Molecular Nutrition & Food Research

WILEY-VCH

Molecular Nutrition & Food Research

REVIEW OPEN ACCESS

The Antiviral Activity of Polyphenols

Markus Burkard[1] | Alban Piotrowsky[1] | Christian Leischner[1] | Katja Detert[1] | Sascha Venturelli[1,2] | Luigi Marongiu[1]

[1]Department of Nutritional Biochemistry, University of Hohenheim, Stuttgart, Germany | [2]Department of Vegetative and Clinical Physiology, Institute of Physiology, University of Tuebingen, Tuebingen, Germany

Correspondence: Luigi Marongiu (luigi.marongiu@uni-hohenheim.de)

Received: 17 December 2024 | **Revised:** 27 February 2025 | **Accepted:** 10 March 2025

Funding: This study was supported by a grant from the Dr. Hans Fritz Stiftung (funding 3140080501) to A.P.; PASCOE pharmazeutische Praeparate GmbH (grant no. D.31.15100 and D.32.22506) to M.B. and S.V.; and Ministry of Rural Affairs and Consumer Protection Baden-Wuerttemberg (AZ: 34–9185.90-1) to L.M. and M.B.

Keywords: antivirals | enveloped virus | polyphenols

ABSTRACT

Polyphenols are secondary metabolites produced by a large variety of plants. These compounds that comprise the class of phenolic acids, stilbenes, lignans, coumarins, flavonoids, and tannins have a wide range of employment, from food production to medical usages. Among the beneficial applications of polyphenols, their antiviral activity is gaining importance due to the increased prevalence of drug-resistant viruses such as herpes and hepatitis B viruses. In the present review, we provide an overview of the most promising or commonly used antiviral polyphenols and their mechanisms of action focusing on their effects on enveloped viruses of clinical importance (double-stranded linear or partially double-stranded circular DNA viruses, negative sense single-stranded RNA viruses with nonsegmented or segmented genomes, and positive sense single-stranded RNA viruses). The present work emphasizes the relevance of polyphenols, in particular epigallocatechin-3-gallate and resveratrol, as alternative or supportive antivirals. Polyphenols could interfere with virtually all steps of viral infection, from the adsorption to the release of viral particles. The activity of polyphenols against viruses is especially relevant given the risk of widespread outbreaks associated with viruses, remarked by the recent COVID-19 pandemic.

1 | Introduction

Polyphenols are secondary metabolites produced by a wide range of plants that have been employed for centuries for their beneficial properties in popular medicine [1]. In addition, polyphenols are used to prepare food and beverages to maintain the organoleptic properties of the preparations, making these molecules particularly suitable for the food processing market [2]. Polyphenols are derivatives of phenol (or benzenol), which is an aromatic compound formed by phenyl (⏣) and hydroxyl (−OH) groups. More than 8000 polyphenols have been described so far, subdivided into six classes (Figure 1 and Table 1) [3]. A

Abbreviations: ACE2, angiotensin-converting enzyme 2; AMR, antimicrobial-resistant microbes; BZLF1, BamHI Z fragment leftward open reading Frame 1; CBH, chronic B hepatitis; CC_{50}, 50% cytotoxic concentration; CDK-9, cyclin-dependent kinase 9; CHIKV, chikungunya virus; DENV, dengue virus; EBOV, Ebola virus; EC_{50}, 50% effective concentration; EGCG, epigallocatechin-3-gallate; FLUV, influenza virus; FXR, farnesoid-X-receptor; GI, gastrointestinal; HA, hemagglutinin; HBcAg, HBV core antigen; HBeAg, HBV extracellular antigen; HBsAg, HBV surface antigen; HBV, hepatitis B virus; HBx, hepatitis B viral protein X; HCoV, human coronavirus; HCV, hepatitis C virus; HHV, human herpesvirus; HO-1, heme oxygenase-1; HVEM, herpesvirus entry mediator; IC_{50}, 50% inhibitory concentration; ICP22, infected-cell protein 22; IE, immediate-early; IFN-I, type one interferon; IRF7, interferon regulatory Factor 7; ISG15, interferon-stimulated gene 15; JEV, Japanese encephalitis virus; LMP-1, latent membrane protein 1; MERS-CoV, Middle East respiratory syndrome coronavirus; MeV, measles virus; M^{pro}, main protease; NA, neuraminidase; Neu5Ac, *N*-acetylneuraminic acid; NF-κB, nuclear factor kappa B; NS3, nonstructural protein 3; NTCP, Na^+/taurocholate cotransporter polypeptide; NTPase, nucleoside-triphosphatase; OAS3, 2′-5′-oligoadenylate synthetase 3; pg, pre-genomic; PGG, pentagalloylglucose; PKR, protein kinase RNA-activated; PL^{pro}, papain-like protease; RdRp, RNA-dependent RNA-polymerase; RNaseH, ribonuclease H; RpII, RNA polymerase II; RSV, respiratory syncytial virus; Rta, replication and transcription activation; RVFV, Rift Valley fever virus; SARS-CoV, severe acute respiratory syndrome coronavirus; SI, selectivity index; SLAM, signaling lymphocytic activation molecule; STAT1, signal transducer and activator of transcription 1; TCQA, 3,4,5-tri-*O*-caffeoylquinic acid; TFIID, transcription Factor II D; TGG, 1,2,3,6-tetragalloyl glucose; TI, therapeutic index; TLR3, toll-like receptor 3; VACV, vaccinia virus; VP16, viral protein 16; VSV, vesicular stomatitis Indiana virus; WNV, West Nile virus; XN, xanthohumol; ZIKV, Zika virus.

This is an open access article under the terms of the Creative Commons Attribution License, which permits use, distribution and reproduction in any medium, provided the original work is properly cited.

© 2025 The Author(s). *Molecular Nutrition & Food Research* published by Wiley-VCH GmbH

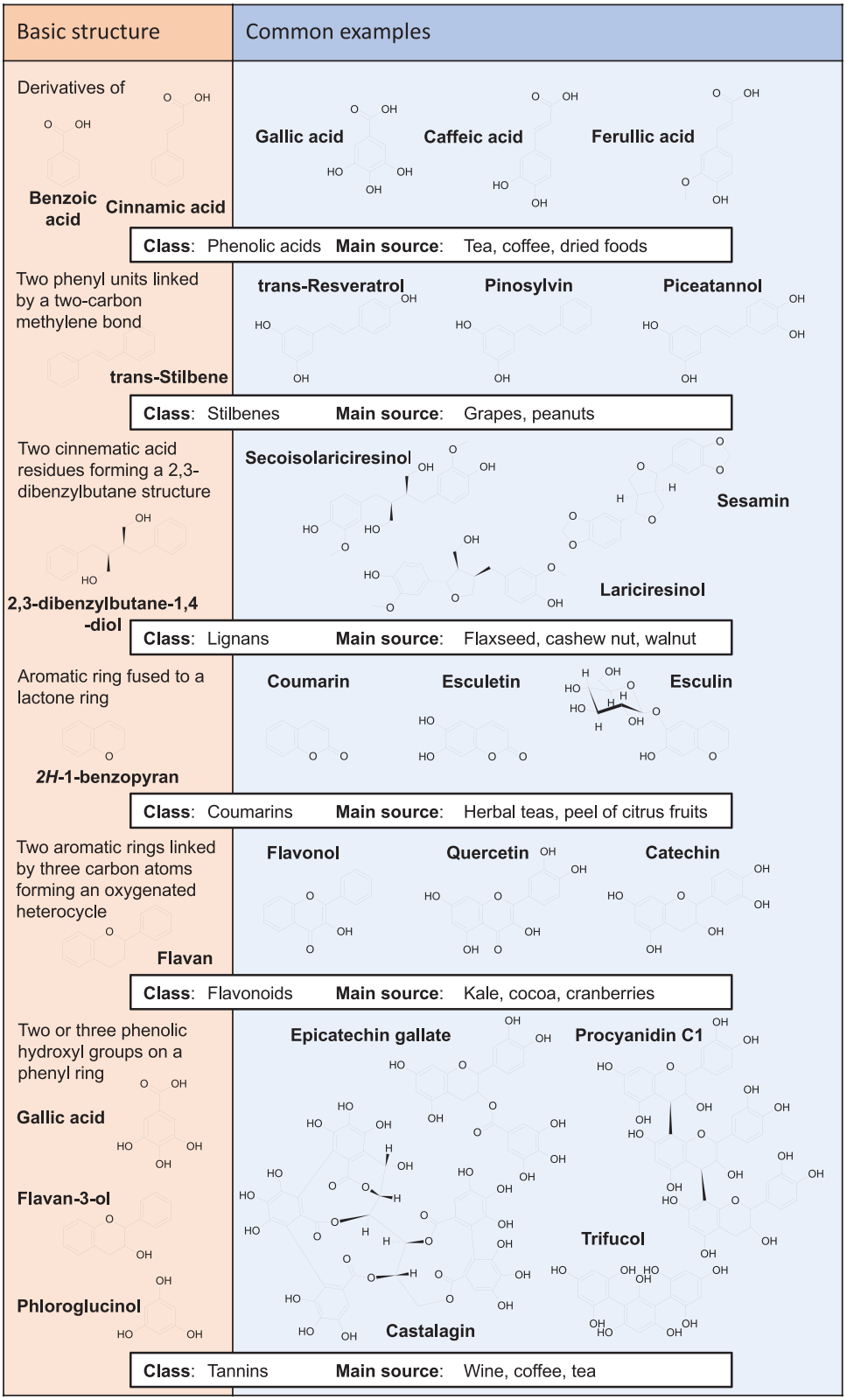


FIGURE 1 | Overview of polyphenols. The basic structure of polyphenols (left column) with some of the most common examples for each class (right column). The main dietary sources for the represented polyphenols are provided in the boxes underneath the structures.

TABLE 1 | Classes of polyphenols mentioned in the present review.

Class	Characteristics	Main dietary sources	Ref.
Phenolic acids	Derivates of benzoic acid or cinnamic acid	Tea, coffee, dried fruits	[170]
Stilbenes	Two phenyl units linked by a two-carbon methylene bond	Grapes, peanuts	[171]
Lignans	Two cinnamic acid residues forming a 2,3-dibenzylbutane structure	Flaxseed, cashew nut, walnut	[171, 172]
Coumarins	Aromatic ring fused to a lactone ring	Herbal teas, peel of citrus fruits	[173]
Flavonoids	Two aromatic rings linked by three carbon atoms forming an oxygenated heterocycle	Citrus fruits, chocolate, berries	[174]
Tannins	Two or three phenolic hydroxyl groups on a phenyl ring	Wine, coffee, tea	[175]

particularly relevant class of polyphenols is that of flavonoids, derivatives of the flavan ring [4]. In recent times, the properties of polyphenols have been investigated scientifically to apply them for applications ranging from immune modulation to antioxidant treatment and blood pressure management [5]. Moreover, polyphenols are attractive for their anti-bacterial properties due to the need for antibiotic alternatives following the increased spreading of antimicrobial-resistant microbes (AMR) [6]. Polyphenols also show antiviral activities.

Viruses are obligate endoparasitic microorganisms composed of a genome encapsulated in a proteinaceous shell [6]. Viruses display an enormous variability in terms of genomes (comprising nucleic acids made of either DNA or RNA, either single or double-stranded, with linear or circular molecules present as a single element or segmented into different entities) and morphologies (with or without an envelope, with either icosahedral or helical symmetry) [7]. Viruses are highly relevant not only for clinical reasons but also for their impact on agriculture and biodiversity [8].

It would be impossible to summarize the whole body of knowledge on the antiviral action of polyphenols, and there are several excellent reviews on the subject [7]. The present review will instead provide an overview of the most characterized molecular mechanisms involved in the hindrance of viral infection associated with the use of polyphenols, focusing on human pathogens belonging to enveloped viruses (Figure 2 and Tables 2, 3).

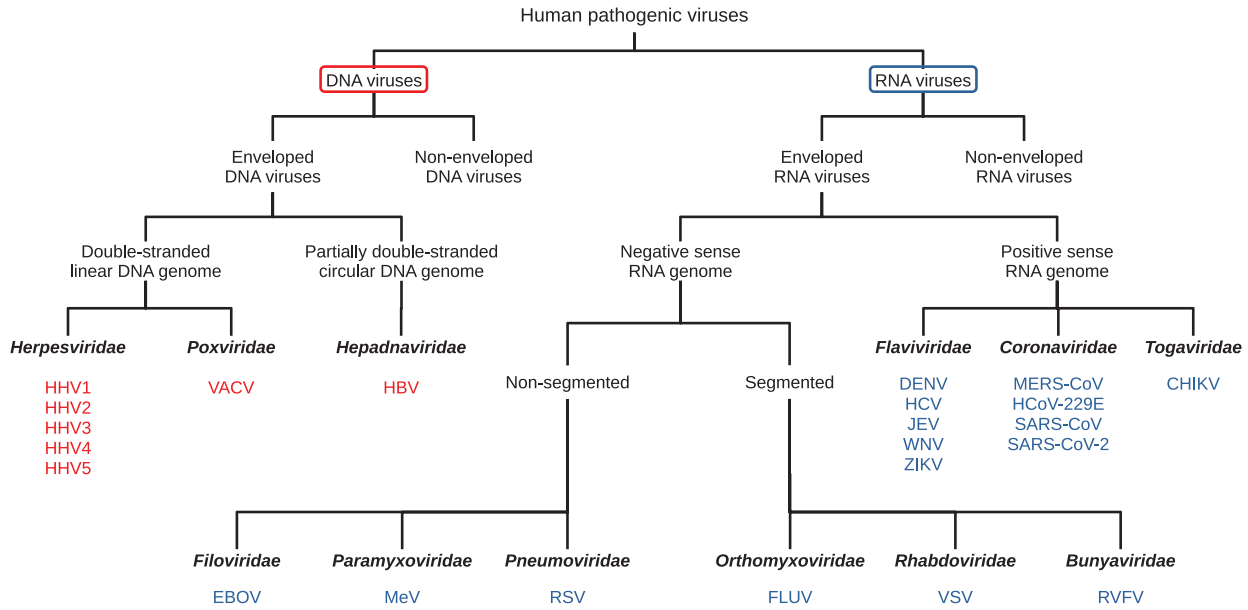


FIGURE 2 | Overview of the viruses reported in the present review. Viruses are stratified by genome (DNA or RNA), presence or absence of an envelope, and type of genome (single- or double-stranded, positive or negative sense). The families of the viruses reported in this review are indicated together with the species. CHIKV, chikungunya virus; DENV, dengue virus; EBOV, Ebola virus; FLUV, influenza virus; HBV, hepatitis B virus; HCoV, human coronavirus; HCV, hepatitis C virus; HHV, human herpesvirus; JEV, Japanese encephalitis virus; MERS-CoV, Middle East respiratory syndrome coronavirus; MeV, measles virus; RSV, respiratory syncytial virus; RVFV, Rift Valley fever virus; SARS-CoV, severe acute respiratory syndrome coronavirus; VACV, vaccinia virus; VSV, vesicular stomatitis Indiana virus; WNV, West Nile virus; ZIKV, Zika virus.

TABLE 2 | Summary of antiviral activity of polyphenols reported in the present review.

