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REVIEW ARTICLE

Exploring the Antiviral Potential of Polyphenols against Re-emerging and Emerging Viral Infections: A Comprehensive Review

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Abstract

The emergence and re-emergence of viral diseases pose significant challenges to global public health. Polyphenols have emerged as promising candidates in the search for effective antiviral strategies because of their diverse biological activities and natural abundance. This comprehensive review aims to provide a detailed analysis of the antiviral potential of polyphenols against a spectrum of viral pathogens. The molecular mechanisms underlying the antiviral activity of polyphenols against coronaviruses, herpesviruses, hepatitis viruses, influenza viruses and noroviruses were thoroughly discussed. Several insights into their general characteristics, extraction methods and general health benefits were also provided. This was followed by an examination of the efficacy of polyphenols as antiviral agents in animal studies and clinical trials. Finally, the promising use of biocompatible nanocarriers was explored to enhance the bioactivity and bioavailability of polyphenols. Despite the progress made in understanding the antiviral activities of polyphenols, several research gaps warrant further investigation. Overall, this knowledge can guide future research and development efforts toward the utilisation of polyphenols as effective therapeutics against a broad range of viral pathogens.

Keywords: Antiviral Activity, Drug Discovery, Polyphenols, Viral Diseases

1. Introduction

The robust virulence of emerging and re-emerging viruses, along with the absence of potent antiviral drugs, presents a significant public health challenge. The development of affordable and low-toxicity broad-spectrum antiviral drugs has long been a priority in virology and pharmaceutics. The urgency for such drugs escalated during the COVID-19 pandemic, emphasising the need for compounds that can hinder viral entry and replication, while regulating the host immune response[1].

Currently, the field of medicine offers a diverse array of antiviral agents that target various stages of viral infections[2]. Synthetic antiviral drugs exhibit rapid action and often yield optimal therapeutic outcomes. However, they are burdened by numerous contraindications, side effects and drug resistance risks. In contrast, herbal antiviral drugs possess a broad array of activities including immunomodulatory, antioxidant and anti-inflammatory effects. They exhibit lower toxicity at effective doses and minimal adverse reactions. Herbal medicine shows promise as both

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a therapeutic and prophylactic approach for viral infections, warranting further exploration[1].

Research on antiviral compounds derived from natural sources has revealed their remarkable potential against viral infections. These compounds exhibit a range of mechanisms of action including immunostimulatory, antiviral, antioxidant and anti-inflammatory effects. Notably, viruses do not easily develop resistance to natural compounds. Consequently, numerous researchers have focused on exploring the potent antiviral activities of various plant-derived polyphenols, which have demonstrated promising results[3].

Polyphenols, a diverse group of secondary plant metabolites consisting of more than 8,000 structural variants (Table 1), have garnered significant interest. These compounds can be categorised as phenolic acids, flavonoids, lignans or stilbenes based on the arrangement of rings and connecting elements[4]. Various dietary sources that are rich in polyphenols including fruits, spices, vegetables, oils and seeds have been identified[5]. Numerous factors, including soil and climatic conditions, storage and processing techniques, harvest maturity, cultivation methods and light exposure, can influence the content of bioactive compounds[3].

Studies conducted both *in vivo* and *in vitro* have demonstrated the anti-inflammatory properties of polyphenols, demonstrating their ability to modulate immune regulation, inhibit cytokine storms and act as immunomodulators. These compounds also exhibit inhibitory effects on proinflammatory cytokines, support cellular immunity and function as free radical scavengers aided by micronutrients and vitamins. However, it is important to note that the effectiveness of polyphenols is contingent on their bioavailability and the quantity consumed[6].

This comprehensive review examines the antiviral activities of polyphenols derived from terrestrial and aquatic plants *in vitro, in vivo*, and clinical settings. This paper also discusses the general characteristics, extraction methods, health benefits and molecular mechanisms of polyphenols, as well as the potential use of biocompatible nanocarriers to augment the bioactivity of polyphenols.

2. Polyphenols: An Overview

2.1 General Characteristics

Polyphenols (PPs) are abundant and highly hydrophilic secondary metabolites found in both terrestrial and aquatic plants. They encompass a diverse group of compounds, including phloroglucinol and its polymers known as phlorotannins[7,8]. Bromophenols, phenolic acids and flavonoids are other phenolic compounds that contribute to the overall polyphenol content, as shown in Figure 1[9].

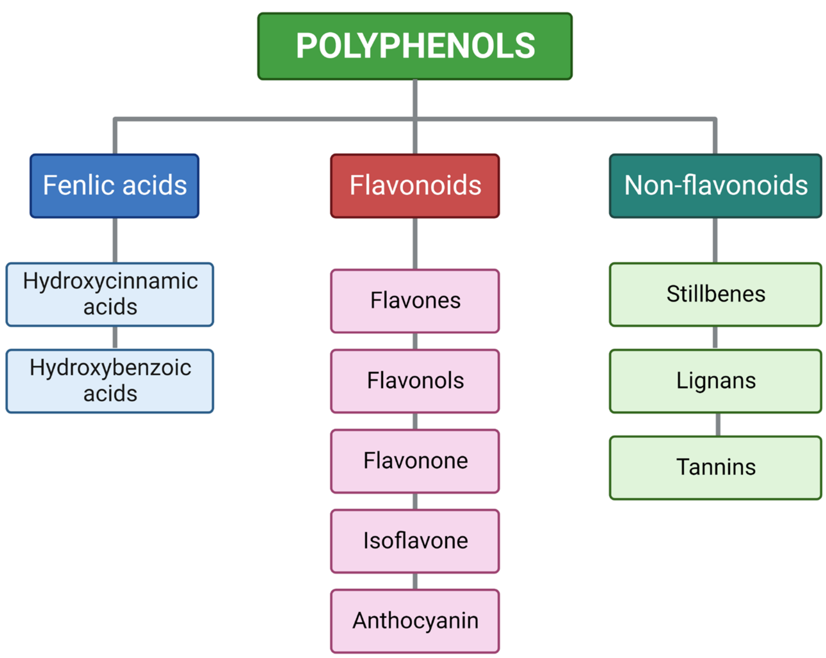


Figure 1. Classification of polyphenols.

Polyphenols are obtained from plants using various extraction techniques followed by purification and concentration. These processes allow for the production of polyphenol-based products for human consumption. However, it is important to consider that polyphenols are susceptible to degradation and reactions with elements such as metal ions and oxygen during storage and processing, which can lead to structural changes and a decrease in their antiviral activity[10,11]. Therefore, ensuring the stability, reactivity, synergism and bioavailability of polyphenols is crucial during their recovery, processing, storage and utilisation in market applications[12]. These factors are discussed in detail below.

