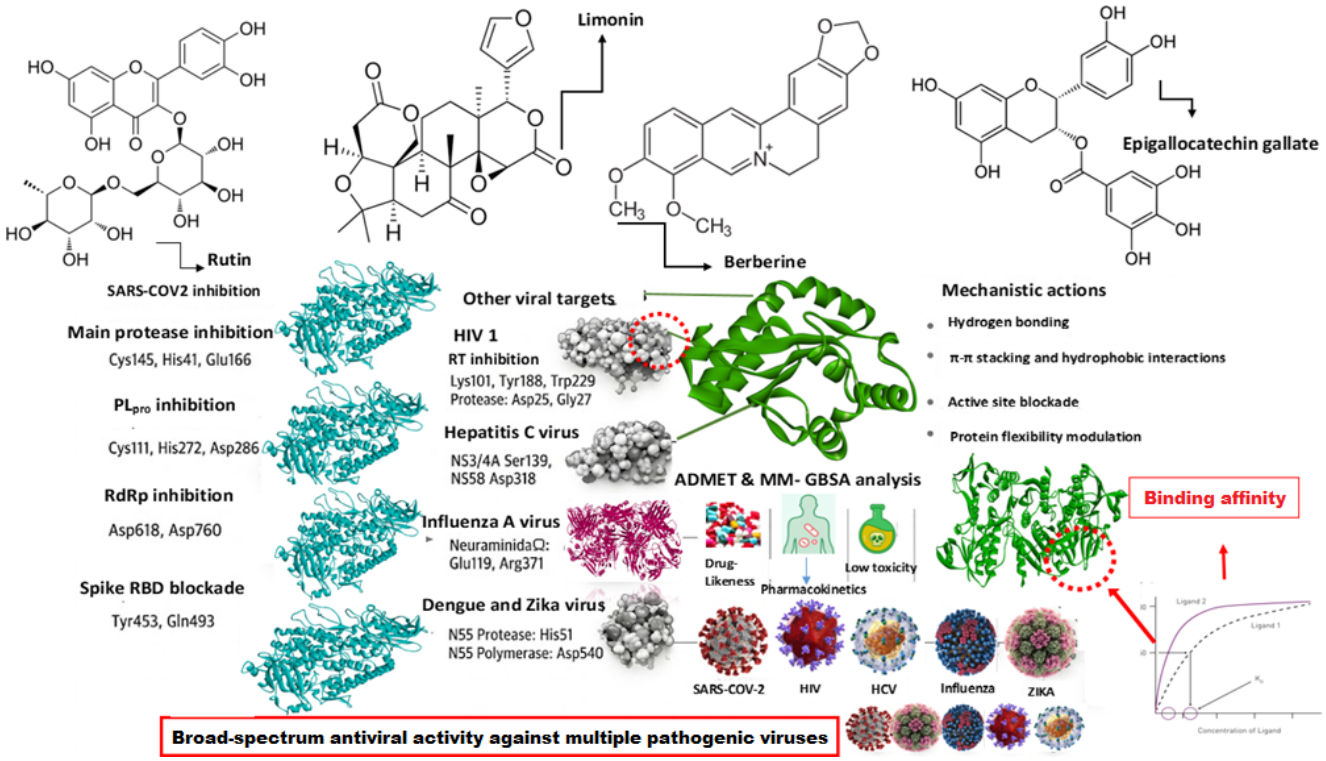


Fig. 4 Natural metabolites as broad-spectrum antiviral agents: molecular docking, dynamics and mechanistic insights (Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2); Papain-like protease (PLpro); RNA-dependent RNA polymerase (RdRp); receptor-binding domain (RBD); Cysteine (Cys); Histidine (His); Glutamic acid (Glutamate) (Glu); Aspartic acid (Aspartate) (Asp); Tyrosine (Tyr); Glutamine (Gln); Lysine (Lys); Tryptophan (Trp); Serine (Ser); Human immunodeficiency virus 1 (HIV 1); Reverse Transcriptase (RT); Non-structural proteins (NS3/4A, NS5B, NS5); Absorption, distribution, metabolism, excretion, and toxicity (ADMET); Molecular mechanics generalized born surface area (MM-GBSA))

While polyphenols, like RA, exhibit borderline drug-likeness because of their high polarity and low predicted permeability, *in silico* ADME/Tox platforms like SwissADME and pkCSM confirm that essential oil monoterpenes typically meet Lipinski and Veber rules and predict high gastrointestinal absorption [155].