Compound	Group	Source	Dosage[a]	Virus	Genome[b]	Pathway affected	Ref.
Baicalin	Flavonoids	*Scutellaria baicalensis*	–	HBV	dsDNA	Replication	[69, 70]
		Radix scudellariae	–	HBV	dsDNA	Transcription	[71]
Caffeic acid	Phenolic acids	*Solanum melangena*	27.2 μM	HHV1	dsDNA	Transcription	[31]
Chebulagic acid	Tannins	*Terminalia chebula*	1.41 μg/mL	HHV2	dsDNA	Attachment	[26]
Chebulinic acid	Tannins	*Terminalia chebula*	0.06 μg/mL	HHV2	dsDNA	Attachment	[26]
Chlorogenic acid	–	–	–	EBOV	(–)RNA	Attachment	[90]
Curcumin	Curcuminoids	–	1.90 μM	ZIKV	(+)RNA	Virion structure	[176]
		–	3.89 μM	CHIKV	(+)RNA	Virion structure	[176]
		–	–	HCV	(+)RNA	Virion strucutre	[143]
EGCG	Flavonoids	*Camellia sinensis*	10 μM	HBV	dsDNA	Viral entry	[74]
		–	21.4 μM	ZIKV	(+)RNA	Viral entry	[129]
		Synthesized	0.73 μM	ZIKV	(+)RNA	Transcription	[131]
		Limonium densiflorum	19 μg/mL	FLUV	(–)RNA	Virion structure	[106]
		–	–	EBOV	(–)RNA	Attachment	[90]
Oleuropein	–	–	–	EBOV	(–)RNA	Attachment	[90]
Gallic acid	Phenolic acids	*Graptopetalum paraguayense*	0.92 μg/mL	HHV1 HHV2	dsDNA	Replication	[29]
Geraniin	Tannins	*Spondias mombin*		HHV1	dsDNA	Attachment	[27]
Ginkgolic acid	Phenolic acids	*Ginkgo biloba*		HHV1	dsDNA	Translation	[24]
		–	–	HHV5	dsDNA	Viral entry	[24]
		–	–	HHV1	dsDNA	Viral entry	[25]
Glycyrrhetinic acid	–	*Glycyrrhiza glabra*	0.13–0.56 μM	ZIKV	(+)RNA	NS1 inhibition	[132]
Honokiol	Lignans	*Magnolia* spp.	10.51 μg/mL	HHV1	dsDNA	Replication Transcription	[39]
Hyperoside	Flavonoids	*Abelmoschus manihot*	–	HBV	dsDNA	–	[65]
Imperatorin	Coumarin	*Angelica archangelica*	–	HHV1	dsDNA	Replication	[37]
Luteolin	Flavonoids	*Swertia macrosperma*	20 μM	HBV	dsDNA	–	[68]
		Synthesized	0.07 μM	FLUV	(–)RNA	Replication	[100]
Manassantin	Lignans	*Saurus chinensis*	12.96 μM	HHV4	dsDNA	Transcription	[177]
Miquelianin	–	–	–	EBOV	(–)RNA	Attachment	[90]
Pentagalloylglucose	Tannins	*Elaeocarpus sylvestris*	14.67 μg/mL	HHV3	dsDNA	Modulation c-Jun Transcription IE62	[42]
Phellopterin	Coumarin	*Angelica archangelica*	–	HHV1	dsDNA	Replication	[37]
Piceatannol	Stilbenes		–	HHV5	dsDNA	Transcription $P16^{INK4a}$ downregulation	[43]
Pinocembrin	Flavonoids	–	17.4 μM	ZIKV	(+)RNA	Replication Translation	[138]
		–	21.5 μM	CHIKV	(+)RNA		[138]
		–	39.0 μM	DENV	(+)RNA		[138]
Protocatechuic acid	Phenolic acids	*Hibiscus sabdariffa*	–	HHV1 HHV2	dsDNA	Replication	[30]

(Continues)

TABLE 2 | (Continued)

Compound	Group	Source	Dosage[a]	Virus	Genome[b]	Pathway affected	Ref.
Psiloxylon	–	*Psiloxylon mauritiitianum*	100 μg/mL	DENV ZIKV	(+)RNA	Attachment	[149]
Punicalagin	Tannins	*Punica granatum*	–	HHV2	dsDNA	Viral protease	[32]
Pyrogallol	–	Synthesized	30 μg/mL	FLUV	(–)RNA	Oxidative stress	[104]
Quercetin	Flavonoids	Synthesized	1.17 μM	ZIKV	(+)RNA	Transcription	[131]
		Synthesized	0.67 μM	FLUV	(–)RNA	Replication	[100]
		Rapanea melanophloeos	150 μM	FLUV	(–)RNA	IFN modulation	[102]
Quinin	–	Synthesized	150 μM	DENV	(+)RNA	Replication	[148]
Resveratrol	Stilbenes	Berries, legumes	–	HHV1	dsDNA	IE inhibition	[34]
			–	HHV2	dsDNA	Oxidative stress	[35]
		Vitis vinifera	0.9 μg/mL	HHV1	dsDNA	Replication	[38]
			–	HHV4	dsDNA	Transcription	[40]
			40 μg/mL	FLUV	(–)RNA	Transcription Nuclear exportation	[105]
		Synthesized	3.5–4.7 μM	VACV	dsDNA	Replication	[178]
Rosmarinic acid	Phenolic acids	–	30 μM	HBV	dsDNA	Replication	[78]
Rutamarin	Coumarins	*Ruta graveolens*	13.8 μM	HHV4	dsDNA	Replication Translation	[28]
Silymarin	–	Synthesized	100 μg/mL	CHIKV	(+)RNA	Replication	[134]
Syringic acid	Phenolic acids	*Graptopetalum paraguayense*	0.92 μg/mL	HHV1 HHV2	dsDNA	Replication	[29]
TCQA	–	*Ilex pubescens*	200 μM	FLUV	(–)RNA	IFN modulation	[103]
TGG	–	–	–	EBOV	(–)RNA	Attachment	[90]
Trans-ferulic acid	Phenolic acids	*Graptopetalum paraguayense*	0.92 μg/mL	HHV1 HHV2	dsDNA	Replication	[29]
Vanillic acid	Phenolic acids	*Graptopetalum paraguayense*	0.92 μg/mL	HHV1 HHV2	dsDNA	Replication	[29]
Wogonin	Flavonoids	*Scutellaria baicalnsis/radix*	–	HBV	dsDNA	–	[66, 67]
Xanthohumol	Chalcon	*Humulus lupulus*	162 μM	SARS-CoV-2	(+)RNA	Inhibition PL^{pro}	[156]

[a]Concentration used in the study, including IC_{50} or EC_{50}.
[b]Legend: ds = double-stranded; p = partial double-stranded; (+) = positive-strand; (–) = negative-strand.

TABLE 3 | Overview of the antiviral activity of polyphenols class.

Virus	Phenolic acid	Stilbenes	Lignans	Coumarins	Flavonoids	Tannins
Arboviruses	–	–	–	–	ZIKV	–
Coronaviruses	–	–	–	–	SARS-CoV-2	–
Filoviridae	EBOV	–	–	–	–	–
Hepadnaviruses	–	–	–	–	HBV	–
Herpesviruses	HHV1, HHV2	HHV1, HHV2	HHV1	HHV1	–	HHV1, HHV2
Poxviruses	–	VACV	–	–	–	–

2 | DNA Viruses

2.1 | Double-Stranded Linear DNA Viruses

2.1.1 | Overview

The group of double-stranded linear DNA viruses includes the *Herpesviridae* family, which is formed by three subfamilies, each containing clinically relevant genera (Figure 2): *Alphaherpesvirinae* with human herpes simplex virus (human herpesvirus [HHV]1 and HHV2) and varicellovirus (HHV3, previously known as varicella-zoster virus); *Betaherpesvirinae* with HHV5 (previously cytomegalovirus) and roseolovirus (HHV6 and HHV7); and *Gammaherpesvirinae* with lymphocryptovirus such as HHV4 (previously Epstein–Barr virus) [8]. The herpesviruses can cause localized mucocutaneous lesions, meningitis, and encephalitis (HHV1, HHV2) and are associated with various malignancies, including lymphomas like Hodgkin's disease (HHV4) [9]. Another relevant viral clade within the group is that of the poxviruses (*Poxviridae* family), with smallpox, monkeypox, and vaccinia virus (VACV) as the most clinically significant species [10].

The *Herpesviridae* share the feature of a large (over 150 kb in length) double-stranded DNA genome encapsulated into an icosahedral capsid further embedded into a proteinaceous tegument (called matrix in other viruses) and a phospholipid envelope [9]. The standard herpesvirus treatment is aciclovir, which interferes with the viral DNA polymerase [11]. Since resistance to this drug is becoming increasingly frequent, polyphenols have gained the spotlight as possible antiherpetic alternatives [12].

Attachment and entry of herpesviruses are best elucidated in HHV1; these steps are mediated by a complex of the surface glycoproteins gB, gD, gH, and gL (Figure 3) [13]. The entry process begins with binding the herpesvirus entry mediator (HVEM), a ubiquitous tumor necrosis factor receptor superfamily member [14]. The viral particle is internalized within endocytic vesicles and released into the cytoplasm [15]. The viral genomes are then released inside the nucleus [16], where the viral genes are transcribed by the cellular RNA polymerase II (RpII) [17]. Viral replication does not occur immediately; the virus establishes a latency phase. The tegument viral protein VP16 is an essential factor in this process: it forms a complex with the cellular transcription factor Oct-1 and the transcription Factor II D (TFIID) that directs RpII to the viral immediate-early (IE) promoters [18]. VP16 additionally promotes latency by facilitating heterochromatin formation within the viral chromosome [19]. VP16 also hampers the antiviral cellular response by downregulating the expression of type one interferon (IFN-I) [20]. Infected-cell protein 22 (ICP22) also hinders IFN-I [21]. In addition, viral protein 16 (VP16) facilitates the assembly of new capsids, which are then released by budding into the perinuclear space as enveloped virions [22].

Herpesviruses also counteract the apoptosis activated by viral infection, a feature particularly relevant in HHV4. For instance, the latent membrane protein 1 (LMP-1) is a *trans*-activator of several cellular pathways, such as the nuclear factor kappa B (NF-κB) that inhibits the apoptotic signal [23].

2.1.2 | Polyphenol Applications

It has been reported that ginkgolic acid from *Ginkgo biloba* impaired HHV1, HHV4, and HHV5 entry by hindrance of gB activity [24, 25], whereas geraniin from *Spondias mombin* and chebulagic/chebulinic acid from *Terminalia chebula* inhibited HHV1 and HHV2 attachment to host cells, respectively [26, 27]. Ginkgolic acid also inhibited HHV1 proteins involved in the translation step, thus hampering virion production [24]. Protein synthesis in HHV4 was inhibited by rutamarin from *Ruta graveolens* [28]. In contrast, a plethora of polyphenol molecules such as protocatechuic acid from *Hibiscus sabdariffa* as well as *trans*-ferulic acid, vanillic acid, syringic acid, and gallic acid from *Graptopetalum paraguayense* could interfere with the replication of HHV1 and HHV2 genomes, mainly through the hindrance of DNA polymerase activity [29, 30].

Polyphenols from *Solanum melangena* were shown to inhibit viral DNA replication by downgrading the expression of HHV1 gB [31]. Punicalagin from *Punica granatum* inhibited HHV2 protease [32]. HHV1 was also hampered by resveratrol, one of the main active molecules in grapes (*Vitis vinifera*), which has antiinflammatory, immune-modulatory, and antiaging capabilities [33]. This polyphenol has been suggested to inhibit the transcription of HHV1 viral IE genes [34] and, in HHV2, modulate the expression of NF-κB and cyclin-dependent kinase 9 (CDK-9) [35]. A preparation from *Geranium sanguineum* inhibited HHV1 and HHV2 with a 50% inhibitory concentration (IC_{50}) of 3.6–6.2 μg/mL [36].

Resveratrol extracted from grape cane (*V. vinifera*), as well as imperatorin and phellopterin from *Angelica archangelica*, could also inhibit HHV1 replication [37, 38]. Downregulation of HHV1 ICP27 and VP16 gene expression was demonstrated using honokiol from *Magnolia* spp., boosting aciclovir activity [39]. Resveratrol could also downregulate the expression of HHV4 replication and transcription activation (Rta) [40]. Further, resveratrol inhibited viral replication and load in piglets as measured by nasal swabs and in brain tissue. Moreover, serum IFN-III was also elevated [41].

Pentagalloylglucose (PGG) from *Elaeocarpus sylvestris* inhibited HHV3 replication by downgrading the viral-driven activation of c-Jun signaling pathway and the expression of the viral modulator IE62 [42]. Piceatannol could block the expression of HHV5 IE genes and downregulate the viral-driven activation of $p16^{INK4a}$ [43]. Massantin from *Saurus chinensis* can inhibit HHV4 BamHI Z fragment leftward open reading Frame 1 (BZLF1) expression [56].

2.2 | Partially Double-Stranded Circular DNA Viruses

2.2.1 | Overview

The group of partially double-stranded circular DNA viruses contains comparatively few representatives (Figure 2). However, the human hepatitis B virus (HBV, *Hepadnaviridae*) represents a significant source of morbidity and mortality despite the availability of an effective vaccine likely to progress toward chronic

B hepatitis (CBH), which causes over 800 000 deaths yearly [44]. CBH treatment is mainly based on administering nucleotide and nucleoside analogs, such as lamivudine and adefovir, which reduce the viral load in infected cells [45]. However, a substantial proportion of treated patients, ranging 13%–39%, developed resistance to the drugs [46]. Hence, plant-based alternatives are actively sought as novel treatments for CBH.

The human HBV genome comprises a linear chain of 3.2 kb in length of negative-sense polarity, or (−)DNA, circularized for the presence of terminal inverted repeats [47]. The 5′-end of this strand is also covalently linked to a tyrosine residue of the viral polymerase P [48], a positive-sense fragment of variable length [49], and an RNA segment leftover of the degradation of a full-length RNA known as pre-genomic (pgRNA) [50]. The pgRNA is enclosed within an icosahedral shell 22 nm in diameter composed of a capsid protein with an antigenic activity called HBV core antigen (HBcAg) [51]. This particle is further surrounded by an envelope decorated with viral protein that also elicits a high immune response and is termed HBV surface antigens (HBsAgs) [52].

HBV gains access to hepatocytes by binding the Na^+/taurocholate co-transporter polypeptide (NTCP), which mediates the import of bile acids inside the hepatocytes (Figure 3) [53]. The viral genome is then released into the nucleus [54], where the cellular DNA repair machinery detaches P, seals the nicks, and produces the complementary strand by extending the small regions of dsDNA to produce a fully functional viral episome [55]. The hepatitis B viral protein X (HBx) ensures proper transcription from the viral genome by epigenetic means [56].

Among the most relevant proteins encoded by HBV is the hepatitis B extracellular antigen (HBeAg), which is secreted and inhibits the activation of the NF-κB and IFN-γ pathways [57]. The weakening of the immune response is associated with the inability of the host to clear the infection and a higher risk of developing chronic infections with associated hepatitis [58]. Another essential viral protein is the HBsAg, the primary marker for HBV infection [59].

The pgRNA chain is bound by P through the recognition of a sequence (ε) of about 70 nucleotides and the complex is encapsulated by the core protein HBcAg [60]. Viral transcription requires a series of cellular factors, including the farnesoid-X-receptor (FXR), which modulates the expression of several genes involved in bile metabolism [61]. P binding to ε activates the enzyme's reverse-transcription activity [62]. Subsequently, P's ribonuclease H (RNaseH) activity is engaged, leading to pgRNA degradation, except for the last 18 nucleotides [63]. The leftover pgRNA is used as a primer for synthesizing the (−)DNA strand and then used as a template to produce (+)DNA strands of different lengths, known as replicative intermediates [64].