Table 1. List of relevant polyphenols classified according to their structure[12]

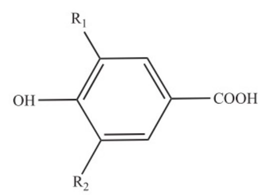
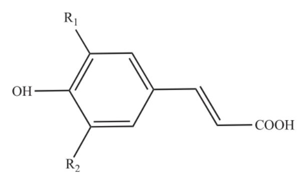
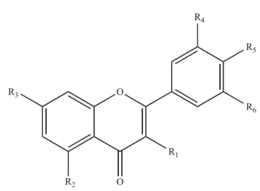
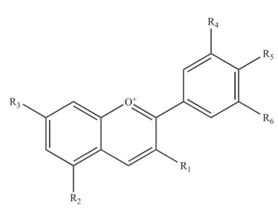
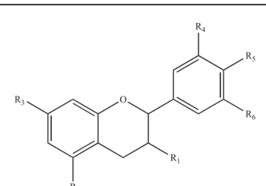
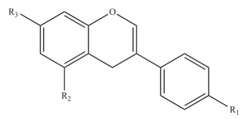
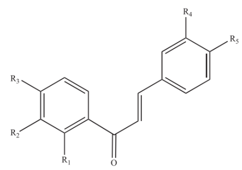
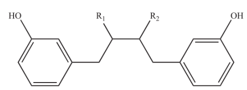
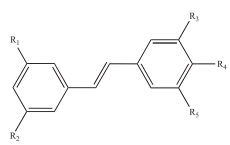
Class	Structure	Substitutions	Examples
Phenolic acids		R1: H, OH, OCH_3	Gallic acid
Hydroxybenzoic acids		R2: H, OH, OCH_3	Vanillic acid
			Procyanidin B1
			Theogallin
Hydroxycinnamic acids		R1: H, OH, OCH_3	Caffeic acid
			Ferulic acid
			p-Coumaric acid
		R2: H, OH, OCH_3	Rosmarinic acid
Flavonoids		R1: H, OH	Hesperidin
Flavonols		R2: H, OH	Naringenin
Flavones		R3: H, OH	Quercetin
Flavanones		R4: H, OH	Kaempferol
		R5: OH, OCH_3	Luteolin
		R6: H, OH	
Anthocyanidins		R1: H, OH	Cyanidin
		R2: OH, OCH_3	Pelargonidin
		R3: OH	
		R4: H, OH	
		R5: OH	
		R6: H, OH	
Catechins		R1-R3: OH	Catechin
		R4: H, OH	Epicatechin
		R5: OH	Epigallocatechin
		R6: H, OH	

Table 1. Continued...

Class	Structure	Substitutions	Examples
Isoflavones		R1: OH	Genistein
		R2-R3: H, OH	Daidzein
Chalcones		R1-R5: H, OH	Xanthohumol
			Phloretin
			Isosalipurpurin
Lignans		R1-R2: H, OH	Enterodiol
			Matairesinol
Stilbenes		R1-R4: H, OH, OCH_3	Resveratrol
		R5: H, OH	Piceatannol

Polyphenols are often susceptible to enzymatic, physical and chemical treatments commonly used in food processing, which can result in instability. Chemical and enzymatic processes can induce oxidation or polymerization, whereas physical treatments may cause phase separation or flocculation, leading to alterations in the nutritional and physicochemical properties of polyphenols[13]. Therefore, ensuring the stability of polyphenols is crucial for preserving their desired attributes.

The reactivity of polyphenols is an important factor affecting their properties during food processing. Enzymatic reactions can lead to the degradation and polymerisation of polyphenols, affecting their colour, taste and nutritional value. These reactions can pose economic challenges by affecting the product quality and shelf life[10]. Therefore, understanding and managing the reactivity of polyphenols is crucial to maintaining the desired characteristics of food products.

The combined action of polyphenols in plant extracts leads to enhanced biological activity compared with individual polyphenols[13]. Nevertheless, the utilisation of polyphenols is currently hindered by their sensitivity to heat, oxygen or light, as well as their poor bioavailability. Encapsulation techniques offer a potential solution for overcoming these limitations[13]. Research has shown that bioactive compounds, including polyphenols, can exhibit synergistic effects, as observed in traditional Chinese medicine[14]. Synergism between polyphenols is crucial in the creation of functional foods that can prevent viral illnesses and enhance overall human health.

The bioavailability of polyphenols, which refers to their absorption, digestion and metabolism in the circulatory system, plays a crucial role in determining their biological properties[15]. Numerous experimental and epidemiological studies have highlighted the protective effects of polyphenols against various illnesses, including inflammation, diabetes and viral diseases[16]. Enhancing the stability of polyphenols in the digestive tract has been achieved through techniques such as encapsulation in nanoparticles using proteins such as zein or polysaccharides like chitosan[17]. Similarly, the encapsulation of polyphenols such as curcumin in zein-caseinate nanoparticles has been shown to improve stability against UV radiation and heat treatments[18]. These strategies contribute to maximising the potential benefits of polyphenols.

2.2 Extraction Methods

Phenolic compounds derived from plant by-products offer a cost-effective and readily available source for recovery, aligning with the principles of circular economy[12]. The increasing focus on polyphenol recovery has prompted the investigation of various extraction technologies that preserve the antiviral properties[19]. Table 2 provides an overview of the diverse methods employed for the isolation and analysis of polyphenols with antiviral activities.

The extraction of polyphenols from plants or their by-products can be accomplished through conventional methods such as mechanical stirring, as well as enhanced techniques, including ultrasound and microwave-assisted extraction. A combination of both approaches utilising organic and/or aqueous solvents can also be employed. To achieve purification, a preliminary clean-up and concentration step can be carried out using resin-based sorption or pressure-driven membrane processes, such as Reverse Osmosis (RO), Nanofiltration (NF), Ultrafiltration (UF) and Microfiltration (MF), with a final purification step employing extraction chromatography[20].

Maceration is a commonly employed technique for extracting polyphenols and involves a solid-liquid process. For instance, maceration has been utilised to extract polyphenols from the *Marrubium deserti*[21]. The results of the antiviral activity tests showed that the ethyl acetate and methanol extracts displayed potent antiviral activity against coxsackie B3 virus[21].

Table 2. Antiviral activity of different polyphenols extracted from plants[12]

Plant source	Polyphenol	Type of virus
Berries, tea, almond, beans, tomato, *Ficus carica* L., capers, caraway, cloves, cumin, Cambuci	Kaempferol	Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus
Propolis, *Oroxylum indicum*	Chrysin	Coronavirus, rotavirus, human cytomegalovirus, HSV-1 and HSV-2, coxsackie B virus
Euphorbia cooperi, *Morus alba*, *Rhus succedanea*	Catechin	HIV, HSV-1
Citrus spp., cocoa, fish mint (*H. cordata*), *Spondias mombin*, *Spondias tuberosa*	Quercetin	Rabies virus, poliovirus, syncytial virus, HSV-2, respiratory syncytial virus, dengue virus, coronavirus
Betula pendula, apple	Quercitrin	Rabies virus, HSV-1, influenza virus
Spondias spp., *Pavetta owariensis* (bark)	Rutin	Rabies virus, influenza virus, dengue virus
Citrus spp., peppermint, grapefruit	Hesperidin	Influenza virus, HSV, poliovirus, syncytial virus, SARS-CoV-2
Chamomile, parsley, oregano, thyme, grapefruit, orange, onion, mango	Apigenin	HSV-1, HIV
Citrus spp., tomato, aromatic plants	Naringin	Respiratory syncytial virus
Broadleaf plantain (*Plantago major*), papaya, peach, avocado	Caffeic acid	HIV, HSV
Broccoli, rosemary, pistachio, lentils, olive, artichoke, lemon, *Aloe vera*	Luteolin	HSV-1 and HSV-2
Berries, pomegranate, walnuts, pecans	Ellagic acid	Dengue virus, hepatitis A and B
Grape, berries, peanuts	Resveratrol	Influenza A, hepatitis C virus, respiratory syncytial virus, varicella-zoster virus, Epstein–Barr virus, HSV, HIV