Advanced formulation techniques can help to lessen these restrictions. It has been reported that the encapsulation quercetin, RA, and cinnamonaldehyde into solid lipid nanoparticles, liposomes, or nanoemulsions improve their solubility, plasma stability, and bioavailability, which increases their *in vivo* antiviral efficacy [156, 157]. While

Table 5 Broad-spectrum antiviral potential of natural compounds (pharmacokinetic and drug-likness)

Compound	Main viral target/mechanism	Antiviral spectrum	Key pharmacokinetic limitation	References
Quercetin	Inhibits proteases, polymerases, spike proteins	SARS-CoV-2, HCV, influenza	Extensive phase II metabolism → low oral bioavailability	[145–147]
Rosmarinic acid	Inhibits replication, modulates antioxidants	Dengue, chikungunya, pseudorabies	High polarity, poor membrane permeability, rapid clearance	[147–149]
Thymol	Disrupts viral envelope, inhibits adsorption	Herpesviruses, enveloped viruses	Rapid metabolism, short systemic persistence	[150–152]
Carvacrol	Membrane disruption, enzyme interference	HSV, respiratory viruses	Hepatic metabolism, conjugation	[150–152]
Eugenol	Envelope destabilization, viral protein binding	Influenza, respiratory viruses	Volatility, toxicity, short half- life	[153]
Cinnamaldehyde	Protein inactivation, envelope destabilization	Influenza, coronaviruses	Instability, rapid clearance; improved with nanoemulsions	[154]
Linalool	Envelope disruption	Broad-spectrum (essential oil mixtures)	Low solubility, fast clearance	[127]
Limonene	Envelope disruption, synergistic activity	Enveloped respiratory viruses	Low solubility, CYP metabolism	[127]

phenolic and essential oil metabolites collectively exhibit a variety of mechanisms, from host antioxidant and immunomodulatory activity to direct enzyme inhibition and envelope disruption, their clinical translation as antivirals necessitates overcoming pharmacokinetic limitations through optimized delivery systems.

4 Conclusions

Based on a thorough literature search that included molecular docking, molecular dynamics, and ADME/Tox studies, we assessed the antiviral potential of plant-derived natural products, concentrating on phenolic compounds, alkaloids, essential oils, and terpenoids. According to our theoretical findings, plants produce and store a variety of secondary metabolites that interact with important viral targets, such as Mpro/3CLpro, PLpro, RdRp, spike glycoprotein, and ACE2. Viral entry, replication, and assembly are inhibited by flavonoids (quercetin, kaempferol, naringenin, EGCG), phenolic acids (caffeic acid, gallic acid, ellagic acid), alkaloids (emetine, lycoline), and components of essential oils (eucalyptol, thymol, carvacrol).

Despite favorable druglikeness, most natural antivirals face low oral bioavailability, rapid metabolism, and high polarity. We achieved the aim of providing a theoretical framework for rational selection of plantbased antivirals. Practical perspectives are as follows stepbystep:

1. ***In vitro* validation:** Test the most promising candidates against SARS-CoV-2, influenza, HIV, and HSV using cellular assays.
2. **SAR studies:** Optimize lead compounds by changing key functional groups (hydroxyl groups, glycosylation structures) to improve potency and stability.
3. **Recipe development:** Encapsulate poorly bioavailable compounds into solid lipid nanoparticles, liposomes, or nanoemulsions to improve their solubility and stability in plasma.
4. **Synergistic combinations:** Test combinations of phenolic compounds and essential oil monoterpenes to achieve additive or synergistic antiviral effects.
5. **Preclinical pharmacokinetics:** Evaluation of oral bioavailability, tissue distribution, and safety profile in animal models.
6. **Clinical trials:** Randomized controlled trials favor natural products that are FDA or generally recognized as safe (GRAS) approved.

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