2.2.2 | Polyphenol Applications

It was widely reported that polyphenols can have anti-HBV activity. For instance, hyperoside from *Abelmoschus manihot* significantly decreased serum HBV DNA as well as the level of liver damage in Peking ducklings compared to controls [65]. Moreover, wogonin from *Scutellaria baicalensis* significantly suppressed HBsAg expression in a dose-dependent manner in the hepatocellular cell line MS-G2 [66]. Wogonin from *Scutellaria radix* also decreased plasma HBV DNA load, and hepatic necrosis and inflammatory cell infiltration in ducks and reduced serum HBsAg in human HBV-transgenic mice compared to controls [67]. Luteolin from *Swertia macrosperma* could decrease the expression of HBsAg and HBeAg in exposed HepG2.2.15 cells [68].

HBsAg, HBeAg, and viral loads were also reduced by baicalin from *S. baicalensis* in hepatic cells constitutively expressing HBV (HepG2, HepG2.2.15, and Huh7) [69, 70]. The authors suggested that baicalin could suppress viral RNA replication. In another report, baicalin from S. radix *Radix scudellariae* stimulated the expression of IFN-I/III in microvascular endothelial cells [71]. Since IFN is known to inhibit the activation of the NF-κB signal pathway essential for HBV activation [72], baicalin might hinder viral gene expression leading to a reduction in viral markers of infection.

The mechanism of action of polyphenols against HBV has been characterized to a greater extent for epigallocatechin-3-gallate (EGCG), one of the main components of green tea (*Camellia sinensis*) [73]. Exposure of immortalized primary human hepatocytes containing HBV (HuS-E/2 cell line) to EGCG (Sigma–Aldrich) resulted in a significant reduction in intracellular viral RNA load and viral infectivity as well as an eight-fold decrease in the proportion of cells expressing HBV core proteins [74]. The authors of this study also showed a reduction in the internalization of NTCP and transferrin, which is also internalized by a clathrin-mediated process [75], upon EGCG exposure while, at the same time, HBV replication and virion production were not affected [74]. Conversely, studies performed on HBV-containing cell lines HepG2.117 showed that exposure to EGCG decreased the synthesis of replicative intermediates of the DNA genome [76]. Others have shown that EGCG binds FXR in HBV-expressing cell line HepG2-N10, hampering the activation of viral genes [77].

Rosmarinic acid hampers the binding of P to the ε sequence, causing a decrease in viral load and HBsAg expression in HEK-293T and HepG2 cells transfected with HBV-containing plasmids [78].

3 | Negative Sense Single-Stranded RNA Viruses

3.1 | Nonsegmented Genomes

3.1.1 | Overview

The main characteristic of negative-sense single-stranded viruses is that the genome comprises a single molecule used as a template for producing the mRNAs encoding the viral proteins [79, 80]. One of the prominent members of this group is the measles virus (MeV) (Figure 2), which belongs to the genus *Morbillivirus* (family *Paramyxoviridae*; subfamily *Orthoparamyxovirinae*) and has a diameter of about 100–300 nm whose prevalence has been increasing in recent years [81]. MeV is highly transmissible and can cause many symptoms, from skin rash to encephalitis and immune suppression [82].

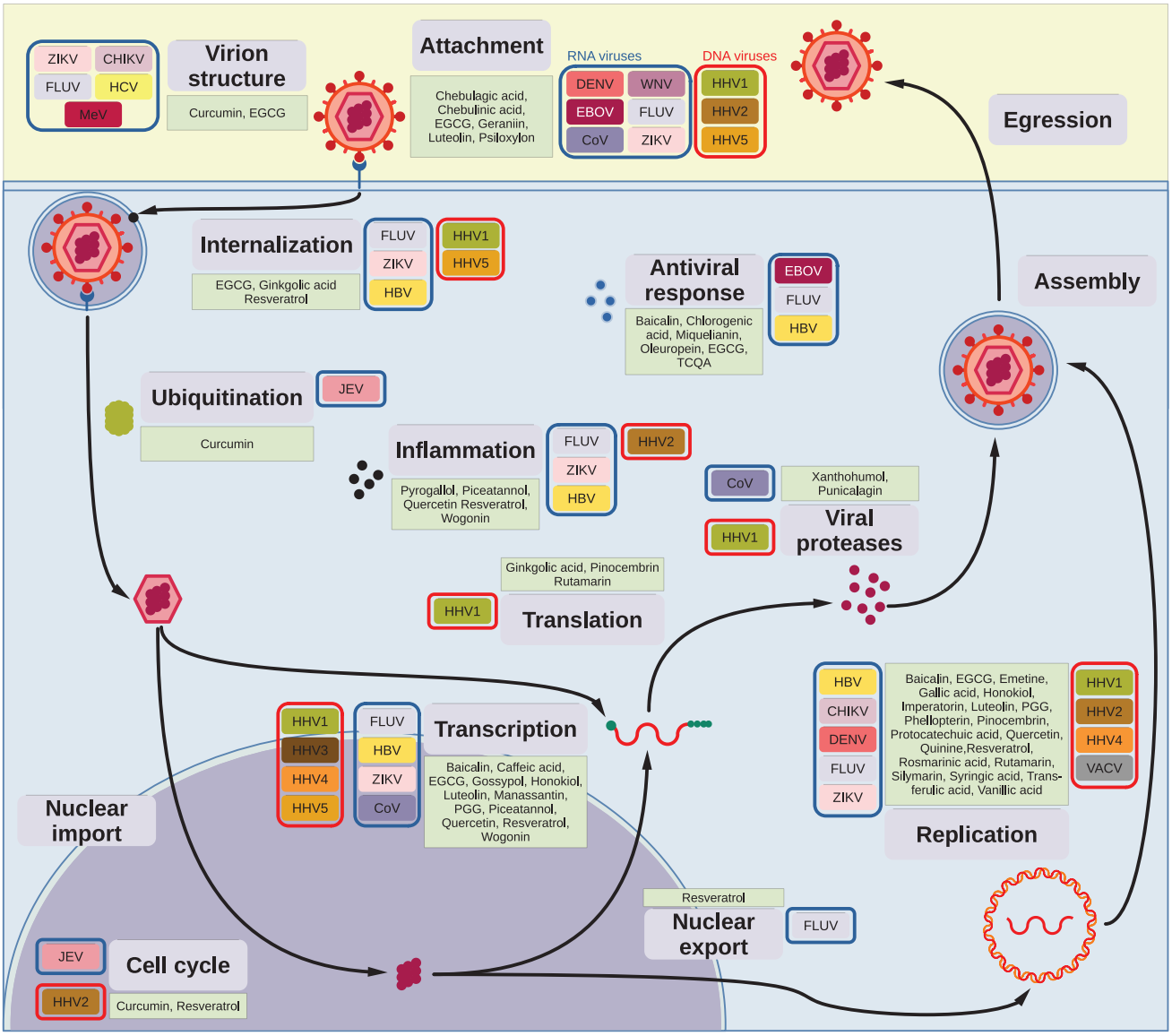


FIGURE 3 | Summary of the antiviral activity of polyphenols. Overview of the viral infection pathways affected by polyphenols. The main aspects of the viral infection are depicted (round boxes) together with the polyphenols involved in the hindrance (green boxes) and the viruses affected (colored boxes). Viruses are further stratified by their genome (DNA or RNA) by a colored box (red or blue, respectively). CHIKV, chikungunya virus; CoV, coronavirus; DENV, dengue virus; EBOV, Ebola virus; FLUV, influenza virus; HBV, hepatitis B virus; HCV, hepatitis C virus; HHV, human herpesvirus; JEV, Japanese encephalitis virus; MeV, measles virus; VACV, vaccinia virus; WNV, West Nile virus; ZIKV, Zika virus.

The virus enters the organism through the respiratory tract but initially does not infect epithelial cells (Figure 3). Instead, it is taken up by dendritic cells and macrophages expressing the signaling lymphocytic activation molecule (SLAM) receptor on their surface [81]. Lymphocytes are also infected after binding the MeV hemagglutinin (HA) protein to the target entry receptor, triggering the modification of the fusion protein (F). MeV uses lymphocytes to infect different tissues, and the new virions infect the respiratory tree epithelial cells by using the nectin-4 receptor, resulting in their destruction that, in turn, causes intense cough with virus-containing droplets [81].

In the infected cells, the cellular RNA-dependent RNA-polymerase (RdRp) initiates the transcription from the viral genome, generating mRNAs and encoding for the viral proteins [81]. During the replication process, the C protein is recruited to the ribonucleocapsid complex supposedly increasing polymerase activity.

Ebola virus (EBOV) is another clinically relevant virus belonging to the group that, unlike MeV, is only present endemic in certain parts of Africa [83]. The largest outbreak of EBOV disease was observed in 2014 in West Africa since the first outbreak in 1976 [84]. EBOV is a highly pathogenic agent associated with acute hemorrhagic fever with a mortality rate of 60%–90% [85]. EBOV belongs to the genus Orthoebolavirus (family *Filoviridae*) and has a helicoidal symmetry with a diameter of about 80 nm and a 970–1200 nm length. The helical nucleocapsid is surrounded by an outer envelope with anchored specific glycoprotein spikes involved in attachment and entry [84]. The Zaire Ebola viral

matrix protein VP24, located between the nucleocapsid and the outer envelope [84], is involved in preventing the interferon-induced antiviral responses by inhibiting the nuclear import of signal transducer and activator of transcription 1 (STAT1).

EBOV can replicate in many human cells, including immune cells, endothelial cells, fibroblasts, hepatocytes, and adrenal cells. EBOV enters the organism through the viral envelope glycoprotein, which is responsible for receptor binding and fusion of the viral envelope with the host membrane [86]. The EBOV targets macrophages, dendritic cells, and endothelial cells and also affects the gastrointestinal (GI) tract (diarrhea), the adrenal glands, and the liver (multifocal necrosis, decreased production of clotting factors) [87]. The virus infection first appears to disable the immune system and subsequently disables the vascular system, which leads to blood leakage (hemorrhage), hypotension, and a drop in blood pressure, followed by shock and death [87].

3.1.2 | Polyphenol Applications

Polyphenols (5 μg/mL) extracted from the seaweed *Ecklonia arborea* and *Solieria filiformis* reduced MeV infectious titers in Vero cells, with negligible cytotoxicity, through a mechanism that involved the alteration of the capsid [88].

Polyphenols extracted from *Cistus incanus* (Ci) display broad-spectrum antiviral activity against multiple unrelated, major human viral pathogens like EBOV with low risk of virus resistance. The mechanism blocks the virus attachment to host cells by selectively targeting the viral envelope glycoproteins. In contrast, other natural products with broad-spectrum antiviral activity target host cell components [89].

Polyphenols like 1,2,3,6-tetragalloyl glucose (TGG), epigallocatechin gallate, chlorogenic acid, oleuropein, and miquelianin may neutralize the threatening action of EBOV by inhibiting of VP24 [90]. Emetine inhibited the infection of HeLa and Vero cells with virus-like particles of EBOV with IC_{50} of 10.2 and 0.017 μM, respectively [91].

3.2 | Segmented Genomes

3.2.1 | Overview

Segmented genomes characterize this group of viruses (Figure 2), a feature indicating that the virion includes several genomic molecules (segments); infectious particles must contain at least one copy of each segment [80]. Although such a strategy might decrease infectivity, it increases the genetic fluidity of the virus by allowing for the phenomenon of recombination and expanding the actual size of the genome [92].

Influenza virus (FLUV) belongs to the *Orthomyxoviridae* family and is a significant cause of morbidity and mortality worldwide, despite the availability of vaccines and antivirals [93]. Genotype A (FLUV-A, *Alphainfluenzavirus* genus), is the most clinically relevant of the family [94]. FLUV virions consist of enveloped particles of about 100 nm in diameter containing a matrix encapsidating eight nucleoprotein segments [95].

The viral entry is mediated by the HA protein, which binds to the sialic acid *N*-acetylneuraminic acid (Neu5Ac), a common element of human cell membranes (Figure 3) [96]. Endocytosis is clathrin-mediated [91] and HA is also responsible for releasing the viral particles into the cytoplasm [92]. After dissociation of the matrix, the nucleocapsids and the viral RdRp are imported into the nucleus where the viral polymerase will transcribe the influenza genes [97]. Newly synthesized viral components accumulate at the plasmalemma, where the virions egress by budding [98]. Since HA in the released virion will interact with Neu5Ac, causing reinfection of the already infected cell, FLUV has developed a specific protein, the neuraminidase (NA), that removes the sialic acid from HA, freeing the newly synthesized virions [99].

3.2.2 | Polyphenol Applications

Quercetin and luteolin exhibited stark inhibitory activity against FLUV-A RdRp with an IC_{50} of 0.67 and 0.07 μM, respectively [100]. Quercetin and chlorogenic acid from *Honeysuckle* spp. increased the survival of BALB/c mice by 16% and 20%, respectively [101]. A quercetin derivative (quercetin-3-*O*-α-L-rhamnopyranoside) from *Rapanea melanophloeos* supplemented at a concentration of 150 μM reduced the expression of the proinflammatory cytokine IL-6 in canine kidney cells MDCK exposed to FLUV-A, suggesting a reduction in the pathogenic activity of the virus [102].

An extract from *Ilex pubescens*, 3,4,5-tri-*O*-caffeoylquinic acid (TCQA), was shown to be active against FLUV-A in human lung epithelial cells H292: cells exposed to 200 μM showed lower infectious foci and altered genetic expression compared to unexposed controls [103]. In particular, TCQA increased the transcription of genes involved in the antiviral response, such as type I IFN, but decreased the activation of signal pathways abnormally stimulated during FLUV-A infection, such as toll-like receptor 3 (TLR3) and interferon regulatory Factor 7 (IRF7). Pyrogallol at a concentration of 30 μg/mL showed an IC_{50} ranging from 0.70 to 1.48 μg/mL according to the FLUV-A strain in an MDCK cells model [104]. The authors of this study reported that the treatment caused an increase in heme oxygenase-1 (HO-1) expression that, in turn, induced a reduction in the oxidative stress to the cell and the cytopathic effect linked to viral infection.

Resveratrol supplemented at a concentration of 10–40 μg/mL reduced FLUV-A titers compared to controls, while cytopathic effects were absent at concentrations below 20 μg/mL [105]. Pretreatment of cells with this molecule did not alter viral infectivity indicating that resveratrol acted in steps following the entry phase. In particular, resveratrol did not inhibit viral RNA synthesis but their transcription and export of viral proteins from the nucleus [105].

EGCG from *Limonium densiflorum* showed an IC_{50} of 19 μg/mL against FLUV-A in MDCK cells with a mechanism supposed to involve the attachment and alteration of the virion [106]. Other studies reported that the mechanism of action of polyphenols is linked to the attachment phase. Polyphenols from *Saccharum officinarum* inhibited FLUV-A replication in MCDK cells in a dose-dependent fashion, with a 95% reduction in viral titers

obtained at a concentration of 1 mg/mL while displaying negligible cytotoxicity [107]. The authors of this study showed that the inhibition was associated with the hindrance of HA binding to sialic acid. A preparation from *G. sanguineum* inhibited H1N1 and H7N1 with a 50% effective concentration (EC_{50}) of 2.2 and 2.1 μg/mL, respectively [36].