The process of purifying plant extracts is complex and typically necessitates the use of multiple methods to obtain the optimal level of separation and purification. The comparison of the efficiency of quercetin separation from *Rubus fruticosus* using NF and RO membranes was performed[22]. The results demonstrated that the RO membrane achieved quantitative recovery (>99%) of the extract, whereas the NF membranes achieved 95% polyphenol recovery. The utilisation of RO membranes was found to lead to increased energy consumption and costs compared to the use of NF membranes, subsequently followed by a sorption stage that utilised magnetic carbon nanocomposite materials for the remaining 5% of the permeate stream[22].

2.3 General Health Benefits

Initially, it was believed that the main mechanism of action for polyphenols was through their direct antioxidant effects. However, it is now recognised that these effects may not be as significant *in vivo* because of the inability of polyphenols to reach sufficiently high concentrations in most tissues to scavenge free radicals effectively[23]. Various molecular and biochemical mechanisms were identified. These include modulation of regulation of nuclear transcription factors, intra and inter-cellular signalling pathways, modulation of the synthesis of inflammatory mediators and influence on fat metabolism[24].

Polyphenols derived from diverse food sources are linked to numerous health benefits, particularly in relation to type 2 diabetes and cardiovascular diseases[25]. These benefits may arise from various mechanisms, including effects on endothelial function, inflammation, platelet function, cholesterol, blood pressure, oxidative stress biomarkers, glucose metabolism and interactions with the gut microbiome[26].

Based on the available data on the effect of polyphenols on cardiovascular health originates from epidemiological investigations that have investigated various dietary patterns and the consumption of specific food groups. For instance, a negative correlation was reported between the overall mortality rate and total nutritional polyphenol intake from the Mediterranean diet[27,28].

Polyphenols are also believed to have positive influences on cognitive function[29]. A recent investigation conducted on middle-aged adults demonstrated a positive correlation of polyphenol intake with cognitive factors, such as language and verbal memory, over a 13-year period[30]. Furthermore, longitudinal investigations have indicated that regular consumption of chocolate can lower the risk of cognitive decline[31], while a meta-analysis of 17 observational studies revealed an inverse linear relationship between tea consumption and cognitive disorders[32]. Additional observational studies have reported a lower risk of cognitive impairment associated with the consumption of green and black tea consumption[33]. Moreover, tea consumption has been independently linked to a reduced risk of depression[34] and a potential protective effect against Parkinson's disease[35].

3. Molecular Mechanism of Polyphenols Against Viruses

Polyphenols exhibit antiviral activity primarily by targeting the replication cycle of viruses via interactions with caspase active sites or protein synthesis (Table 3 and Figure 2). Various studies, such as those involving curcumin, gallic acid[36,37] and catechin[38], have demonstrated their inhibitory effects on the influenza virus, each employing distinct mechanisms of action. Curcumin inhibits hemagglutinin activity and viral neuraminidase activity while catechin disrupts viral synthesis and M2 protein expression by binding to viral functional sites. Gallic acid interacted with neuraminidase, thereby affecting the viral replication (Table 4). These findings indicate a lack of consistent correlation between antiviral activity and specific mechanisms, underscoring the need for further research in this area[39].

Chlorogenic acid[40] and EGCG[41] demonstrated distinct mechanisms of action against different viruses (Table 4), including HBV, with common inhibition of DNA synthesis. EGCG primarily hinders viral replication, while chlorogenic acid binds to specific cell lines. These variations in inhibition mechanisms make it challenging to establish a definitive correlation, emphasising the need for additional research to elucidate the precise antiviral effects of these compounds[37].

Although the antiviral activity of polyphenols can be determined based on the stage of infection or replication inhibition, the specific mechanisms and interactions with other compounds remain uncertain[41].

