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Phenolic Compounds: Promising Anti-Viral Agents A review

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Abstract

Phenolic compounds are a class of the most widely distributed secondary metabolites and found in most plant tissues. They may function as pollination, pigment constituents and protection against UV radiation. Phenolics have been investigated for their biological activities. They showed great activity against various viruses such as herpes simplex, Epstein-Barr virus, equid herpes virus, hepatitis B virus, human immunodeficiency virus and respiratory syncytial. This review summarized some phenolic compounds which showed antiviral activities, and expected to provide guides for rational design of antiviral drugs.

Keywords: Medicinal plants, Phenolic compounds, Antiviral activit

1. INTRODUCTION

Natural products have long been the major source of lead compounds for the development of a great variety of therapeutics including anticancer and antiviral agents. According to the WHO (World Health Organization), more than 80% of the world's population relies on traditional medicine for their primary healthcare needs [1]. Plant phenolics are the major source of compounds for the development of a great variety of antiviral agents [2]. Many studies revealed that a large number of phenolics has been isolated from medicinal plants. Medicinal plants synthesize and preserve a variety of biochemical products possessing potential inhibition of viruses. **Table 1** showed some medicinal plants which reported to have antiviral activity against different viruses and their chemical constituents. The tabulated plants are found to be rich in phenolic compounds.

Table 1: Some medicinal plants with antiviral activity against numerous viruses

Plant name	Family	Virus name	Isolated compounds	References
Zataria multiflora	Labiate	HSV-1	Rosmarinic acid	[3]
Spondias lutea	Anacardiaceae	Human rotavirus,	Flavonoids, phenolic acids, tannins	[4]
Psidium guajava	Myrtaceae	HSV-1	Polyphenols, tannins.	[5,6]
Moringa oleifera	Moringaceae	H1N1	Flavonoids, phenolic acids	[7,8]
Aloe barbadensis	Asphodelaceae	HIV, HSV, HBV, EBV, FMDV, NDV.	Polyphenols, Flavonoids, phenolic acids	[9-12]
Curcuma longa	Zingiberaceae	HCV, EBV, HIV-1, H1N1, H6N6, parainfluenza viruses 1, 2, 3, VSV, RV	Phenolics (Curcumin)	[13,14]
Camellia sinensis	Theaceae	HIV, HSV-I, IAV, HCV.	Catechins, quercetin,	[15-18]
Euphorbia hirta	Euforbiacee	HIV-1, HIV-2	Flavonoids	[19]

Table 1(cont.):

Glycyrrhiza uralensis	Fabaceae	HCV, Rotavirus diarrhea	Glycycoumarin, Liquiritigenin, glabridin isoliquiritigenin, licochalcone A,	[20,21]
Panax ginseng	Araliaceae	RSV, influenza virus, HIV, HSV, HBV, enterovir	Epigallocatechin gallate, theaflavin digallate, genistein, diosmin	[22,23]

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		s, norovirus, coxsackie-virus.	hesperidin, neohesperidin	
Citrus aurantium	Rutaceae	DENV, HIV-1, HSV-1 and 2, influenza, yellowfever.	Polyphenols	[24,25]
Diospyros kaki	Ebenaceae	Influenza virus H3N2, H5N3, HSV-1, VSV, SEV, HFMD, ADV, RSV, NDV.	Licocoumarone, apigenin, licoflavonol, luteolin, vitexin, glucoside, tannins	[26,27]
Citrus sinensis	Rutaceae	HAV,SARS-CoV-2	Flavonoids	[28]
Ficus benjamina	Moraceae	HSV-1, HSV-2	Flavonoids	[29]
Vitis labrusca	Vitaceae	(SA-11), human (HCR3) rotaviruses	Resveratrol, piceatannol, trans-arachidin-1, trans-arachidin-3	[30]
Allium cepa	Amaryllidaceae	SARS-COV	Quercetin	[31]
Allium sativum	Amaryllidaceae	DENV, common cold virus, influenza virus A,B, HIV, HSV-1, HSV-2	Quercetin	[32]

Abbreviations: HSV herpes simplex virus, VSV vesicular stomatitis virus, HBV hepatitis B virus, HIV human immunodeficiency virus, ADV adenovirus, FMDV foot and mouth disease virus, HCV hepatitis C virus, DENV dengue virus, RSV respiratory syncytial virus, EBV Epstein–Barr virus, RV rhinovirus, SEV Sendai Virus, HFMD hand, foot, and mouth disease,

Phenolic compounds are a class of plant secondary metabolites which are characterized by an aromatic ring system bonded with one or more hydroxyl groups. The structures vary in terms of complexity, from simple molecules to polymers of high molecular weight [33]. According to Harbone and Simmonds, these compounds can be classified into different groups according to carbon numbers [34]. **Table 2** showed the different class of phenolic compounds.