4 | Positive Sense Single-Stranded RNA Viruses

4.1 | Overview

The group of single-stranded positive-sense RNA viruses is characterized by genomes that can be used directly as transcripts to produce viral proteins [108]. The group includes several human pathogens including the *Coronaviridae* family, a clade the comprise the etiological agent of the COVID-19 pandemic (the severe acute respiratory syndrome coronavirus [SARS-CoV]-2), other viruses characterized by high mortality and transmissibility (SARS-CoV and the Middle East respiratory syndrome coronavirus [MERS-CoV]) as well as nonsevere acute respiratory syndrome viruses human coronavirus (HCoV) 229E (Figure 2) [109]. Another major class within the group encompasses the viruses transmitted by arthropods (arboviruses) [110], with the family *Flaviridae* having a special clinical importance because it incorporates severe human pathogens with wide distribution, such as Zika virus (ZIKV), dengue virus (DENV), West Nile virus (WNV), and Japanese encephalitis virus (JEV) [111]. Another relevant arbovirus is the chikungunya virus (CHIKV), which belongs to the *Togaviridae* family [112]. In addition, the *Flaviviridae* family includes hepatitis C virus (HCV), which is not transmitted by arthropods [113].

The group of single-stranded positive-sense RNA viruses has a high potential for generating pandemics. ZIKV is currently endemic in 86 countries [114] and, in 2016, the World Health Organization declared ZIKV a global public health concern [115]. By comparison, DENV has been reported in 141 countries around the world [116]. COVID-19 is a still ongoing pandemic that has so far killed more than 7 million people worldwide since its outbreak in 2019 [117]. Moreover, treatments for these viruses are still missing. There are neither vaccines nor drugs to treat or prevent ZIKV infections [118].

The flaviviruses share the feature of an enveloped capsid formed by the capsid (C), envelope (E), and membrane (M) proteins surrounding a genome composed of positive-sense single-stranded RNA that is 3´-capped with conserved secondary structures at both ends of the genome [119]. The attachment to the host cell is initiated by binding the E protein to surface glycosaminoglycans (Figure 3) [120]. Once released into the cytoplasm, the genome is recognized as a bona fide mRNA and is translated by cellular transcription machinery. The viral genome contains a single ORF encoding a single polyprotein cleaved by several cellular peptidases and the viral serine protease nonstructural protein 3 (NS3) [121]. NS1, NS3, and NS5 are of particular interest. NS1's primary function is that of a scaffold protein to form the replication complex [122]. NS1 interacts with many cellular factors and is the only excreted viral protein in the form of a soluble homo-hexamer (sNS1) [123]. Secreted NS1 modulates the immune response and triggers autoimmune reactions and vascular permeability [124]. NS3 is the viral serine protease [125] and NS5 is the RdRp [126]. The coronaviruses also produce a single polyprotein that is matured by cleavage [127].

4.2 | Polyphenol Applications

Polyphenols have been shown to affect essentially all aspects of the ZIKV infection cycle. For instance, EGCG supplied in a 1–10 μM concentration range inhibited viral adsorption and internalization of ZIKV, DENV, and WNV [128]. Regarding the inhibition of ZIKV entry, EGCG showed a strain-specific activity: isolate ZIKVBR was inhibited by 50 μM of EGCG, but ZIKV MR766 required only 25 μM; the EC_{50} was calculated as 21.4 μM [129]. Cell toxicity was reported for exposures of at least 200 μM [129]. EGCG (from Sigma–Aldrich) hampered ZIKV nucleoside-triphosphatase (NTPase) with an IC_{50} 0.296 μM in an enzymatic assay [130].

Both quercetin and EGCG inhibited NS3 activity with an EC_{50} of 1.17 and 0.73 μM, respectively [131], while glycyrrhetinic acid, one of the main active molecules of licorice (*Glycyrrhiza glabra*) inhibited NS1 [132], and extracts from *Andrographis paniculata* impaired RNA replication by hampering NS5 [133]. Silymarin, the main component of *Silybum marianum*, was shown to be even more effective than quercetin in inhibiting CHIKV replication, with a concentration of 100 μg/mL, whereas quercetin showed no significant reduction of viral titers [134].

Resveratrol (from Sigma–Aldrich) inhibited ZIKV replication in Vero and Huh7 cells [135]. Emodin was effective against ZIKV but also many other viruses [136]. Further, emetine was characterized as an inhibitor of ZIKV replication (IC_{50}: 8.74 nM) that also decreases viral entry. NS1 levels declined in the presence of emetine (IC_{50}: 52.9 nM) [91].

Pinocembrin, which is one of the main active components of propolis [137], was used against ZIKV in hamster (BHK-21), human embryonic kidney (HEK293T), human carcinoma (Huh7), and human epithelial (JEG-3) cell lines [138]. This study determined the 50% cytotoxic concentration (CC_{50}) and IC_{50} in 251 and 17.4 μM. Interestingly, pinocembrin treatment (19.5 or 39.0 μM) was effective against ZIKV only in Huh7 cells without affecting cell viability. In addition, pretreatment of JEG-3 cell with pinocembrin at a concentration of 156 μM 2 h before infection did not affect viral replication, while postinfection treatment inhibited the synthesis of viral RNA as well as envelope proteins, indicating that this molecule interfered with the virus after the attachment step [138]. Moreover, pinocembrin was also active against other flaviviruses. For instance, treatment of Huh7 cells with 39 μM and HeLa cells with 21.5 μM of pinocembrin determined a significant reduction of DENV and CHIKV titers compared to untreated controls [138].

Curcumin is well tolerated by human cells, but its low bioavailability limits its use [139]. It has been employed against DENV2 (EC_{50}; 13.95 μM, CC_{50}: 49.01 μM, selectivity index [SI]: 3.51) determined by plaque formation assay, but also against respiratory syncytial virus (RSV), vesicular stomatitis Indiana virus (VSV), ZIKV, FLUV, and HCV [140, 141a, 142, 141b, 143]. Curcumin could also weakly inhibit the viral protease (IC_{50}: 66.01 μM),

the expression of genes related to lipid biosynthesis, and it further inhibited actin polymerization [140]. Several curcuminoids have been tested against DENV2, and many of them showed even higher activity in plaque-forming assays than their parent compound, curcumin [140].

Curcumin (from Sigma–Aldrich) showed a dose-dependent reduction in ZIKV titers, with 5 μM being the minimal inhibiting concentration, which was below the amount needed to markedly decrease cell viability (10 μM) [142]. Unlike pinocembrin, curcumin treatment (5 μM) was effective against ZIKV and CHIKV both before and after infection, although pretreatment showed the strongest inhibitory effect [142]. Interestingly, curcumin did not affect the accumulation of viral RNA or proteins after infection, indicating that the molecule affected an early stage of the infection process.

Since curcumin induced alteration in vesicle fluidity, reducing the attachment rate and entry into human liver cells of all tested genotypes of HCV [143], the authors suggested a similar mechanism to explain the observed ZIKV repression [142]. Interestingly, curcumin did not downregulate HCV replication and reduced the infectivity of HCV without disrupting the integrity of the virus particles [143].

Nonetheless, this mechanism might not be the only one carried out by this curcumin. It has been suggested that the reduction in JEV infectious particles observed while treating porcine kidney cells with 5 μM curcumin could be due to the increased ubiquitination that possibly removed, along with other proteins, viral products from the cytoplasm [144] and decreasing NF-κB activation in Rift Valley fever virus (RVFV) infections [145]. Curcumin, EGCG, and resveratrol inhibit the NF-κB pathways [146].

Quinine has been used for centuries as an anti-malaria treatment, although in recent times, the frequency of resistant infection has increased, and plant-based alternatives are actively sought [147]. Its administration at a concentration of 150 μM reduced DENV viral load in three human cell lines (HepG2, A549, and EA.hy926) in a dose-dependent manner, with an increase in the expression of showing an increase in IFN-I, 2′-5′-oligoadenylate synthetase 3 (OAS-3), RNase L, and protein kinase RNA-activated (PKR) compared to untreated controls, suggesting that this molecule interfered with viral replication in several points [148].

Psiloxylon from *Psiloxylon mauritianum* showed a CC_{50} of 1044 μg/mL and caused a reduction in both DENV and ZIKV's viral replication at a 100 μg/mL concentration [149]. In particular, exposure to psiloxylon concomitantly to infection resulted in a significant reduction of infected cells but pretreatment was ineffective, suggesting that this molecule acted in the attachment phase of infection. The authors of the study demonstrated that exposure to extracts of *P. mauritianum* caused a ten-fold reduction in the number of particles attached to host cells [149].

Polyphenols also showed the capability of disrupting other targets than the viral proteases. For instance, in silico analysis identified several plant derivatives capable of binding SARS-CoV-2 RdRp, particularly theaflavin, hesperidin, EGCG, myricetin, and quercetagetin [150]. There are several plant-derived molecules active against SARS-COV-2; we refer to more exhaustive reviews for further information [151], and we focus on some of the most effective reported so far.

Resveratrol is active against FLUV-A, RSV, SARS-CoV, and MERS-CoV [152]. Neutrophils isolated from COVID-19 patients and exposed to 100 μM resveratrol (*Sigma–Aldrich*) showed reduced liberation of DNA, suggesting a reduced activation of these cells [33]. In SARS-CoV-2, resveratrol was found to hamper viral replication, the viral main protease (M^{pro}) (IC_{50}: 16.5 μM) [153, 154].

In our laboratory, we experimentally established that xanthohumol (XN), a prenylated chalcone produced by the female hop cones [155], impaired the SARS-CoV-2 papain-like protease (PL^{pro}). Our docking analysis suggested that XN could block the PL^{pro} binding site to the viral polyprotein; such hindrance resulted in a IC_{50} values of 3.3 μM [156]. In particular, our docking analysis showed that all these molecules could bind to the active site of the viral PL^{pro}, an enzyme involved in the maturation of the viral polyprotein precursors and, therefore, a suitable target for antiviral therapy [157]. The theoretical hindrance determined by molecular docking was confirmed by our enzymatic testing, which showed a reduction of PL^{pro} activity in cleaving the reporter protein interferon-stimulated gene 15 (ISG15).

Resveratrol also inhibited SARS-CoV_2 viroporin ORF3a (IC_{50}: 6.7 μM) [153, 154]. Channel activity of ORF3a was also inhibited by kaempferol (IC_{50}: 5.2 μM), quercetin (IC_{50}: 2.5 μM), EGCG (IC_{50}: 1.6 μM), nobiletin (IC_{50}: 3.8 μM), and curcumin (IC_{50}: 1.6 μM). Resveratrol inhibited MERS-CoV by downregulating the expression of the nucleocapsid [158] and resveratrol (from Sigma–Aldrich) further inhibited HCoV-229E replication (EC_{50}: 4.6 μM, CC_{50}: 210 μM, SI: 45.65) [159]. Resveratrol is hampered by diminished water solubility and an extensive metabolism in the GI tract and liver [152]. Alternatives are actively sought to improve its efficacy in vivo. PEG-stabilized resveratrol prohibited inflammatory storm and oxidative stress in MERS-CoV with an EC_{50} of 0.0127 μg/mL and an SI of 724.4 with the nanocarrier compared to 7.3 without nanocarrier [28, 152].

Luteolin inhibits SARS-CoV binding to Vero E6 host cells (EC_{50}: 10.6 μM, CC_{50}: 155 μM, SI: 14,6), while quercetin was not only less effective but also less toxic (EC_{50}: 83.4 μM, CC_{50}: 3320 μM) [160]. Hesperidin, EGCG, and kaempferol inhibited SARS-CoV-2 M^{pro} and spike protein in silico [161]. Luteolin, daidzein, apigenin, amentoflavone, epigallocatechin, and gallocatechin gallate also showed inhibition of M^{pro} [162].

In silico, catechins and curcumin interact with angiotensin-converting enzyme 2 (ACE2), hampering the S protein binding to the receptor [163]. Resveratrol, together with low fat, had favorable effects on ACE2 expression [164].

Gossypol was characterized as a pan-coronavirus-inhibitor, for example, by targeting RdRps [165], and was particularly antiviral against SARS-CoV-2 with an EC_{50} of 0.76 μM, CC_{50} of 39.7 μM, and a therapeutic index (TI) of 52.07 [165].

5 | Discussion

Polyphenols have gained medicinal attention as they exhibit antiinflammatory, antioxidant, and antimicrobial activities [166]. This review underscored the antiviral potential of polyphenols against enveloped viruses of clinical relevance. The most active polyphenols were the flavonoids, which could affect the infection cycles of arboviruses, coronaviruses, and hepadnaviruses. The molecules with the broader effects were EGCG (which affected virion structure, attachment, internalization, transcription, replication, and antiviral response) and reseveratrol (which hampers internalization, antiviral response, transcription, replication, and cell cycle modulation). The most sensitive viruses were the herpesviruses, which were susceptible to all classes of polyphenols, except for flavonoids.

The antiviral properties inherent in the polyphenols are based on several pathways. The most commonly affected step in viral infection is the replication phase due to interference of either DNA (herpesviruses, poxviruses, and hepadnaviruses) or RNA (arboviruses and FLUVs) polymerases. Virtually all polyphenols described herein were shown to interfere with this step, reflecting the complexity and susceptibility to disruption of this process. Equally affected was the attachment phase. This step was affected by fewer poylphenols than replication (chebulagic and chebulinic acids, EGCG, geraniin, luteolin, and psiloxylon) but involved several viruses (arboviruses, herpesviruses, coronaviruses, filoviruses, and FLUVs).

The second most common pathway affected by polyphenols (baicalin, caffeic acid, EGCG, gossypol, honokiol, luteolin, manassantin, PGG, piceatannol, quercetin, resveratrol, and wogonin) was transcription of viral genes. The lower susceptibility of viruses to transcriptional hindrance might be explained by the fact that this step relies on cellular enzymes more than the replicative step. Hindrance of transcription affected a wide range of viruses (herpesviruses, HBV, ZIKV, and FLUV). Since both replication and transcription are postinfection steps, it is feasible to assume that polyphenols can be used as therapeutic agents.

The therapeutic value of polyphenols can also be extended for specific viruses (herpesviruses, FLUVs, and coronaviruses) by the hindrance of steps such as nuclear export (resveratrol), translation (ginkgolic acid and pinocembrin), proteolysis (XN and punicalagin), modulation of inflammation (piceatanol, pyrogallol, resveratrol), and enhancement of antiviral response (TCQA). Since the latter two steps involve the modulation of the cellular oxidative stress, the polyphenols involved in these processes might have a particular clinical interest.

In addition, some polyphenols can act as prophylactic molecules by affecting the attachment (chebulagic acid, chebulinic acid, geraniin, luteolin, EGCG, and psiloxylon), internalization (EGCG, ginkgolic acid), and even viral structure (curcumin and EGCG), suggesting that these molecules can prevent the infection of selected viruses (arboviruses, FLUVs, and herpesviruses).

Despite the auspicious preclinical effects reported by in silico, in vitro, and in vivo experiments, further studies are required to discover the mechanisms of antiviral components in suppressing viral infections, like impaired entry mechanisms, eliciting a high immune response, and overcoming resistance to established drugs like boosting drug activities. There are specific positions within the flavan structure that are more relevant for determining the biological activities of flavonoids (Figure 4) [167]. Interestingly, it has been shown that the groups more involved in modulating the antioxidant activity of flavonoids also determine the biological activity of these molecules. The presence of hydroxyl or methoxy groups, double carbon bonds in the C-ring, and glycosylation in the B-ring have been associated with an enhancement of their antimicrobial properties [168]. In EGCG, the presence of 3-galloyl and hydroxyl groups in position 5′ of the B-ring has been associated with the antiviral activity of this molecule [169]. For the other polyphenols, the link between structure and antimicrobial function is still poorly understood.