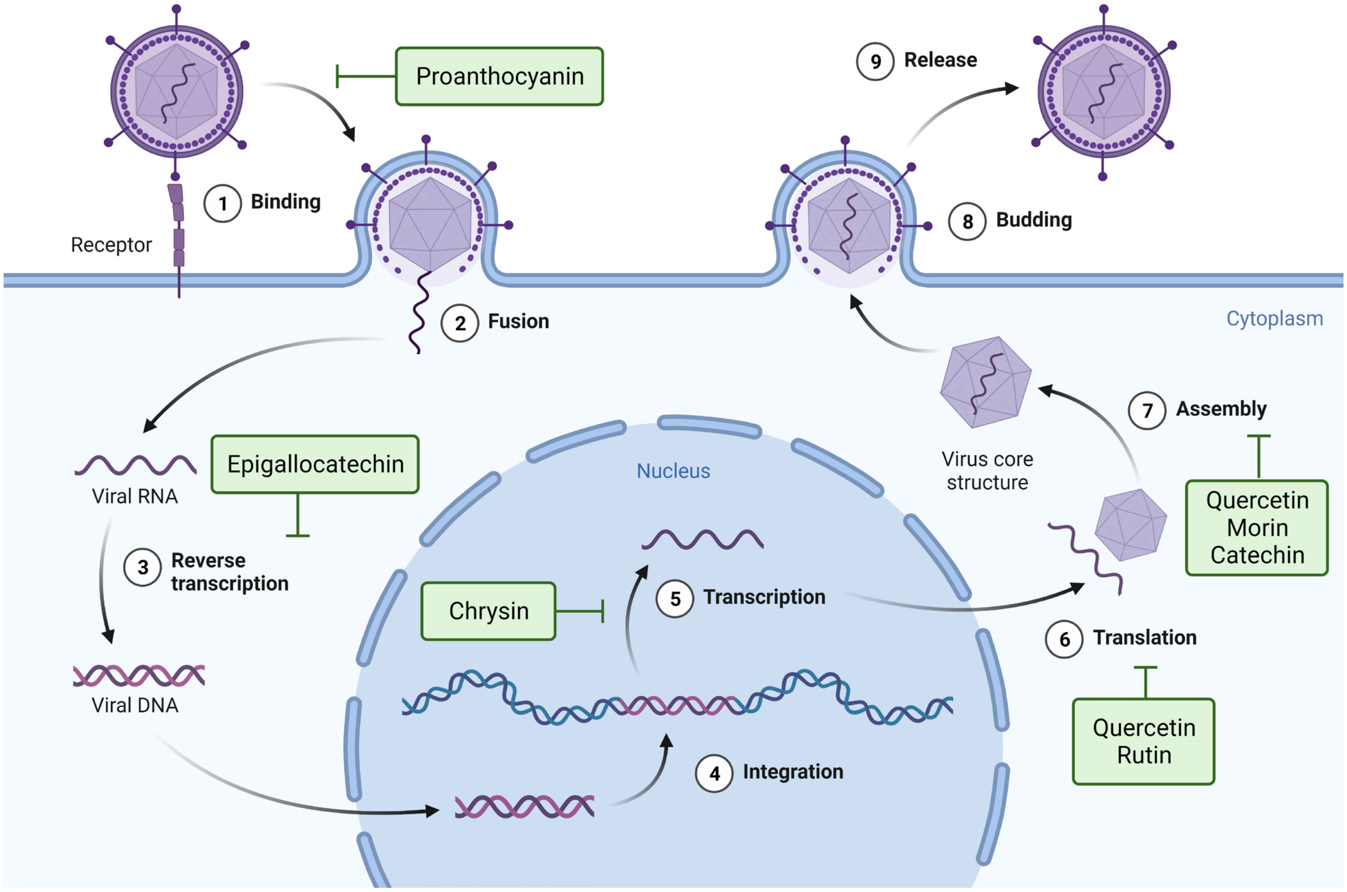


Figure 1. Virus replication and polyphenol targets.

Table 3. Methods of polyphenol isolation and determination[39]

Material	Pretreatment	Polyphenol Isolation	Time	Polyphenol Determination
soursop leaves	-	water and ethanol/water (70:30 v/v) extraction	10–20 min	HPLC
olive waste	-	ultrasound-assisted enzyme catalyzed hydrolysis	-	1H NMR and 13C NMR
Heliotropium taltalense	-	methanol extraction in an ultrasonic bath	1 h	UPLC
maritime pine	removing lipophilic compounds with a petroleum ether/ ethyl acetate (50:50 v/v) mixture	ethanol/water (85:15 v/v) extraction	2 h	LC-MS and NMR
Cuspidaria convoluta	-	methanol maceration	24 h	UV-VIS and HPLC-MS/ MS
Gaultheria phillyreifolia and *G. poeppigii* berries	-	methanol/formic acid (99:1 v/v) extraction	-	HPLC

Table 3. Continued...

Material	Pretreatment	Polyphenol Isolation	Time	Polyphenol Determination
green tea	-	ethanol/water (70:10, v/v) extraction in ultrasonic cleaner	1 h	HPLC and LC-MS
Aronia melanocarpa	defatting with n-hexane and with dichloromethane	methanol/acetic acid (19:1, v/v) extraction with stirring	8 h	HPLC
Saharan myrtle tea	-	methanol/water (80:20, v/v) extraction	3 · 24 h	UPLC
Syzygium alternifolium	removing lipophilic compounds with a dichloromethane	methanol/water (80:20, v/v) or acetone/water (80:20 v/v) extraction with sonification	15 min	UV-VIS
pomegranate peels	removing of extractable polyphenols using ethyl acetate	non-extractable polyphenols obtained via acid hydrolysis (6M HCl)	2 h	TLC, CC, NMR, MALDI-TOF-MS
grape processing lees	-	supercritical fluid extraction (SFE) with 90% of supercritical carbon dioxide and 10% (*w/w*) of ethanol	10 min	TLC and HPLC
Myrtus communis L. leaves	-	extraction with aqueous ethanol with assistance of microwaves	30–90 s	Folin–Ciocalteu colorimetric method
goldenberry	-	ethanol/water solution (70:30, v/v) pressurized liquid extraction (PLE)	10–60 min	HPLC-DAD
grape pomace	-	pressurized hot water extraction (PHWE)	5 or 30 min	MALDI-TOF-MS
Phyllanthus emblica	-	soxlet extraction with ethanol/water (7:3, v/v)	30 min	Folin–Ciocalteu colorimetric method

Table 4. Antiviral activity mechanism of individual polyphenols[39]

Polyphenol	Virus Type	Activity Mechanism
Quercetin	SARS-CoV-2	interaction with Spike occurs between amino acid Thr 445, Ile 446; as for main protease it binds to Thr 26
		superior main protease docking result compared to spike docking, better inhibitory effect on replication cycle of the virus rather than penetration/adsorption cycle
Resveratrol	Epstein–Barr virus	decreasing levels of reactive oxygen species, blocking protein synthesis and inhibiting virus-induced activation of transcription factors, which affects replication of the individual virus
	rotavirus	inhibition of the replication in the Caco-2 cell line
	vesicular stomatitis virus	suppression of the spread of the virus by interaction with the active sites of caspase-3 and -7

Table 4. Continued...

Polyphenol	Virus Type	Activity Mechanism
Curcumin	SARS-CoV-2	entry into host cells is also blocked by blocking the enzyme ACE2; curcumin has a high affinity for ACE2 ligands
	influenza virus	reduction of viral NA activity and blocking HA activity
	SARS-CoV-2	inhibition due to interaction with Mpro receptor of SARS-CoV-2, which occurs by binding with amino acid Thr26, His41, Gln189
EGCG	HCV	suppressing by blocking virus entry via viral envelope proteins and inhibiting cell-to-cell transmission
	HBV	inhibition of DNA synthesis during virus replication
	the duck Tembusu virus (DTMUV)	reduction of the viral infection in BHK-21 cells, expressions of the viral E protein and virus titers. EGCG affects the adsorption step of the infection and replication stage of the virus in BHK-21 cells
Chlorogenic acid	infectious bursal disease virus	inhibiting histamine production, NF-kB activation, which affects the production of the pro-inflammatory cytokines TNF-a and IL-1b
	HBV	inhibiting DNA of the virus by binding to HepG2.2.15 and HepG2.A64
Catechin	influenza A virus	binding to functional sites PHE47A and LEU43A, which inhibits M2 viral mRNA synthesis as well as M2 protein expression
	dengue virus	interaction with NS5 protein, by binding to amino acids Asn609, Asp663, His798
Gallic acid	influenza A virus	inhibition of replication of the virus, by binding to Arg152 of neuraminidase protein
	paramyxoviruses	affects replication cycle of the virus by inhibiting ribonucleotide reductase enzyme

Detailed studies are required to investigate the antiviral mechanisms of polyphenols against various viruses. Comprehensive research is needed to explore the effects of polyphenols on a wider range of viruses and examine synergistic interactions with other compounds such as those found in plant extracts, which may modify antiviral mechanisms and enhance their efficacy.

4. Antiviral Activity of Polyphenols Against Major Viral Infections

4.1 Coronaviruses

Coronaviruses are RNA viruses that spread primarily through avian and mammalian hosts. These viruses are named after the crown-like appearance of their envelope, as observed by electron microscopy. Notably, SARS-CoV-1 and SARS-CoV-2, which cause Severe Acute Respiratory Syndrome (SARS) are well-known coronaviruses[42].

The impact of polyphenols against coronaviruses is multifaceted. Certain polyphenols, such as luteolin, exhibit a strong binding affinity for the S protein (Table 5), effectively preventing virus entry[43]. Polyphenols found in rhubarb roots, turmeric and citrus fruits are particularly effective in inhibiting the S protein. Additionally, compounds present in tea and herbs such as herbacetin, EGCG and naringenin also have the potential to block the S protein[44]. Another approach is to hinder the function of the ACE2 enzyme, which acts as a pathway for SARS-CoV-2 to enter. Polyphenols present in red grapes, yerba mate and turmeric, including resveratrol, eriodicytol, catechin and curcumin, exhibit a high affinity for ACE2 ligands, offering potential benefits in this regard (Table 5)[45].

Upon the entry of the virus into the human host cells, polyphenols play a crucial role in inhibiting RNA replication and subsequent viral multiplication. One key action involves protease inhibition which effectively blocks the replication and transcription of viral genome. Polyphenols derived from citrus fruits and turmeric demonstrated significant potential in this regard (Table 5)[45]. Furthermore, polyphenols such as

EGCG, myricetin, and quercetagetin exhibit strong binding affinities for SARS-CoV-2 RdRp (Table 5)[46].

4.2 Herpesviruses

Herpesviruses are a type of DNA virus that belongs to the Herpesviridae family. They are capable of entering a state of latent infection that can last a lifetime and they can reactivate periodically[47]. These viruses cause a wide range of diseases, from common cold sores to cancer and continue to pose a significant threat to the health and well-being of immunocompromised individuals[48].

An *in vitro* investigation revealed that ginkgolic acid, a phenolic compound found in *Ginkgo biloba* fruits and leaves, demonstrated inhibitory effects on HSV-1 replication in 293T and HEp-2 cells (Table 6). Inhibition occurred at various concentrations (2.5 to 50 µM) and was observed to suppress the synthesis of viral proteins involved in different stages of infection. In addition, ginkgolic acid reduced the assembly of new viral progenies[49].

In a separate investigation, the antiviral effect of geraniin derived from *Spondias mombin* leaves against HSV-1 was examined using both *in silico* and *in vitro* approaches (Table 6). *In vitro,* findings indicated that geraniin exhibited antiviral activity by inhibiting viral attachment. Molecular docking analysis further predicted that geraniin targeted glycoprotein gB on the surface of HSV-1, elucidating its mechanism of action[50].

Coumarins derived from *Angelica archangelica*, such as imperatorin and phellopterin, exhibited activity against HSV-1 replication (Table 6). Imperatorin reduced the virus titer by 3.48 log and 4.7 log at 15.62 and 31.25µg/mL concentrations, respectively. Phellopterin decreased the virus production by 3.01 log at 7.81µg/mL concentration, whereas the combination of phellopterin and imperatorin reduced the virus production by 3.73 log at 31.25µg/mL concentration. The mechanism of action was attributed to inhibition of HSV-1 genome replication[51].

Table 5. The role of polyphenols against coronaviruses[42]

Polyphenols	Representative	Form/Source	Virus	Mechanism
Phenolic acids				
Hydrobenzoic acids	Gallic acid	Tetra-*O*-galloyl-β-D glucose from *Galla chinensis*	SARS-CoV	Avidly binds with surface spike protein of SARS-CoV.
	Hydrobenzoic acid	Desmethoxyreserpine	SARS-CoV-2	Inhibit replication of 3CLpro, and entry.
Flavonoids				
Flavonols	Kaempferol	Kaempferol derivatives, Kaempferol	SARS-CoV	Inhibit 3a ion channel of CoVs.
			MERS-CoV, SARS-CoV	Inhibit PLpro.
				Inhibit SARS-3CLpro activity.
	Quercetin	Quercetin, Quercetin 3-β-D-glucoside, isobavachalcone, and helichrysetin	MERS	Inhibit cleavage activity of MERS-3CLpro enzyme.
		Quercetin, Quercetin-β-galactoside	MERS-CoV, SARS-CoV	Inhibit PLpro.
				Inhibit SARS-3CLpro activity.
		Quercetin and TSL-1 from *Toona sinensis* Roem	SARS-CoV	Inhibit the cellular entry of SARS-CoV.
		Quercetin	SARS-CoV-2	PLpro and 3CLpro enzyme.

Table 5. Continued...

Polyphenols	Representative	Form/Source	Virus	Mechanism
	Myricetin	Myricetin	SARS-CoV	Inhibit nsP13 by affecting the ATPase activity.
				SARS-CoV helicase inhibitor.
	Herbacetin	Herbacetin	MERS	Inhibit cleavage activity of MERS-3CLpro enzyme.
			SARS-CoV	block the enzymatic activity of SARS-CoV 3CLpro.
	Papyriflavonol A	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibit PLpro.
	Kazinol A, B, F and J, and broussoflavan A			Inhibit SARS-3CLpro activity.
	Amentoflavone,	*Torreya nucifera* leaves	SARS-CoV 3CL pro inhibitor	
	Kaempferol, quercetin, luteolin-7-glucoside, demethoxycurcumin, naringenin, apigenin-7-glucoside, oleuropein, curcumin, catechin, epicatechingallate, zingerol, gingerol, and allicin	Traditional herbs	Inhibitors of SARS-CoV-2-Mpro	block the enzymatic activity of SARS-CoV 3CLpro.
Flavones	Apigenin	*Ocimum basilicum*	SARS-CoV	Inhibit PLpro.
				Inhibit SARS-CoVpro activity.
	Baicalin	*Scutellaria baicalensis*	SARS-CoV	Inhibit Angiotensin-converting enzyme.
	Scutellarein	*Scutellaria lateriflora*	SARS-CoV	Inhibit nsP13 by affecting the ATPase activity.
	Rhoifolin	*Rhus succedanea*	SARS-CoV	Inhibit SARS-3CLpro activity.
	Luteolin	luteolin, from *Veronicalina riifolia*	SARS-CoV	Avidly binds with surface spike protein of SARS-CoV.
	Daidzein	Plant-derived phenolic compounds and root extract of *Isatis indigotica*	SARS-CoV	Not active.
	30-(3-methylbut-2-enyl)-30,4,7-trihydroxyflavone	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibition of cysteine proteases CoV
	neobavaisoflavone	*Psoralea corylifolia*	SARS-CoV	Inhibitory activity toward SARS-CoV PLpro.

Table 5. Continued...