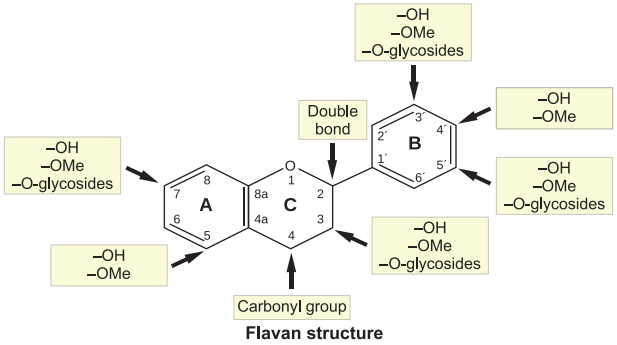


FIGURE 4 | Biologically relevant residues of flavonoids. Basic structure of the flavan skeleton with numeration of the carbon atoms and identification of the two aromatic and the heterocyclic rings (A–C) with indication of the most relevant positions and their main substituents like hydroxyl groups (–OH), methoxy groups (–OMe), or –*O*-glycosides, which are important for the antimicrobial activity of the flavonoids.

Although natural compounds are expected to have good tolerability and a low rate of side effects, the low bioavailability and rapid degradation of many polyphenols like resveratrol in the body is one of a variety of causes that hamper the development of antiviral drugs from natural compounds. Strategies to enhance bioavailability could provide an attractive subject for future studies.

6 | Conclusions

According to the literature gathered by the present review, polyphenols can affect the replication of enveloped human pathogenic viruses at several molecular points. In particular, EGCG and resveratrol had the broader effect on the viral infection, whereas herpesviruses were the viruses most affected by polyphenols. Numerous in silico, in vitro, and in vivo studies underline the great potential of various polyphenols for use in viral infections.

Acknowledgments

The authors thank Monika Schumacher, University of Hohenheim, for her technical assistance.

Open access funding enabled and organized by Projekt DEAL.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Peer Review

The peer review history for this article is available at https://publons.com/publon/10.1002/mnfr.70042.

References

1. H. El Gharras, "Polyphenols: food sources, properties and applications – a review," *International Journal of Food Science and Technology* 44 (2009): 2512, https://doi.org/10.1111/j.1365-2621.2009.02077.x.

2. D. B. M. Ficco, K. Petroni, L. Mistura, and L. D'Addezio, "Polyphenols in Cereals: State of the Art of Available Information and Its Potential Use in Epidemiological Studies," *Nutrients* 16 (2024): 2155, https://doi.org/10.3390/nu16132155.

3. I. Hossen, W. Hua, L. Ting, et al., "Phytochemicals and Inflammatory Bowel Disease: A Review," *Critical Reviews in Food Science and Nutrition* 60 (2020): 1321, https://doi.org/10.1080/10408398.2019.1570913.

4. T. T. Cushnie and A. J. Lamb, "Antimicrobial Activity of Flavonoids," *International Journal of Antimicrobial Agents* 26 (2005): 343, https://doi.org/10.1016/j.ijantimicag.2005.09.002.

5. I. Dini and L. Grumetto, "Recent Advances in Natural Polyphenol Research," *Molecules (Basel, Switzerland)* 27 (2022): 8777, https://doi.org/10.3390/molecules27248777.

6. B. Aslam, W. Wang, M. I. Arshad, et al., "Antibiotic Resistance: A Rundown of a Global Crisis," *Infection and Drug Resistance* 11 (2018): 1645, https://doi.org/10.2147/IDR.S173867.

7. a) Z. Wang, X. Song, W. Xu, S. Lei, H. Zhang, and L. Yang, "Stand Up to Stand Out: Natural Dietary Polyphenols Curcumin, Resveratrol, and Gossypol as Potential Therapeutic Candidates Against Severe Acute Respiratory Syndrome Coronavirus 2 Infection," *Nutrients* 15 (2023): 3885, https://doi.org/10.3390/nu15183885. b) M. Vajdi, A. Karimi, S. Hassanizadeh, et al., "Effect of Polyphenols Against Complications of COVID-19: Current Evidence and Potential Efficacy," *Pharmacological Reports* 76 (2024): 307, https://doi.org/10.1007/s43440-024-00585-6. c) A. D. Mahapatra, I. Paul, S. Dasgupta, et al., "Antiviral Potential and In Silico Insights of Polyphenols as Sustainable Phytopharmaceuticals: A Comprehensive Review," *Chemistry and Biodiversity* (2024): 202401913, https://doi.org/10.1002/cbdv.202401913. d) S. Davidova, A. S. Galabov, and G. Satchanska, "Antibacterial, Antifungal, Antiviral Activity, and Mechanisms of Action of Plant Polyphenols," *Microorganisms* 12 (2024): 2502, https://doi.org/10.3390/microorganisms12122502.

8. A. J. Davison, "Herpesvirus Systematics," *Veterinary Microbiology* 143 (2010): 52, https://doi.org/10.1016/j.vetmic.2010.02.014.

9. P. G. Spear and R. Longnecker, "Herpesvirus Entry: An Update," *Journal of Virology* 77 (2003): 10179, https://doi.org/10.1128/jvi.77.19.10179-10185.2003.

10. D. J. Hata, E. A. Powell, M. W. Starolis, and S. E. Realegeno, "What the Pox? Review of Poxviruses Affecting Humans," *Journal of Clinical Virology* 174 (2024): 105719, https://doi.org/10.1016/j.jcv.2024.105719.

11. C. L. Poole and S. H. James, "Antiviral Therapies for Herpesviruses: Current Agents and New Directions," *Clinical Therapeutics* 40 (2018): 1282, https://doi.org/10.1016/j.clinthera.2018.07.006.

12. a) S. T. S. Hassan, M. Šudomová, A. Mazurakova, and P. Kubatka, "Insights Into Antiviral Properties and Molecular Mechanisms of Non-Flavonoid Polyphenols Against Human Herpesviruses," *International Journal of Molecular Sciences* 23 (2022): 13891, https://doi.org/10.3390/ijms232213891. b) A. Majewska and B. Mlynarczyk-Bonikowska, "40 Years After the Registration of Acyclovir: Do We Need New Anti-Herpetic Drugs?" *International Journal of Molecular Sciences* 23 (2022): 3431, https://doi.org/10.3390/ijms23073431.

13. K. Madavaraju, R. Koganti, I. Volety, T. Yadavalli, and D. Shukla, "Herpes Simplex Virus Cell Entry Mechanisms: An Update," *Frontiers in Cellular and Infection Microbiology* 10 (2021): 617578, https://doi.org/10.3389/fcimb.2020.617578.

14. D. Atanasiu, W. T. Saw, R. J. Eisenberg, and G. H. Cohen, "Regulation of Herpes Simplex Virus Glycoprotein-Induced Cascade of Events Governing Cell-Cell Fusion," *Journal of Virology* 90 (2016): 10544, https://doi.org/10.1128/JVI.01501-16.

15. T. Gianni, R. Massaro, and G. Campadelli-Fiume, "Dissociation of HSV gL From gH by αvβ6- or αvβ8-Integrin Promotes gH Activation and Virus Entry," *PNAS* 112 (2015): 3901, https://doi.org/10.1073/pnas.1506846112.

16. K. Döhner, A. Cornelius, M. C. Serrero, and B. Sodeik, "The Journey of Herpesvirus Capsids and Genomes to the Host Cell Nucleus," *Current Opinion in Virology* 50 (2021): 147, https://doi.org/10.1016/j.coviro.2021.08.005.

17. P. Boehmer and A. Nimonkar, "Herpes Virus Replication," *IUBMB Life* 55 (2003): 13, https://doi.org/10.1080/1521654031000070645.

18. J. Wysocka and W. Herr, "The Herpes Simplex Virus VP16-Induced Complex: The Makings of a Regulatory Switch," *Trends in Biochemical Sciences* 28 (2003): 294, https://doi.org/10.1016/S0968-0004(03)00088-4.

19. X. Ding, D. M. Neumann, and L. Zhu, "Host Factors Associated With Either VP16 or VP16-Induced Complex Differentially Affect HSV-1 Lytic Infection," *Reviews in Medical Virology* 32 (2022): 2394, https://doi.org/10.1002/rmv.2394.

20. J. Xing, L. Ni, S. Wang, K. Wang, R. Lin, and C. Zheng, "Herpes Simplex Virus 1-Encoded Tegument Protein VP16 Abrogates the Production of Beta Interferon (IFN) by Inhibiting NF-κB Activation and Blocking IFN Regulatory Factor 3 To Recruit Its Coactivator CBP," *Journal of Virology* 87 (2013): 9877, https://doi.org/10.1128/JVI.01440-13.

21. J. Zaborowska, S. Baumli, C. Laitem, et al., "Herpes Simplex Virus 1 (HSV-1) ICP22 Protein Directly Interacts With Cyclin-Dependent Kinase (CDK)9 to Inhibit RNA Polymerase II Transcription Elongation," *PLoS ONE* 9 (2014): 107654, https://doi.org/10.1371/journal.pone.0107654.

22. a) D. Fan, M. Wang, A. Cheng, et al., "The Role of VP16 in the Life Cycle of Alphaherpesviruses," *Frontiers in Microbiology* 11 (2020): 1910, https://doi.org/10.3389/fmicb.2020.01910. b) H. Hirai, T. Tani, and N. Kikyo, "Structure and Functions of Powerful Transactivators: VP16, MyoD and FoxA," *International Journal of Developmental Biology* 54 (2010): 1589, https://doi.org/10.1387/ijdb.103194hh.

23. K. M. Izumi, E. D. Cahir McFarland, A. T. Ting, E. A. Riley, B. Seed, and E. D. Kieff, "The Epstein-Barr Virus Oncoprotein Latent Membrane Protein 1 Engages the Tumor Necrosis Factor Receptor-Associated Proteins TRADD and Receptor-Interacting Protein (RIP) but Does Not Induce Apoptosis or Require RIP for NF-κB Activation," *Molecular and Cellular Biology* 19 (1999): 5759, https://doi.org/10.1128/MCB.19.8.5759.

24. R. Borenstein, B. A. Hanson, R. M. Markosyan, et al., "Ginkgolic Acid Inhibits Fusion of Enveloped Viruses," *Scientific Reports* 10 (2020): 4746, https://doi.org/10.1038/s41598-020-61700-0.

25. M. Sochocka, M. Sobczyński, M. Ochnik, K. Zwolińska, and J. Leszek, "Hampering Herpesviruses HHV-1 and HHV-2 Infection by Extract of *Ginkgo biloba* (EGb) and Its Phytochemical Constituents," *Frontiers in Microbiology* 10 (2019): 2367, https://doi.org/10.3389/fmicb.2019.02367.

26. A. Kesharwani, S. K. Polachira, R. Nair, A. Agarwal, N. N. Mishra, and S. K. Gupta, "Anti-HSV-2 Activity of *Terminalia chebula* Retz Extract and Its Constituents, Chebulagic and Chebulinic Acids," *BMC Complementary and Alternative Medicine* 17 (2017): 110, https://doi.org/10.1186/s12906-017-1620-8.

27. E. M. Siqueira S. da, T. L. C. Lima, et al., "Antiviral Potential of Spondias mombin L. Leaves Extract Against Herpes Simplex Virus Type-

1 Replication Using In Vitro and In Silico Approaches", *Planta Medica* 86 (2020): 505, https://doi.org/10.1055/a-1135-9066.

28. Y. Lin, Q. Wang, Q. Gu, et al., "Semisynthesis of (−)-Rutamarin Derivatives and Their Inhibitory Activity on Epstein–Barr Virus Lytic Replication," *Journal of Natural Products* 80 (2017): 53, https://doi.org/10.1021/acs.jnatprod.6b00415.

29. S. T. S. Hassan, E. Švajdlenka, and K. Berchová-Bímová, "*Hibiscus sabdariffa* L. and Its Bioactive Constituents Exhibit Antiviral Activity Against HSV-2 and Anti-enzymatic Properties Against Urease by an ESI-MS Based Assay," *Molecules (Basel, Switzerland)* 22 (2017): 722, https://doi.org/10.3390/molecules22050722.

30. N. Todorova, M. Rangelov, I. Dincheva, I. Badjakov, V. Enchev, and N. Markova, "Potential of Hydroxybenzoic Acids From *Graptopetalum paraguayense* for Inhibiting of Herpes Simplex Virus DNA Polymerase—Metabolome Profiling, Molecular Docking and Quantum-Chemical Analysis," *Pharmacia* 69 (2022): 113, https://doi.org/10.3897/pharmacia.69.e79467.

31. J. Langland, B. Jacobs, C. E. Wagner, G. Ruiz, and T. M. Cahill, "Antiviral Activity of Metal Chelates of Caffeic Acid and Similar Compounds Towards Herpes Simplex, VSV-Ebola Pseudotyped and Vaccinia Viruses," *Antiviral Research* 160 (2018): 143–150, https://doi.org/10.1016/j.antiviral.2018.10.021.

32. J. Arunkumar and S. Rajarajan, "Study on Antiviral Activities, Drug-Likeness and Molecular Docking of Bioactive Compounds of *Punica granatum* L. to Herpes Simplex Virus-2 (HSV-2)," *Microbial Pathogenesis* 118 (2018): 301, https://doi.org/10.1016/j.micpath.2018.03.052.

33. M. M. de Souza Andrade, V. N. C. Leal, I. G. Fernandes, et al., "Resveratrol Downmodulates Neutrophil Extracellular Trap (NET) Generation by Neutrophils in Patients With Severe COVID-19," *Antioxidants (Basel)* 11 (2022): 1690, https://doi.org/10.3390/antiox11091690.

34. J. J. Docherty, M. M. Fu, B. S. Stiffler, R. J. Limperos, C. M. Pokabla, and A. L. DeLucia, "Resveratrol Inhibition of Herpes Simplex Virus Replication," *Antiviral Research* 43 (1999): 145, https://doi.org/10.1016/s0166-3542(99)00042-x.

35. L. Ding, P. Jiang, X. Xu, et al., "Resveratrol Promotes HSV-2 Replication by Increasing Histone Acetylation and Activating NF-κB," *Biochemical Pharmacology* 171 (2020): 113691, https://doi.org/10.1016/j.bcp.2019.113691.

36. J. Serkedjieva and A. J. Hay, "In Vitro Anti-Influenza Virus Activity of a Plant Preparation From *Geranium sanguineum* L.," *Antiviral Research* 37 (1998): 121, https://doi.org/10.1016/s0166-3542(97)00067-3.

37. B. Rajtar, K. Skalicka-Woźniak, Ł. Świątek, A. Stec, A. Boguszewska, and M. Polz-Dacewicz, "Antiviral Effect of Compounds Derived From *Angelica archangelica* L. on Herpes Simplex Virus-1 and Coxsackievirus B3 Infections," *Food and Chemical Toxicology* 109 (2017): 1026, https://doi.org/10.1016/j.fct.2017.05.011.

38. G. Squillaci, C. Zannella, V. Carbone, et al., "Grape Canes From Typical Cultivars of Campania (Southern Italy) as a Source of High-Value Bioactive Compounds: Phenolic Profile, Antioxidant and Antimicrobial Activities," *Molecules (Basel, Switzerland)* 26 (2021): 2746, https://doi.org/10.3390/molecules26092746.

39. S. Liu, L. Li, L. Tan, and X. Liang, "Inhibition of Herpes Simplex Virus-1 Replication by Natural Compound Honokiol," *Virologica Sinica* 34 (2019): 315, https://doi.org/10.1007/s12250-019-00104-5.

40. F.-Y. Tang, C.-Y. Chen, H.-W. Shyu, et al., "Resveratrol Induces Cell Death and Inhibits Human Herpesvirus 8 Replication in Primary Effusion Lymphoma Cells," *Chemico-Biological Interactions* 242 (2015): 372, https://doi.org/10.1016/j.cbi.2015.10.025.