Polyphenols	Representative	Form/Source	Virus	Mechanism
Flavanones	Herbacetin,	Plant-derived phenolic compounds and Root extract of *Isatis indigotica*	SARS-CoV	Inhibit the cleavage activity of the SARS-3CLpro enzyme.
	Rhoifolin pectolinarin Tetra-*O*-galoyl-β-d-glucose (TGG) luteoline			
	Pelargonidin	*Pimpinella anisum*	SARS-CoV-2	Binding affinities to 3C-like protease of SARS-CoV-2
	Bavachinin	*Psoralea corylifolia*	SARS-CoV	Inhibitory activity toward SARS-CoV PLpro.
Anthocyanidins	10 polyacylated and monomeric anthocyanins	Bure components	SARS-CoV-2	Constructively network with catalytic dyad residues of 3CLpro of SARS-CoV-2.
Flavanols	Epigallocatechin gallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro activity.
	Gallocatechin gallate and epicatechingallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro activity.
	gallocatechin-3-gallate	Green tea	SARS-CoV	Inhibit SARS-3CLpro activity.
Chalcone	Isoliquiritigenin	*Glycyrrhiza glabra*	MERS-CoV, SARS-CoV	Inhibit PLpro.
				Inhibit SARS-3CLpro activity.
	Broussochalcone B, broussochalcone A, and 4-hydroxyisolonchocarpin	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibit PLpro.
				Inhibit SARS-3CLpro activity.
	isobavachalcone	*Psoralea corylifolia*	SARS-CoV	inhibitory activity toward SARS-CoV PLpro.
	4′-*O*-methylbavachalcone	*Broussonetia papyrifera*	MERS-CoV, SARS-CoV	Inhibit PLpro.
				Inhibit SARS-3CLpro activity.
Tannins	19 hydrolysable tannins	Bure components	SARS-CoV-2	Efficacious and selective *anti*-COVID-19 therapeutic compounds.

Table 6. The role of polyphenols against human herpesviruses[47]

Compound	Chemical Class	Herpesvirus	Mechanisms of Action (Inhibition/Downregulation)
Ginkgolic acid	Phenolic acids	HSV-1, HCMV, and EBV	HSV-1 DNA replication, viral structure, ICP27, ICP8, US11, and viral progeny production.
			HCMV entry and its DNA replication.
			EBV membrane fusion and gB.

Table 6. Continued...

Compound	Chemical Class	Herpesvirus	Mechanisms of Action (Inhibition/Downregulation)
Trans-ferulic acid, gentisic acid, vanillic acid, syringic acid, and gallic acid	Phenolic acids	HSV-1 and EBV	HSV-1 DNA polymerase, HSV-1 gB (by vanillic acid), and EBV-EA (by gallic acid).
Polyphenol esters consisting of gallic acid and ferulic acid	Phenolic acids	EBV	EBV reactivation.
Ellagic acid	Phenolic acids	HSV-2	HSV-2 DNA replication.
Chlorogenic acid and caffeic acid	Phenolic acids	HSV-1 and EBV	HSV-1 gB and EBV-EA (by chlorogenic acid).
Caffeic acid chelates	Phenolic acids	HSV-1 and HSV-2	Enhancement of anti-HSV activity by inhibiting viral DNA replication and viral attachment.
Protocatechuic acid	Phenolic acids	HSV-2 and EBV	HSV-2 DNA replication and virion production.
			EBV-EA.
Chebulagic acid and chebulinic acid	Tannins	HSV-2	HSV-2 DNA replication.
Geraniin	Tannins	HSV-1	HSV-1 gB.
Tannic acid formulated as TA-AgNPs and purified tannic acid	Tannins (gallotannins)	HSV-1 and HSV-2	HSV-1 replication, gC, and gB (purified and formulated tannic acid), HSV-2 replication and improving the anti-HSV-2 immune response by activating B cells.
1,2,3,4,5-penta-*O*-digalloyl-*β*-*D*-glucopyranose, 1,2,3,4,5-penta-*O*-digalloyl-*α*-*D*-glucopyranose, and *α*/*β*-3-*O*-digalloyl-*D*-glucopyranose (1:1 mixture).	Tannins (gallotannins)	HSV-1	HSV-1 replication and viral glycoproteins.
Pentagalloylglucose	Tannins (gallotannins)	VZV	VZV replication, VZV-induced JNK, and VZV-IE62.
Castalagin and vescalagin	Tannins (ellagitannins)	HSV-1 and HSV-2	In combination with acyclovir, notable inhibition of HSV-1 and HSV-2 replications was observed.
Epiacutissimin B, epiacutissimin A, acutissimin A, and mongolicain	Tannins (ellagitannins)	HSV-1	HSV-1 DNA replication and viral glycoproteins.
Punicalagin	Tannins (ellagitannins)	HSV-2	HSV-2 DNA replication.
			HSV-2 protease.
Mangiferin	Xanthones	HSV-1	HSV-1 DNA replication and virus particles.
Resveratrol	Stilbenes	HSV-1, HSV-2, and KSHV	HSV-1 and HSV-2 replications, viral IE, and CDK9.
			KSHV latent infection, Rta, and formation of virus progeny.
Greco extract contains resveratrol C-glucoside, resveratrol, and epsilon-viniferin	Stilbenes	HSV-1	HSV-1 particles and viral DNA replication.
Piceatannol	Stilbenes	HSV-1, HSV-2, and HCMV	HSV-1 and HSV-2 replications and viral particles.
			HCMV replication, IE, E, and p16INK4a.

Table 6. Continued...

Compound	Chemical Class	Herpesvirus	Mechanisms of Action (Inhibition/Downregulation)
Bicoloketone	Stilbenes	HSV-1	HSV-1 DNA replication.
Honokiol	Lignans	HSV-1	HSV-1 DNA replication, ICP27, VP16, and gD.
Arctium lappa L. extract (rich in arctiin and arctigenin)	Lignans	HSV-1	Viral load and HSV-1 DNA replication.
Manassantin B	Lignans	EBV	EBV lytic DNA replication, virion production, BZLF1, AP-1, and mTORC2-mediated phosphorylation of AKT Ser/Thr at Ser-473 and PKCα at Ser-657.
Deightonin	Neolignans	HSV-2	HSV-2 DNA replication.
Emodin	Anthraquinones	HSV-1, HSV-2, HCMV, and EBV	HSV-1 and HSV-2 replications, TLR3 pathway and its downstream molecules (TRIF, TRADD, TRAF6, traf3, Nemo, IRF3, and p38), IL-6, TNF-α, and IFN-β.
			HCMV DNA replication and synthesis.
			EBV lytic proteins, virion production, SP1, Zta, Rta, EBNA1, BRLF1, BNLF1, and LMP1.
Aloe-emodin	Anthraquinones	EBV	EBV lytic cycle and Rta.
5,5′ -Bisoranjidiol, rubiadin 1-methyl ether, soranjidiol 1-methyl ether, damnacanthol, soranjidiol, rubiadin, and heterophylline	Anthraquinones	HSV-1	HSV-1 DNA replication and HSV-1 particles (photo-inactivation).
1,4-Anthraquinone	Anthraquinones	HSV-1	HSV-1 DNA replication.
Curcumin	Curcuminoids	HSV-1, HSV-2, HCMV, EBV, and KSHV	HSV-1 and HSV-2 replications and their adsorption, HSV-1 TK, HSV-1 IE, p300, CBP and HSV-1 DNA polymerase.
			HCMV (IEA, UL83A, IL-6, TNF-α, Hsp90, ROS, inflammatory cytokines, HMGB1-TLRS-NF-κB).
			Protection against HCMV by inducing anti-inflammatory and antioxidant activities.
			EBV (latent and lytic replication, BZLF1, and EBNA1.
			KSHV (Rta, K8, and APE1-mediated redox function).
Imperatorin and phellopterin	Coumarins	HSV-1	HSV-1 DNA replication.
Scoparon	Coumarins	HSV-2	HSV-2 DNA replication.
7-hydroxycoumarin and 7-hydroxy-6-[2-(R)-hydroxy-3-methyl-but-3-enyl] hydroxycoumarin	Coumarins	EBV	EBV-EA.
Psoralen	Furanocoumarins	EBV	EBV-EA.
(+)-Rutamarin	Furanocoumarins	EBV and KSHV	EBV (lytic DNA and viral protein synthesis).
			KSHV (lytic DNA replication and virion production).
Phloroglucinol-rich extract (PGRE)	Other polyphenols (phloroglucinol)	HSV-2	HSV-2 DNA replication and viral protein synthesis.

4.3 Hepatitis Viruses

Hepatitis, caused by various viruses, including Hepatitis A Virus (HAV), Hepatitis B Virus (HBV) and Hepatitis C Virus (HCV), can lead to chronic liver disease and complications. Current treatment options such as interferon and nucleoside analogs have limitations. Therefore, there is a growing interest in exploring natural compounds as potential antiviral agents. *In vitro* studies have identified non-cytotoxic compounds with inhibitory effects on HBV. Notably, quercetin demonstrated maximum inhibition of HBsAg antigen (73%)[52]. Quercetin has also been found to inhibit viral DNA replication and its efficacy against HBV is enhanced when combined with nucleoside analogs[53].

The antiviral properties of green tea polyphenols such as Epigallocatechin-3-Gallate (EGCG), Epigallocatechin (EGC), Epicatechin Gallate (ECG) and Epicatechin (EC) have been well-documented. Notably, EGCG, which constitutes a significant portion of green tea polyphenols, exhibits broad-spectrum virucidal activity against different viruses. It effectively prevents HCV entry by inhibiting cell-to-cell transmission and targeting viral envelope proteins[54]. Furthermore, EGCG can be combined with other antiviral drugs to enhance the therapeutic efficacy[55]. Black tea contains theaflavins which have direct antiviral effects on HCV by interacting with the virus before cellular entry[56]. Tannic acid, present in numerous plant sources, demonstrates a similar inhibitory effect and effectively blocks HCV entry into Huh7.5 cells, with an IC_{50} concentration of 5.8μM[57].

Curcumin possesses antiviral properties and has the potential to treat HBV infections. It shows its effects by inhibiting various metabolic and cellular pathways involved in HBV pathogenesis, including anti-apoptotic proteins, adhesion molecules, transcription factors, inflammatory cytokines and protein kinases. Curcumin modulates the level of PGC-1α protein, enhances cellular glutathione content and activates the PPAR-γ receptor in the adipose tissue. Consequently, this leads to downregulation of the NF-κB signalling pathway[58].

4.4 Influenza Viruses

Phlorotannins can interact with important proteins involved in the influenza virus, particularly Neuraminidase (NA). The NA protein performs the function of a sialidase by breaking the bond between sialic acid and the HA protein, which aids in the egress of progeny virions. As NA is crucial for the influenza virus replication cycle, it is a potential target for the development of antiviral therapies. Therefore, phlorotannins (PT) are promising candidates for the development of preparations targeting NA and combating influenza[59].

PTs derived from algae are potential candidates for antiviral agents. The antiviral activities of 13 PTs obtained from the seaweed *Ecklonia cava* against influenza A virus strains H1N1 and H9N2 were investigated[60]. Phlorofucofuroeckol A exhibited the highest antiviral activity with an IC_{50} of 13.48 ± 1.93 μM. Six PTs showed moderate-to-high antiviral activity at a concentration of 20μM. Phlorofucofuroeckol A successfully blocked viral protein synthesis, including the NA and HA proteins[61]. These findings demonstrate the potential of phlorotannins as antiviral compounds against the influenza virus.

4.5 Noroviruses

Norovirus, a non-enveloped enterovirus, is the primary cause of epidemics associated with symptoms such as vomiting, diarrhoea, fever, abdominal cramps and nausea[62]. These viruses have high resistance, frequent mutations, low infectious dose, genetic variability, and long incubation period[63]. To search for safe, therapeutic and preventive measures, researchers have explored potential alternatives derived from terrestrial and marine organisms[64].

In this context, a study investigated the potential of *Eisenia bicyclis* extract as a possible agent against norovirus[65]. The Ethyl Acetate (EtOAc)-soluble extract of *E. bicyclis* yielded two fractions: Dieckol (DE) and Phlorofucofuroeckol A (PFE). The EtOAc extract exhibited potent virucidal activity with low cytotoxicity. Previous research highlighted that PFE showed stronger inhibition against norovirus infection compared to DE[65]. The Selective Index (SI) values for DE and PFE were approximately 20- and 25-fold higher than those of green tea epigallocatechin gallate. These findings suggest the promising inhibitory activity of phlorotannins against norovirus infection. The authors propose further investigation of the mechanisms underlying the antiviral effects of these compounds, particularly against norovirus.

5. *In Vivo* Antiviral Activity of Polyphenols

5.1 Quercetin

Similar to other flavonoids, quercetin is a polyphenolic compound characterised by a structural framework consisting of two aromatic rings linked by a 3-C bridge that forms a pyrone or pyran ring[66]. These compounds have been recognised for their potential as therapeutic agents for combating respiratory tract infections[67].

Hence, the *in vivo* effectiveness of Quercetin-3 Rhamnoside (Q3R) against the influenza virus was assessed[68]. The results demonstrated a considerable decrease in mortality and weight loss in the Q3R-treated group. Moreover, the use of Q3R delays the progression of lung lesions. These findings suggest that Q3R is a potential anti-influenza drug candidate. Furthermore, flavonol derivatives such as Q3R are known to exhibit improved bioavailability compared to the aglycone form. Notably, flavonols have a prolonged half-life and can accumulate in the blood plasma with repeated administration[69].

Studies have demonstrated that quercetin can inhibit oxidative stress caused by the influenza virus[70]. In an *in vivo* investigation, the administration of quercetin resulted in a significant reduction in lipid peroxidation levels and increased levels of antioxidant enzymes[71]. Given these findings, quercetin and rutin have been suggested as potential additions to post-infection treatment[70].

Quercetin 3-β-O-D-glucoside exhibits inhibitory activity against the Ebola virus. Notably, the compound protected Ebola even though it was administered 30 min before the infection, suggesting its potential as a prophylactic agent[72]. Nevertheless, further comprehensive research is needed to fully determine its effectiveness when administered via various routes, at different doses and under different conditions.

5.2 Baikalin

Baikalin is derived from *Scutellaria baicalensis* roots and is utilised as a dietary supplement in Asian countries. Numerous agents, including baicalin and its combinations, have been approved for various conditions, based on their proven efficacy *in vivo*. Extensive *in vivo* research has focused on investigating the use of baicalin against influenza virus infections[73].