41. Z. Zhao, K.-W. Tang, I. Muylaert, T. Samuelsson, and P. Elias, "CDK9 and SPT5 Proteins Are Specifically Required for Expression of Herpes Simplex Virus 1 Replication-Dependent Late Genes," *Journal of Biological Chemistry* 292 (2017): 15489, https://doi.org/10.1074/jbc.M117.806000.

42. S. Bae, S. Y. Kim, M. H. Do, C. H. Lee, and Y.-J. Song, "1,2,3,4,6-Penta-O-galloyl-ß-D-Glucose, a Bioactive Compound in *Elaeocarpus sylvestris* Extract, Inhibits Varicella-Zoster Virus Replication," *Antiviral Research* 244 (2017): 266, https://doi.org/10.1016/j.antiviral.2017.06.018.

43. S.-Y. Wang, J. Zhang, X.-G. Xu, et al., "Inhibitory Effects of Piceatannol on Human Cytomegalovirus (hCMV) In Vitro," *Journal of Microbiology (Seoul, Korea)* 58 (2020): 716, https://doi.org/10.1007/s12275-020-9528-2.

44. W.-J. Jeng, G. V. Papatheodoridis, and A. S. F. Lok, "Hepatitis B," *Lancet* 401 (2023): 1039, https://doi.org/10.1016/S0140-6736(22)01468-4.

45. K. B. Bang and H. J. Kim, "Management of Antiviral Drug Resistance in Chronic Hepatitis B," *World Journal of Gastroenterology* 20 (2014): 11641, https://doi.org/10.3748/wjg.v20.i33.11641.

46. a) M. Rezanezhadi, A. Mohebbi, F. S. Askari, S. D. Hosseini, and A. Tabarraei, "Hepatitis B Virus Reverse Transcriptase Polymorphisms Between Treated and Treatment-Naïve Chronically Infected Patients," *Virusdisease* 30 (2019): 219, https://doi.org/10.1007/s13337-018-00510-5. b) M. S. Gomes-Gouvêa, A. C. Ferreira, R. Teixeira, et al., "HBV Carrying Drug-Resistance Mutations in Chronically Infected Treatment-Naive Patients," *Antiviral Therapy* 20 (2015): 387, https://doi.org/10.3851/IMP2938.

47. J. A. Saldanha, H. Qiu, H. C. Thomas, and J. Monjardino, "Mapping of 5′ Ends of Virion-Derived HBV DNA," *Virology* 188 (1992): 358, https://doi.org/10.1016/0042-6822(92)90765-h.

48. D. Cai, R. Yan, J. Z. Xu, et al., "Characterization of the Termini of Cytoplasmic Hepatitis B Virus Deproteinated Relaxed Circular DNA," *Journal of Virology* 95 (2020): 00922, https://doi.org/10.1128/JVI.00922-20.

49. J. Summers, A. O'Connell, and I. Millman, "Genome of Hepatitis B Virus: Restriction Enzyme Cleavage and Structure of DNA Extracted From Dane Particles," *PNAS* 72 (1975): 4597, https://doi.org/10.1073/pnas.72.11.4597.

50. L. A. M. R. Suping, E. Christine, et al., "Hepatitis B Virus Capsid Assembly Modulators, but Not Nucleoside Analogs, Inhibit the Production of Extracellular Pregenomic RNA and Spliced RNA Variants", *Antimicrobial Agents and Chemotherapy* 61 (2017): 00680, https://doi.org/10.1128/aac.00680-17.

51. B. Venkatakrishnan and A. Zlotnick, "The Structural Biology of Hepatitis B Virus: Form and Function," *Annual Review of Virology* 3 (2016): 429, https://doi.org/10.1146/annurev-virology-110615-042238.

52. K. Ito, M. Yoneda, K. Sakamoto, and M. Mizokami, "Virological and Clinical Characteristics of Hepatitis B Virus Genotype A," *Journal of Gastroenterology* 53 (2018): 18, https://doi.org/10.1007/s00535-017-1367-5.

53. C. Stross, S. Kluge, K. Weissenberger, E. Winands, D. Häussinger, and R. Kubitz, "A Dileucine Motif Is Involved in Plasma Membrane Expression and Endocytosis of Rat Sodium Taurocholate Cotransporting Polypeptide (Ntcp)," *American Journal of Physiology Gastrointestinal and Liver Physiology* 305 (2013): G722, https://doi.org/10.1152/ajpgi.00056.2013.

54. a) Y. Ni, F. A. Lempp, S. Mehrle, et al., "Hepatitis B and D Viruses Exploit Sodium Taurocholate Co-Transporting Polypeptide for Species-Specific Entry Into Hepatocytes," *Gastroenterology* 146 (2014): 1070, https://doi.org/10.1053/j.gastro.2013.12.024. b) B. Rabe, A. Vlachou, N. Panté, A. Helenius, and M. Kann, "Nuclear Import of Hepatitis B Virus Capsids and Release of the Viral Genome," *PNAS* 100 (2003): 9849, https://doi.org/10.1073/pnas.1730940100.

55. C. Königer, I. Wingert, M. Marsmann, C. Rösler, J. Beck, and M. Nassal, "Involvement of the Host DNA-Repair Enzyme TDP2 in Formation of the Covalently Closed Circular DNA Persistence Reservoir of Hepatitis B Viruses," *PNAS* 111 (2014): 4244, https://doi.org/10.1073/pnas.1409986111.

56. a) W. Yan, D. Rao, F. Fan, H. Liang, Z. Zhang, and H. Dong, "Hepatitis B Virus X Protein and TGF-β: Partners in the Carcinogenic Journey of Hepatocellular Carcinoma," *Frontiers in Oncology* 14 (2024): 1407434, https://doi.org/10.3389/fonc.2024.1407434. b) L. Yang, T. Zou, Y. Chen, et al., "Hepatitis B Virus X Protein Mediated Epigenetic Alterations in the paThogenesis of Hepatocellular Carcinoma," *Hepatology International* 16 (2022): 741, https://doi.org/10.1007/s12072-022-10351-6.

57. F. Bonino, P. Colombatto, and M. R. Brunetto, "HBeAg-Negative/Anti-HBe-Positive Chronic Hepatitis B: A 40-Year-Old History," *Viruses* 14 (2022): 1691, https://doi.org/10.3390/v14081691.

58. F. Zhao, X. Xie, X. Tan, et al., "The Functions of Hepatitis B Virus Encoding Proteins: Viral Persistence and Liver Pathogenesis," *Frontiers in Immunology* 12 (2021): 691766, https://doi.org/10.3389/fimmu.2021.691766.

59. a) S. Schädler and E. Hildt, "HBV Life Cycle: Entry and Morphogenesis," *Viruses* 1 (2009): 185, https://doi.org/10.3390/v1020185. b) R. A. A. Pondé and G. S. P. Amorim, "Exchanges in the 'a' Determinant of the Hepatitis B Virus Surface Antigen Revisited," *Virology* 599 (2024): 110184, https://doi.org/10.1016/j.virol.2024.110184.

60. A. Kramvis and M. C. Kew, "Structure and Function of the Encapsidation Signal of Hepadnaviridae," *Journal of Viral Hepatitis* 5 (1998): 357, https://doi.org/10.1046/j.1365-2893.1998.00124.x.

61. A.-F. Legrand, J. Lucifora, B. Lacombe, et al., "Farnesoid X Receptor Alpha Ligands Inhibit HDV In Vitro Replication and Virion Infectivity," *Hepatology Communications* 7 (2023): 0078, https://doi.org/10.1097/HC9.0000000000000078.

62. J. E. Tavis and D. Ganem, "Evidence for Activation of the Hepatitis B Virus Polymerase by Binding of Its RNA Template," *Journal of Virology* 70 (1996): 5741, https://doi.org/10.1128/JVI.70.9.5741-5750.1996.

63. M. Nassal, "Hepatitis B Viruses: Reverse Transcription a Different Way," *Virus Research* 134 (2008): 235, https://doi.org/10.1016/j.virusres.2007.12.024.

64. a) D. D. Loeb, R. C. Hirsch, and D. Ganem, "Sequence-Independent RNA Cleavages Generate the Primers for Plus Strand DNA Synthesis in Hepatitis B Viruses: Implications for Other Reverse Transcribing Elements," *The EMBO Journal* 10 (1991): 3533, https://doi.org/10.1002/j.1460-2075.1991.tb04917.x. b) J. Beck and M. Nassal, "Hepatitis B Virus Replication," *World Journal of Gastroenterology* 13 (2007): 48, https://doi.org/10.3748/wjg.v13.i1.48.

65. L.-L. Wu, X.-B. Yang, Z.-M. Huang, H.-Z. Liu, and G.-X. Wu, "In Vivo and In Vitro Antiviral Activity of Hyperoside Extracted From *Abelmoschus manihot* (L) Medik," *Acta Pharmacologica Sinica* 28 (2007): 404, https://doi.org/10.1111/j.1745-7254.2007.00510.x.

66. R. L. Huang, C. C. Chen, H. L. Huang, et al., "Anti-Hepatitis B Virus Effects of Wogonin Isolated From *Scutellaria baicalensis*," *Planta Medica* 66 (2000): 694, https://doi.org/10.1055/s-2000-9775.

67. Q. Guo, L. Zhao, Q. You, et al., "Anti-Hepatitis B Virus Activity of Wogonin In Vitro and In Vivo," *Antiviral Research* 74 (2007): 16, https://doi.org/10.1016/j.antiviral.2007.01.002.

68. H.-L. Wang, C.-A. Geng, Y.-B. Ma, X.-M. Zhang, and J.-J. Chen, "Three New Secoiridoids, Swermacrolactones A–C and Anti-Hepatitis B Virus Activity From *Swertia macrosperma*," *Fitoterapia* 89 (2013): 183, https://doi.org/10.1016/j.fitote.2013.06.002.

69. H. Huang, W. Zhou, H. Zhu, P. Zhou, and X. Shi, "Baicalin Benefits the Anti-HBV Therapy via Inhibiting HBV Viral RNAs," *Toxicology and Applied Pharmacology* 323 (2017): 36, https://doi.org/10.1016/j.taap.2017.03.016.

70. T. Pollicino, C. Musolino, N. Irrera, et al., "Flavocoxid Exerts a Potent Antiviral Effect Against Hepatitis B Virus," *Inflammation Research* 67 (2018): 89, https://doi.org/10.1007/s00011-017-1099-2.

71. G. Hu, J. Xue, J. Liu, et al., "Baicalin Induces IFN-α/β and IFN-γ Expressions in Cultured Mouse Pulmonary Microvascular Endothelial Cells," *Journal of Integrative Agriculture* 11 (2012): 646, https://doi.org/10.1016/S2095-3119(12)60052-5.

72. S. G. Park, H. M. Ryu, S.-O. Lim, Y.-I. Kim, S. B. Hwang, and G. Jung, "Interferon-γ Inhibits Hepatitis B Virus-Induced NF-κB Activation Through Nuclear Localization of NF-κB-Inducing Kinase," *Gastroenterology* 128 (2005): 2042, https://doi.org/10.1053/j.gastro.2005.03.002.

73. P. Bakun, D. T. Mlynarczyk, T. Koczorowski, et al., "Tea-Break With Epigallocatechin Gallate Derivatives—Powerful Polyphenols of Great Potential for Medicine," *European Journal of Medicinal Chemistry* 261 (2023): 115820, https://doi.org/10.1016/j.ejmech.2023.115820.

74. H.-C. Huang, M.-H. Tao, T.-M. Hung, J.-C. Chen, Z.-J. Lin, and C. Huang, "(−)-Epigallocatechin-3-Gallate Inhibits Entry of Hepatitis B Virus Into Hepatocytes," *Antiviral Research* 111 (2014): 100, https://doi.org/10.1016/j.antiviral.2014.09.009.

75. I. Mellman, "Endocytosis and Molecular Sorting," *Annual Review of Cell and Developmental Biology* 12 (1996): 575–625, https://doi.org/10.1146/annurev.cellbio.12.1.575.

76. W. He, L.-X. Li, Q.-J. Liao, C.-L. Liu, and X.-L. Chen, "Epigallocatechin Gallate Inhibits HBV DNA Synthesis in a Viral Replication—Inducible Cell Line," *World Journal of Gastroenterology* 17 (2011): 1507, https://doi.org/10.3748/wjg.v17.i11.1507.

77. J. Xu, W. Gu, C. Li, et al., "Epigallocatechin Gallate Inhibits Hepatitis B Virus via Farnesoid X Receptor Alpha," *Journal of Natural Medicines* 70 (2016): 584, https://doi.org/10.1007/s11418-016-0980-6.

78. Y. Tsukamoto, S. Ikeda, K. Uwai, et al., "Rosmarinic Acid Is a Novel Inhibitor for Hepatitis B Virus Replication Targeting Viral Epsilon RNA-Polymerase Interaction," *PLoS ONE* 13 (2018): 0197664, https://doi.org/10.1371/journal.pone.0197664.

79. D. K. Lvov, M. Y. Shchelkanov, S. V. Alkhovsky, and P. G. Deryabin, *Zoonotic Viruses in Northern Eurasia* (Academic Press, 2015), https://doi.org/10.1016/B978-0-12-801742-5.00008-8.

80. A. C. Lowen, "It's in the Mix: Reassortment of Segmented Viral Genomes," *PLoS Pathogens* 14 (2018): 1007200, https://doi.org/10.1371/journal.ppat.1007200.

81. J. M. Hübschen, I. Gouandjika-Vasilache, and J. Dina, "Measles," *Lancet* 399 (2022): 678, https://doi.org/10.1016/S0140-6736(21)02004-3.

82. a) L. Amurri, O. Reynard, D. Gerlier, B. Horvat, and M. Iampietro, "Measles Virus-Induced Host Immunity and Mechanisms of Viral Evasion," *Viruses* 14 (2022): 2641, https://doi.org/10.3390/v14122641. b) P. A. Rota, W. J. Moss, M. Takeda, R. L. de Swart, K. M. Thompson, and J. L. Goodson, "Measles," *Nature Reviews Disease Primers* 2 (2016): 16049, https://doi.org/10.1038/nrdp.2016.49.

83. B. Ahmad, M. Sagide, S. Ntamwinja, et al., "National Burden of Ebola Virus Disease in Democratic Republic of the Congo: The Urgency to Act," *Annals of Medicine and Surgery (Lond)* 86 (2024): 4579, https://doi.org/10.1097/MS9.0000000000002213.

84. B. Zawilińska and M. Kosz-Vnenchak, "General introduction into the Ebola virus biology and disease", *Folia Medica Cracoviensia* 54 (2014): 57.

85. E. M. Leroy, J.-P. Gonzalez, and S. Baize, "Ebola and Marburg Haemorrhagic Fever Viruses: Major Scientific Advances, but a Relatively Minor Public Health Threat for Africa," *Clinical Microbiology and Infection* 17 (2011): 964, https://doi.org/10.1111/j.1469-0691.2011.03535.x.

86. Z. Y. Yang, H. J. Duckers, N. J. Sullivan, A. Sanchez, E. G. Nabel, and G. J. Nabel, "Identification of the Ebola Virus Glycoprotein as the Main Viral Determinant of Vascular Cell Cytotoxicity and Injury," *Nature Medicine* 6 (2000): 886, https://doi.org/10.1038/78645.

87. A. A. Ansari, "Clinical Features and Pathobiology of Ebolavirus Infection," *Journal of Autoimmunity* 55 (2014): 1, https://doi.org/10.1016/j.jaut.2014.09.001.

88. K. Morán-Santibañez, M. A. Peña-Hernández, L. E. Cruz-Suárez, et al., "Virucidal and Synergistic Activity of Polyphenol-Rich Extracts of Seaweeds Against Measles Virus," *Viruses* 10 (2018): 465, https://doi.org/10.3390/v10090465.

89. S. Rebensburg, M. Helfer, M. Schneider, et al., "Potent In Vitro Antiviral Activity of *Cistus incanus* Extract Against HIV and Filoviruses Targets Viral Envelope Proteins," *Scientific Reports* 6 (2016): 20394, https://doi.org/10.1038/srep20394.

90. S. Pleško, H. Volk, M. Lukšič, and Č. Podlipnik, "In Silico Study of Plant Polyphenols' Interactions With VP24–Ebola Virus Matrix Protein," *Acta Chimica Slovenica* 62 (2015): 555.

91. S. Yang, M. Xu, E. M. Lee, et al., "Emetine Inhibits Zika and Ebola Virus Infections Through Two Molecular Mechanisms: Inhibiting Viral Replication and Decreasing Viral Entry," *Cell Discovery* 4 (2018): 31, https://doi.org/10.1038/s41421-018-0034-1.

92. A. Varsani, P. Lefeuvre, P. Roumagnac, and D. Martin, "Notes on Recombination and Reassortment in Multipartite/Segmented Viruses," *Current Opinion in Virology* 33 (2018): 156, https://doi.org/10.1016/j.coviro.2018.08.013.

93. M. von Itzstein, "The war against influenza: discovery and development of sialidase inhibitors", *Nature Reviews Drug Discovery* 6 (2007): 967, https://doi.org/10.1038/nrd2400.

94. M. Kang, L.-F. Wang, B.-W. Sun, et al., "Zoonotic Infections by Avian Influenza Virus: Changing Global Epidemiology, Investigation, and Control," *The Lancet Infectious Diseases* 24 (2024): 522, https://doi.org/10.1016/S1473-3099(24)00234-2.

95. A. J. Eisfeld, G. Neumann, and Y. Kawaoka, "At the Centre: Influenza A Virus Ribonucleoproteins," *Nature Reviews Microbiology* 13 (2015): 28, https://doi.org/10.1038/nrmicro3367.

96. I. A. Wilson, J. J. Skehel, and D. C. Wiley, "Structure of the Haemagglutinin Membrane Glycoprotein of Influenza Virus at 3 Å Resolution," *Nature* 289 (1981): 366, https://doi.org/10.1038/289366a0.

97. M. Bui, G. Whittaker, and A. Helenius, "Effect of M1 Protein and Low pH on Nuclear Transport of Influenza Virus Ribonucleoproteins," *Journal of Virology* 70 (1996): 8391, https://doi.org/10.1128/jvi.70.12.8391-8401.1996.

98. T. Carter and M. Iqbal, "The Influenza A Virus Replication Cycle: A Comprehensive Review," *Viruses* 16 (2024): 316, https://doi.org/10.3390/v16020316.

99. P. Palese, K. Tobita, M. Ueda, and R. W. Compans, "Characterization of Temperature Sensitive Influenza Virus Mutants Defective in Neuraminidase," *Virology* 61 (1974): 397, https://doi.org/10.1016/0042-6822(74)90276-1.

100. V. Zima, K. Radilová, M. Kožíšek, et al., "Unraveling the Anti-Influenza Effect of Flavonoids: Experimental Validation of Luteolin and Its Congeners as Potent Influenza Endonuclease Inhibitors," *European Journal of Medicinal Chemistry* 208 (2020): 112754, https://doi.org/10.1016/j.ejmech.2020.112754.

101. Z. Liu, J. Zhao, W. Li, et al., "Computational Screen and Experimental Validation of Anti-Influenza Effects of Quercetin and Chlorogenic Acid From Traditional Chinese Medicine," *Scientific Reports* 6 (2016): 19095, https://doi.org/10.1038/srep19095.

102. P. Mehrbod, S. N. Ebrahimi, F. Fotouhi, et al., "Experimental Validation and Computational Modeling of Anti-Influenza Effects of Quercetin-3-O-α-L-Rhamnopyranoside From Indigenous South African Medicinal Plant *Rapanea melanophloeos*," *BMC Complementary and Alternative Medicine* 19 (2019): 346, https://doi.org/10.1186/s12906-019-2774-3.

103. F. Wang, Y.-S. Tang, F. Cao, J.-W. Shou, C.-K. Wong, and P.-C. Shaw, "3,4,5-Tri-O-Caffeoylquinic Acid Attenuates Influenza A Virus Induced Inflammation Through Toll-Like Receptor 3/7 Activated Signaling Pathway," *Phytomedicine* 132 (2024): 155896, https://doi.org/10.1016/j.phymed.2024.155896.

104. B. Zhou, L. Wang, S. Yang, et al., "Pyrogallol Protects Against Influenza A Virus-Triggered Lethal Lung Injury by Activating the Nrf2–PPAR-γ–HO-1 Signaling Axis," *MedComm (2020)* 5 (2024): 531, https://doi.org/10.1002/mco2.531.

105. A. T. Palamara, L. Nencioni, K. Aquilano, et al., "Inhibition of Influenza A Virus Replication by Resveratrol," *Journal of Infectious Diseases* 191 (2005): 1719, https://doi.org/10.1086/429694.

106. F. Medini, R. Ksouri, K. Msaada, and J. Legault, "Phenolic Compounds From *Limonium densiflorum*: A Multifaceted Approach to Antioxidant, Anti-Inflammatory, Anticancer, and Anti-Influenza Activities," *International Journal of Environmental Health Research* 35 (2025): 94, https://doi.org/10.1080/09603123.2024.2342572.

107. C. Tang, J. Carrera Montoya, S. Fritzlar, M. Flavel, S. L. Londrigan, and J. M. Mackenzie, "Polyphenol Rich Sugarcane Extract (PRSE) Has Potential Antiviral Activity Against Influenza A Virus In Vitro," *Virology* 590 (2024): 109969, https://doi.org/10.1016/j.virol.2023.109969.

108. S. Modrow, D. Falke, U. Truyen, and H. Schätzl, "Characterization of *Herpesvirus saimiri* and *Herpesvirus ateles* Structural Proteins," *Molecular Virology* 125 (1983): 251, https://doi.org/10.1007/978-3-642-20718-1_14.

109. a) B. Salzberger, F. Buder, B. Lampl, et al., "Epidemiology of SARS-CoV-2," *Infection* 49 (2021): 233, https://doi.org/10.1007/s15010-020-01531-3. b) D. Isaacs, D. Flowers, J. R. Clarke, H. B. Valman, and M. R. MacNaughton, "Epidemiology of Coronavirus Respiratory Infections," *Archives of Disease in Childhood* 58 (1983): 500, https://doi.org/10.1136/adc.58.7.500. c) D. Raoult, A. Zumla, F. Locatelli, G. Ippolito, and G. Kroemer, "Coronavirus Infections: Epidemiological, Clinical and Immunological Features and Hypotheses," *Cell Stress* 4 (2020): 66, 10.15698/cst2020.04.216.

110. T. M. Yuill, "The Ecology of Tropical Arthropod-Borne Viruses," *Annual Review of Ecology and Systematics* 17 (1986): 189.

111. E. G. Westaway, M. A. Brinton, S. Gaidamovich, et al., "Flaviviridae," *Intervirology* 24 (1985): 183, https://doi.org/10.1159/000149642.

112. D. M. Vu, D. Jungkind, and A. D. LaBeaud, "Chikungunya Virus," *Clinics in Laboratory Medicine* 37 (2017): 371, https://doi.org/10.1016/j.cll.2017.01.008.

113. M. Lauer Georg and D. Walker Bruce, "Hepatitis C Virus Infection," *New England Journal of Medicine* 345 (2001): 41, https://doi.org/10.1056/NEJM200107053450107.

114. C. J. Puntasecca, C. H. King, and A. D. LaBeaud, "Measuring the Global Burden of Chikungunya and Zika Viruses: A Systematic Review," *PLoS Neglected Tropical Diseases* 15 (2021): 0009055, https://doi.org/10.1371/journal.pntd.0009055.

115. S. Voss and C. Nitsche, "Inhibitors of the Zika Virus Protease NS2B-NS3," *Bioorganic & Medicinal Chemistry Letters* 30 (2020): 126965, https://doi.org/10.1016/j.bmcl.2020.126965.

116. D. R. Perera, N. D. Ranadeva, K. Sirisena, and K. J. Wijesinghe, "Roles of NS1 Protein in Flavivirus Pathogenesis," *ACS Infectious Diseases* 10 (2024): 20, https://doi.org/10.1021/acsinfecdis.3c00566.

117. World Health Organization, COVID-19 Deaths | WHO COVID-19 Dashboard: Datadot, accessed December, 2024, https://data.who.int/dashboards/covid19/cases.

118. K. Gorshkov, S. A. Shiryaev, S. Fertel, et al., "Zika Virus: Origins, Pathological Action, and Treatment Strategies," *Frontiers in Microbiology* 9 (2019): 3252, https://doi.org/10.3389/fmicb.2018.03252.

119. M. A. Brinton and M. Basu, "Functions of the 3′ and 5′ Genome RNA Regions of Members of the Genus Flavivirus," *Virus Research* 206 (2015): 108, https://doi.org/10.1016/j.virusres.2015.02.006.

120. a) J. L. Miller, B. J. M. de Wet, L. Martinez-Pomares, et al., "The Mannose Receptor Mediates Dengue Virus Infection of Macrophages," *PLoS Pathogens* 4 (2008): 17, https://doi.org/10.1371/journal.ppat.0040017. b) N. L. Miller, T. Clark, R. Raman, and R. Sasisekharan, "Glycans In Virus-Host Interactions: A Structural Perspective," *Frontiers in Molecular Biosciences* 8 (2021): 666756, https://doi.org/10.3389/fmolb.2021.666756.

121. C. Nitsche, "Proteases From Dengue, West Nile and Zika Viruses as Drug Targets," *Biophysical Reviews* 11 (2019): 157, https://doi.org/10.1007/s12551-019-00508-3.

122. S. Welsch, S. Miller, I. Romero-Brey, et al., "Composition and Three-Dimensional Architecture of the Dengue Virus Replication and Assembly Sites," *Cell Host & Microbe* 5 (2009): 365, https://doi.org/10.1016/j.chom.2009.03.007.

123. a) B. L. Alvin Chew, Q. Pan, H. Hu, and D. Luo, "Structural Biology of Flavivirus NS1 Protein and Its Antibody Complexes," *Antiviral Research* 227 (2024): 105915, https://doi.org/10.1016/j.antiviral.2024.105915. b) S. Noisakran, S. Sengsai, V. Thongboonkerd, et al., "Identification of Human hnRNP C1/C2 as a Dengue Virus NS1-Interacting Protein," *Biochemical*

and Biophysical Research Communications 372 (2008): 67, https://doi.org/10.1016/j.bbrc.2008.04.165.

124. A. K. Falconar, "The Dengue Virus Nonstructural-1 Protein (NS1) Generatesantibodies to Common Epitopes on Human Blood Clotting, Integrin/Adhesin Proteins and Binds to Humanendothelial Cells: Potential Implications in Haemorrhagic Fever Pathogenesis," *Archives of Virology* 142 (1997): 897, https://doi.org/10.1007/s007050050127.

125. T. Teramoto, K. H. Choi, and R. Padmanabhan, "Flavivirus Proteases: The Viral Achilles Heel to Prevent Future Pandemics," *Antiviral Research* 210 (2023): 105516, https://doi.org/10.1016/j.antiviral.2022.105516.

126. V. Boldescu, M. A. M. Behnam, N. Vasilakis, and C. D. Klein, "Broad-Spectrum Agents for Flaviviral Infections: Dengue, Zika and Beyond," *Nature Reviews Drug Discovery* 16 (2017): 565, https://doi.org/10.1038/nrd.2017.33.

127. a) J. Nithya Shree, T. Premika, S. Sharlin, and A. Annie Aglin, "Diverse Approaches to Express Recombinant Spike Protein: A Comprehensive Review," *Protein Expression and Purification* 223 (2024): 106556, https://doi.org/10.1016/j.pep.2024.106556. b) S. Yuan, B. Yan, J. Cao, et al., "SARS-CoV-2 Exploits Host DGAT and ADRP for Efficient Replication," *Cell Discovery* 7 (2021): 100, https://doi.org/10.1038/s41421-021-00338-2.

128. Á. Vázquez-Calvo, N. Jiménez de Oya, M. A. Martín-Acebes, E. Garcia-Moruno, and J.-C. Saiz, "Antiviral Properties of the Natural Polyphenols Delphinidin and Epigallocatechin Gallate Against the Flaviviruses West Nile Virus, Zika Virus, and Dengue Virus," *Frontiers in Microbiology* 8 (2017): 1314, https://doi.org/10.3389/fmicb.2017.01314.

129. B. M. Carneiro, M. N. Batista, A. C. S. Braga, M. L. Nogueira, and P. Rahal, "The Green Tea Molecule EGCG Inhibits Zika Virus Entry," *Virology* 496 (2016): 215, https://doi.org/10.1016/j.virol.2016.06.012.

130. D. Kumar, N. Sharma, M. Aarthy, S. K. Singh, and R. Giri, "Mechanistic Insights into Zika Virus NS3 Helicase Inhibition by Epigallocatechin-3-Gallate", *ACS Omega* 5 (2020): 11217, https://doi.org/10.1021/acsomega.0c01353.

131. M. Zou, H. Liu, J. Li, et al., "Structure-Activity Relationship of Flavonoid Bifunctional Inhibitors Against Zika Virus Infection," *Biochemical Pharmacology* 177 (2020): 113962, https://doi.org/10.1016/j.bcp.2020.113962.

132. L. A. Baltina, H.-C. Lai, Y.-C. Liu, et al., "Glycyrrhetinic Acid Derivatives as Zika Virus Inhibitors: Synthesis and Antiviral Activity In Vitro," *Bioorganic & Medicinal Chemistry* 41 (2021): 116204, https://doi.org/10.1016/j.bmc.2021.116204.

133. W. Qian, G.-F. Zhou, X. Ge, et al., "Discovery of Dehydroandrographolide Derivatives With C19 Hindered Ether as Potent Anti-ZIKV Agents With Inhibitory Activities to MTase of ZIKV NS5," *European Journal of Medicinal Chemistry* 243 (2022): 114710, https://doi.org/10.1016/j.ejmech.2022.114710.

134. R. Lani, P. Hassandarvish, C. W. Chiam, et al., "Antiviral Activity of Silymarin Against Chikungunya Virus," *Scientific Reports* 5 (2015): 11421, https://doi.org/10.1038/srep11421.

135. A. Mohd, N. Zainal, K.-K. Tan, and S. AbuBakar, "Resveratrol Affects Zika Virus Replication In Vitro," *Scientific Reports* 9 (2019): 14336, https://doi.org/10.1038/s41598-019-50674-3.

136. Q. Shao, T. Liu, W. Wang, T. Liu, X. Jin, and Z. Chen, "Promising Role of Emodin as Therapeutics to Against Viral Infections," *Frontiers in Pharmacology* 13 (2022): 902626, https://doi.org/10.3389/fphar.2022.902626.

137. C. C. S. Menezes da Silveira, D. A. Luz, C. C. S. da Silva, et al., "Propolis: A Useful Agent on Psychiatric and Neurological Disorders? A Focus on CAPE and Pinocembrin Components," *Medicinal Research Reviews* 41 (2021): 1195–1215, https://doi.org/10.1002/med.21757.

138. J. L. Lee, M. W. C. Loe, R. C. H. Lee, and J. J. H. Chu, "Antiviral Activity of Pinocembrin Against Zika Virus Replication," *Antiviral Research* 167 (2019): 13, https://doi.org/10.1016/j.antiviral.2019.04.003.