The efficacy of baicalin against the human influenza A/PR/8/34 strain was examined in mice[74]. When administered different doses of baicalin, the survival rates on day 8 were 70%, 80% and 80%, respectively. Moreover, 60, 70 and 80% of the mice in these groups survived until day 14, showing no weight loss. The virus titers in untreated mice reached 106.3 pfu/mL on day 7, whereas in baicalin-treated groups, the titers were significantly lower (102.7, 102.3, and 102.2 pfu/mL). Baicalin also demonstrated inhibitory activity against viral replication, as indicated by the reduction in hemagglutination titers. Furthermore, baicalin suppressed the inflammatory response in the lungs and induced interferon gamma (IFNγ) secretion, which contributed to its antiviral activity. This effect was not observed in mice with a knockout of the IFNγ gene[73].

5.3 Resveratrol

Resveratrol, a potent polyphenolic compound, is currently the subject of extensive research as an antiviral agent[75]. Its virucidal activity is attributed to its ability to inhibit various viral processes including nucleic acid synthesis, replication, gene expression and protein synthesis[76].

Resveratrol has shown potential in reducing airway hypersensitivity and airway inflammation caused by Respiratory Syncytial Virus (RSV)[75]. Resveratrol inhibits viral replication and reduces the number of infiltrating lymphocytes, thereby mitigating inflammation[77]. Furthermore, resveratrol has been shown to significantly decrease IFNγ levels, which are correlated with airway inflammation caused by RSV[75].

Furthermore, resveratrol has demonstrated strong activity against rotavirus that causes early childhood viral gastroenteritis[76]. In an *in vivo* investigation, resveratrol treatment resulted in reduced viral titers and reduced severity of diarrhoea. Moreover, resveratrol supplementation resulted in a significant decrease in the mRNA expression of various cytokines and chemokines. These findings highlight the potential of resveratrol as a promising therapeutic compound for the treatment of rotavirus infections[76].

6. Clinical Trials for Polyphenols

Assessment of their effectiveness through clinical trials is a crucial aspect in the development of novel formulations[77]. While many studies have predominantly investigated the effects of polyphenols on isolated animals[78,79] or human cell lines[80], numerous studies demonstrated the effectiveness of these compounds in clinical trials[81,82].

In clinical trials, the effectiveness of dactavira for treating HCV has been established. The combination of EGCG, daclatisvir, and sofosbuvir was compared with conventional treatment (daclatisvir and sofosbuvir) and demonstrated a marked reduction in virus titers. The addition of EGCG disrupts viral entry, leading to a substantial decrease in relapse rates[83].

Numerous cell-based experiments have demonstrated the beneficial effects of green tea catechins on viral infections in reproductive organs[84]. An ointment with green tea polyphenols (Polyphenon E) effectively treated external genital warts[85]. A separate investigation revealed that 53% of the patients treated with Polyphenon E achieved complete resolution of the primary genital and anal warts, with adverse effects limited to the application site[86]. Sinecatechin-containing ointments at concentrations of 10% and 15% resulted in approximately 60% complete wart removal, with a 10% recurrence rate and mild-to-moderate local adverse reactions observed in up to 50% of patients[87]. Clinical trials assessing the efficacy of green tea extracts (Polyphenon E, poly E, and (-)-epigallocatechin-3-gallate) in ointment or capsule form for human papillomavirus-infected patients demonstrated a response rate of approximately 69%, suggesting the potential use of green tea extracts for treating cervical lesions caused by human papillomavirus[88].

7. Biocompatible Nanocarriers for Augmenting Antiviral Activity of Polyphenols

Phytochemicals can be enhanced through the use of nanotechnology by improving their bioavailability and combining them with other components to create synergistic effects[89]. However, a major limitation of this technique is the inherent toxicity of most nanomaterials (such as metallic and non-metallic nanoparticles, metal oxides, and metal sulfides), which can negatively impact human health. To mitigate or eliminate this toxicity, researchers have focused on developing biocompatible nanocarriers using green synthesis methods. Several nanocarriers, including lipid nanocarriers, metallic/non-metallic nanoparticles and water-soluble macromolecules were investigated to enhance the antiviral efficacy of phytochemicals[90].

To enhance the solubility of curcumin, researchers have used Polyvinylpyrrolidone (PVP), a hydrophilic and biocompatible polymer, through complexation methods. A water-soluble curcumin-PVP complex was synthesised by spray drying, resulting in a significantly increased solubility and release efficiency[91]. A recent investigation comparing curcumin-PVP with physical mixtures was conducted. The results showed only minimal release from the physical mixture, whereas the curcumin-PVP dispersions exhibited 100% dissolution within 30 minutes[91].

To overcome the challenges associated with the high hydrophobicity and low oral bioavailability of ursolic acid, researchers have utilised TPGS 1000 stabilizer in an antisolvent precipitation method to create ursolic acid nanoparticles[92]. The orally administered ursolic acid nanosuspension showed significantly improved bioavailability and maximum plasma concentration compared with raw ursolic acid. The nanosuspension exhibited higher bioavailability and higher maximum plasma concentration in rats. These results indicated that the combination of ursolic acid NPs with TPGS 1000 has the potential to enhance its absorption[92].

In a noteworthy discovery, the use of iron oxide nanoparticles was explored to target influenza viruses. They found that iron oxide NPs induced peroxidation of the lipid envelope, leading to the degradation of nearby proteins such as hemagglutinin, neuraminidase and matrix proteins[93,94]. This degradation process effectively inactivates the influenza A virus and protects against viral transmission and infection. The researchers utilised iron oxide NPs as a facemask, which enhanced their ability to protect against human-threatening subtypes[94]. These findings highlight the potential of these nanoparticles to enhance the bioavailability of bioactive polyphenols and call for further research in this area.

8. Conclusions

This review article provides a comprehensive discussion of the antiviral activities of polyphenols against a wide range of viruses, including coronaviruses, herpesviruses, hepatitis viruses, influenza viruses and norovirus. Polyphenols have demonstrated promising potential as effective agents against viral infections, exhibiting antiviral effects through various mechanisms, such as inhibition of nucleic acid synthesis, viral replication, gene expression and protein synthesis. These multifaceted activities highlight the versatility of polyphenols for combating viral diseases.

Despite the progress made in understanding the antiviral activities of polyphenols, several research gaps still warrant further investigation. Firstly more studies are needed to elucidate the structure-activity relationships of different polyphenols, their derivatives and their specific interactions with viral targets. Second, the *in vivo* efficacy and safety profiles of polyphenols should be further explored to establish their potential for clinical applications. Thirdly, the development of polyphenol-based combination therapies and the exploration of synergistic effects with conventional antiviral drugs might enhance antiviral activity and help overcome the issue of viral resistance. Finally, the use of biocompatible nanocarriers offers exciting prospects for improving the bioavailability and targeted delivery of polyphenols, paving the way for future advancements in antiviral therapy. Overall, polyphenols represent a promising avenue for combating viral diseases and their exploration in the context of emerging and re-emerging viral threats holds great promise for the future.

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