139. P. Anand, S. G. Thomas, A. B. Kunnumakkara, et al., "Biological Activities of Curcumin and Its Analogues (Congeners) Made by Man and Mother Nature," *Biochemical Pharmacology* 76 (2008): 1590, https://doi.org/10.1016/j.bcp.2008.08.008.

140. A. Balasubramanian, R. Pilankatta, T. Teramoto, et al., "Inhibition of Dengue Virus by Curcuminoids," *Antiviral Research* 162 (2019): 71, https://doi.org/10.1016/j.antiviral.2018.12.002.

141. a) F. Zahedipour, S. A. Hosseini, T. Sathyapalan, et al., "Potential Effects of Curcumin in the Treatment of COVID-19 Infection," *Phytotherapy Research* 34 (2020): 2911, https://doi.org/10.1002/ptr.6738. b) T.-Y. Chen, D.-Y. Chen, H.-W. Wen, et al., "Inhibition of Enveloped Viruses Infectivity by Curcumin," *PLoS ONE* 8 (2013): 62482, https://doi.org/10.1371/journal.pone.0062482.

142. B. C. Mounce, T. Cesaro, L. Carrau, T. Vallet, and M. Vignuzzi, "Curcumin Inhibits Zika and Chikungunya Virus Infection by Inhibiting Cell Binding," *Antiviral Research* 142 (2017): 148, https://doi.org/10.1016/j.antiviral.2017.03.014.

143. C. C. C. Anggakusuma, L. M. Schang, H. Rachmawati, et al., "Turmeric Curcumin Inhibits Entry of All Hepatitis C Virus Genotypes Into Human Liver Cells," *Gut* 63 (2014): 1137, https://doi.org/10.1136/gutjnl-2012-304299.

144. K. Dutta, D. Ghosh, and A. Basu, "Curcumin Protects Neuronal Cells From Japanese Encephalitis Virus-Mediated Cell Death and Also Inhibits Infective Viral Particle Formation by Dysregulation of Ubiquitin–Proteasome System," *Journal of Neuroimmune Pharmacology* 4 (2009): 328, https://doi.org/10.1007/s11481-009-9158-2.

145. A. Narayanan, K. Kehn-Hall, S. Senina, et al., "Curcumin Inhibits Rift Valley Fever Virus Replication in Human Cells," *Journal of Biological Chemistry* 287 (2012): 33198, https://doi.org/10.1074/jbc.M112.356535.

146. T. Ohishi, S. Goto, P. Monira, M. Isemura, and Y. Nakamura, "Anti-Inflammatory Action of Green Tea," *Anti-Inflammatory & Anti-Allergy Agents in Medicinal Chemistry* 15 (2016): 74, https://doi.org/10.2174/1871523015666160915154443.

147. Q. T. Ain, N. Saleem, N. Munawar, R. Nawaz, F. Naseer, and S. Ahmed, "Quest for Malaria Management Using Natural Remedies," *Frontiers in Pharmacology* 15 (2024): 1359890, https://doi.org/10.3389/fphar.2024.1359890.

148. S. Malakar, L. Sreelatha, T. Dechtawewat, et al., "Drug Repurposing of Quinine as Antiviral Against Dengue Virus Infection," *Virus Research* 255 (2018): 171, https://doi.org/10.1016/j.virusres.2018.07.018.

149. E. Clain, J. G. Haddad, A. C. Koishi, et al., "The Polyphenol-Rich Extract From *Psiloxylon mauritianum*, an Endemic Medicinal Plant From Reunion Island, Inhibits the Early Stages of Dengue and Zika Virus Infection," *International Journal of Molecular Sciences* 20 (2019): 1860, https://doi.org/10.3390/ijms20081860.

150. a) S. Singh, A. Sonawane, and S. Sadhukhan, "Plant-Derived Natural Polyphenols as Potential Antiviral Drugs Against SARS-CoV-2 via RNA-Dependent RNA Polymerase (RdRp) Inhibition: An In-Silico Analysis," *Journal of Biomolecular Structure & Dynamics* 39 (2021): 6249, https://doi.org/10.1080/07391102.2020.1796810. b) C. Wu, Y. Liu, Y. Yang, et al., "Analysis of Therapeutic Targets for SARS-CoV-2 and Discovery of Potential Drugs by Computational Methods," *Acta Pharmaceutica Sinica B* 10 (2020): 766, https://doi.org/10.1016/j.apsb.2020.02.008.

151. L. Yang and Z. Wang, "Natural Products, Alone or in Combination With FDA-Approved Drugs, to Treat COVID-19 and Lung Cancer," *Biomedicines* 9 (2021): 689, https://doi.org/10.3390/biomedicines9060689.

152. M. Y. Zakaria, I. Zaki, M. Alhomrani, A. S. Alamri, O. Abdulaziz, and M. A. S. Abourehab, "Boosting the Anti-MERS-CoV Activity and Oral Bioavailability of Resveratrol via PEG-Stabilized Emulsomal Nano-Carrier: Factorial Design, In-Vitro and In-Vivo Assessments," *Drug Delivery* 29 (2022): 3155, https://doi.org/10.1080/10717544.2022.2126028.

153. M. Bahun, M. Jukić, D. Oblak, et al., "Inhibition of the SARS-CoV-2 3CLpro Main Protease by Plant Polyphenols," *Food Chemistry* 373 (2022): 131594, https://doi.org/10.1016/j.foodchem.2021.131594.

154. M. S. Fam, C. A. Sedky, N. O. Turky, H.-G. Breitinger, and U. Breitinger, "Channel Activity of SARS-CoV-2 Viroporin ORF3a Inhibited by Adamantanes and Phenolic Plant Metabolites," *Scientific Reports* 13 (2023): 5328, https://doi.org/10.1038/s41598-023-31764-9.

155. J. L. Bolton, T. L. Dunlap, A. Hajirahimkhan, et al., "The Multiple Biological Targets of Hops and Bioactive Compounds," *Chemical Research in Toxicology* 32 (2019): 222, https://doi.org/10.1021/acs.chemrestox.8b00345.

156. A.-M. Herzog, K. Göbel, L. Marongiu, et al., "Compounds Derived From *Humulus lupulus* Inhibit SARS-CoV-2 Papain-Like Protease and Virus Replication," *Phytomedicine* 123 (2024): 155176, https://doi.org/10.1016/j.phymed.2023.155176.

157. G. J. Soufi and S. Iravani, "Potential Inhibitors of SARS-CoV-2: Recent Advances," *Journal of Drug Targeting* 29 (2021): 349, https://doi.org/10.1080/1061186X.2020.1853736.

158. S.-C. Lin, C.-T. Ho, W.-H. Chuo, S. Li, T. T. Wang, and C.-C. Lin, "Effective Inhibition of MERS-CoV Infection by Resveratrol," *BMC Infectious Diseases* 17 (2017): 144, https://doi.org/10.1186/s12879-017-2253-8.

159. S. Pasquereau, Z. Nehme, S. Haidar Ahmad, et al., "Resveratrol Inhibits HCoV-229E and SARS-CoV-2 Coronavirus Replication In Vitro," *Viruses* 13 (2021): 354, https://doi.org/10.3390/v13020354.

160. L. Yi, Z. Li, K. Yuan, et al., "Small Molecules Blocking the Entry of Severe Acute Respiratory Syndrome Coronavirus Into Host Cells," *Journal of Virology* 78 (2004): 11334, https://doi.org/10.1128/JVI.78.20.11334-11339.2004.

161. T. E. Tallei, S. G. Tumilaar, N. J. Niode, et al., "Potential of Plant Bioactive Compounds as SARS-CoV-2 Main Protease (M^{pro}) and Spike (S) Glycoprotein Inhibitors: A Molecular Docking Study". *Scientifica (Cairo)* 2020 (2020): 6307457, https://doi.org/10.1155/2020/6307457.

162. C. Lammi and A. Arnoldi, "Food-Derived Antioxidants and COVID-19," *Journal of Food Biochemistry* 45 (2021): 13557, https://doi.org/10.1111/jfbc.13557.

163. A. B. Jena, N. Kanungo, V. Nayak, G. B. N. Chainy, and J. Dandapat, "Catechin and Curcumin Interact With S Protein of SARS-CoV2 and ACE2 of Human Cell Membrane: Insights From Computational Studies," *Scientific Reports* 11 (2021): 2043, https://doi.org/10.1038/s41598-021-81462-7.

164. J. R. Horne and M.-C. Vohl, "Biological Plausibility for Interactions Between Dietary Fat, Resveratrol, ACE2, and SARS-CoV Illness Severity," *American Journal of Physiology. Endocrinology and Metabolism* 318 (2020): 830, https://doi.org/10.1152/ajpendo.00150.2020.

165. W. Wang, W. Li, Z. Wen, et al., "Gossypol Broadly Inhibits Coronaviruses by Targeting RNA-Dependent RNA Polymerases," *Advanced Science (Weinh)* 9 (2022): 2203499, https://doi.org/10.1002/advs.202203499.

166. a) Y. Wu, L. Jiang, W. Ran, K. Zhong, Y. Zhao, and H. Gao, "Antimicrobial Activities of Natural Flavonoids Against Foodborne Pathogens and Their Application in Food Industry," *Food Chemistry* 460 (2024): 140476, https://doi.org/10.1016/j.foodchem.2024.140476. b) Y. Liu, N. Yan, Q. Chen, et al., "Research Advances in citrus Polyphenols: Green Extraction Technologies, Gut Homeostasis Regulation, and Nano-Targeted Delivery System Application," *Critical Reviews in Food Science and Nutrition* 64 (2024): 11493, https://doi.org/10.1080/10408398.2023.2239350. c) J. I. Obeme-Nmom, R. O. Abioye, S. S. Reyes Flores, and C. C. Udenigwe, "Regulation of Redox Enzymes by Nutraceuticals: A Review of the Roles of Antioxidant Polyphenols and Peptides," *Food & Function* 15 (2024): 10956, https://doi.org/10.1039/d4fo03549f.

167. M. Latos-Brozio and A. Masek, "Structure-Activity Relationships Analysis of Monomeric and Polymeric Polyphenols (Quercetin, Rutin and Catechin) Obtained by Various Polymerization Methods," *Chemistry and Biodiversity* 16 (2019): 1900426, https://doi.org/10.1002/cbdv.201900426.

168. a) K. E. Heim, A. R. Tagliaferro, and D. J. Bobilya, "Flavonoid Antioxidants: Chemistry, Metabolism and Structure-Activity Relationships," *Journal of Nutritional Biochemistry* 13 (2002): 572, https://doi.org/10.1016/s0955-2863(02)00208-5. b) T. Wu, X. Zang, M. He, S. Pan, and X. Xu, "Structure–Activity Relationship of Flavonoids on Their Anti-*Escherichia coli* Activity and Inhibition of DNA Gyrase," *Journal of Agricultural and Food Chemistry* 61 (2013): 8185, https://doi.org/10.1021/jf402222v. c) O. Farkas, J. Jakus, and K. Héberger, "Quantitative Structure—Antioxidant Activity Relationships of Flavonoid Compounds," *Molecules (Basel, Switzerland)* 9 (2004): 1079, https://doi.org/10.3390/91201079. d) S. Burda and W. Oleszek, "Antioxidant and Antiradical Activities of Flavonoids," *Journal of Agricultural and Food Chemistry* 49 (2001): 2774, https://doi.org/10.1021/jf001413m. e) A. J. Dugas Jr, J. Castañeda-Acosta, G. C. Bonin, K. L. Price, N. H. Fischer, and G. W. Winston, "Evaluation of the Total Peroxyl Radical-Scavenging Capacity of Flavonoids: Structure−Activity Relationships," *Journal of Natural Products* 63 (2000): 327, https://doi.org/10.1021/np990352n. f) A.-L. Liu, H.-D. Wang, S. M. Lee, Y.-T. Wang, and G.-H. Du, "Structure–Activity Relationship of Flavonoids as Influenza Virus Neuraminidase Inhibitors and Their In Vitro Anti-Viral Activities," *Bioorganic & Medicinal Chemistry* 16 (2008): 7141, https://doi.org/10.1016/j.bmc.2008.06.049.

169. K. Kaihatsu, M. Yamabe, and Y. Ebara, "Antiviral Mechanism of Action of Epigallocatechin-3-O-Gallate and Its Fatty Acid Esters," *Molecules (Basel, Switzerland)* 23 (2018): 2475, https://doi.org/10.3390/molecules23102475.

170. a) K. Gryko, M. Kalinowska, P. Ofman, et al., "Natural Cinnamic Acid Derivatives: A Comprehensive Study on Structural, Anti/Pro-Oxidant, and Environmental Impacts," *Materials (Basel)* 14 (2021): 6098, https://doi.org/10.3390/ma14206098. b) J. Godos, F. Caraci, A. Micek, et al., "Dietary Phenolic Acids and Their Major Food Sources Are Associated With Cognitive Status in Older Italian Adults," *Antioxidants (Basel)* 10 (2021): 700, https://doi.org/10.3390/antiox10050700.

171. K. B. Pandey and S. I. Rizvi, "Plant Polyphenols as Dietary Antioxidants in Human Health and Disease," *Oxidative Medicine and Cellular Longevity* 2 (2009): 270, https://doi.org/10.4161/oxim.2.5.9498.

172. C. Rodríguez-García, C. Sánchez-Quesada, E. Toledo, M. Delgado-Rodríguez, and J. J. Gaforio, "Naturally Lignan-Rich Foods: A Dietary Tool for Health Promotion?" *Molecules (Basel, Switzerland)* 24 (2019): 917, https://doi.org/10.3390/molecules24050917.

173. M. Lončar, M. Jakovljević, D. Šubarić, et al., "Coumarins in Food and Methods of Their Determination," *Foods* 9 (2020): 645, https://doi.org/10.3390/foods9050645.

174. a) S. Egert and G. Rimbach, "Which Sources of Flavonoids: Complex Diets or Dietary Supplements?" *Advances in Nutrition* 2 (2011): 8, https://doi.org/10.3945/an.110.000026. b) T. T. H. Huynh, W. Wongmaneepratip, and K. Vangnai, "Relationship Between Flavonoid Chemical Structures and Their Antioxidant Capacity in Preventing Polycyclic Aromatic Hydrocarbons Formation in Heated Meat Model System," *Foods* 13 (2024): 1002, https://doi.org/10.3390/foods13071002.

175. T. Okuda and H. Ito, "Tannins of Constant Structure in Medicinal and Food Plants—Hydrolyzable Tannins and Polyphenols Related to Tannins," *Molecules (Basel, Switzerland)* 16 (2011): 2191, https://doi.org/10.3390/molecules16032191.

176. B. C. Mounce, T. Cesaro, L. Carrau, T. Vallet, and M. Vignuzzi, "Curcumin Inhibits Zika and Chikungunya Virus Infection by Inhibiting Cell Binding," *Antiviral Research* 142 (2017): 148, https://doi.org/10.1016/j.antiviral.2017.03.014.

177. Q. Wang, N. Zhu, J. Hu, et al., "The mTOR Inhibitor Manassantin B Reveals a Crucial Role of mTORC2 Signaling in Epstein-Barr Virus Reactivation," *Journal of Biological Chemistry* 295 (2020): 7431, https://doi.org/10.1074/jbc.RA120.012645.

178. S. Cao, S. Realegeno, A. Pant, P. S. Satheshkumar, and Z. Yang, "Suppression of Poxvirus Replication by Resveratrol," *Frontiers in Microbiology* 8 (2017): 2196, https://doi.org/10.3389/fmicb.2017.02196.