Table 2: Groups of phenolic compounds

Number of Carbon	Basic Skeleton	Class	Example
6	C6	Simple phenols, benzoquinone	Catechol, hydroquinone, 2,6-dimethoxy-benzoquinone
7	C_6-C_1	Phenolic acids	Gallic acid, salicylic acid
8	C_6-C_2	Acetophenones, tyrosine derivatives, phenylacetic acids	3-Acetyl-6-methoxy-benzaldehyde, tyrosol, *p*-hydroxyphenyl-acetic acid
9	C_6-C_3	Hydroxycinnamic acids, phenylpropenes, coumarins, isocoumarins, chromones	Caffeic acid, ferulic acid, myristicin, eugenol umbelliferone, aesculetin, bergenon, eugenin
10	C_6-C_4	Naphthoquinones	Juglone, plumbagin
13	C_6-C_1-C_6	Xanthones	Mangiferin
14	C_6-C_2-C_6	Stilbenes, anthraquinones	Resveratrol, emodin
15	C_6-C_3-C_6	Flavonoids	Quercetin, cyaniding, genistein
18	$(C_6$-$C_3)_2$	Lignans, neolignans	Pinoresinol, eusiderin
30	$(C_6$-C_3-$C_6)_2$	Biflavonoids	Amento-flavone
N	$(C_6$-$C_3)n$, $(C_6)_n$, $(C_6$-C_3-$C_6)n$	Lignins, condensed tannins	Proantho-cyanidins, phlobaphenes

2. PLANT PHENOLICS WITH ANTI-VIRAL ACTIVITY

The antiviral activities of some isolated natural phenolics are tabulated in **Table 3.** The name of the natural phenolic compounds and the references are provided. Structures of some selected phenolic compounds are shown in **Fig. 1.**

Table 3: Antiviral activity of phenolic compounds

Compd No.	Compound	Virus name	IC_{50} (μM)	EC_{50} (μM)	Ref.
1	Gallic acid	HSV	23.9		[35]
2	Methyl-gallate	HSV	0.20		[36]
3	Chloro-genic acid	HSV, ADV, HBV, influenzza virus	1.3 84	47.6 13.3	[37,38]
4	Caffeic acid	HSV, ADV, HBV, influenzza virus	3.5 0.70 100	14.2	[39,40]

Table 3: Cont.

5	Ferulic acid	HSV CDV	3.6	>100	[41,42]

6	Resveratrol	EBV, HCMV, VZV, HIV, HRV, VACV, MPXV	1.70 50.0 3.5 15.23	52.20 19.0 >2.5	[43-48]
7	Epicatechin	HSV, RABV, influenza virus	 145.1	2.5 85.4	[49]
8	Curcumin	HSV HIV HBV	33.0 40.0 150.0		[50-52]
9	Catachin	HSV,		4.0	[53]
10	Theaflavin	ADV, HIV, RSV, influenza virus	13.6 5.3 68.5 16.2		[53]
11	Epigallocatechin 3-gallate	HSV, EBV, ADV, HBV, HIV, RSV, Enterovirus HCV	38.6 57.6 39.4 9.9 57.6 10.0 2.5	 5.7	[54]
12	Luteolin	EBV JEV H3N2	6-8 4.56 7.15		[55,56]
13	Baicalein	H3N2 DENV CVB3 JEV	49.6 13.5 42.9 7.27		[57-60]
14	Hesperetin	CHIKV	8.5		[61]
15	Naringenin	CHIKV ZIKV HCV	6.18 58.79	 200	[61,62]
16	Apigenin	HSV-2 ADV-3 HBV HCMV	 22±3	9.7 11.1 7.1	[63,64]
17	Geraniin	EV71 HSV HIV EBV HCV	10 18.4±2 6.3 15.7 8.91		[65]
18	Nordihydroguaiaretic acid	HIV HCV	20	 30	[65]
19	Salidroside	RSV CVB3	10.3±1.5 39±1.2		[65]
20	Genistein	BV HSV-1	33 14.02 ± 0.97		[66, 67]
21	Quercetin	H1N1 DENV ZIKV HSV-1	7.75±1 28.9 2.30 ± 0.50	 1.69	[60,62, 68, 69, 71]
22	Myricetin	ZIKV	).58 ± 0.17		[62]

Abbreviations: ND virulent Newcastle disease, VSV Vesicular Stomatitis Virus, IAV Influenza A virus, HAV Hepatitis A virus, CDV Canine Distemper Virus, HCMV Human Cytomegalovirus,, VZV Varicella-Zoster Virus, HRV Human Rhinoviruses, VACV Vaccinia Virus, MPXV monkeypox virus, RABV Rabies virus, JEV Japanese encephalitis virus, CVB Coxsackievirus B, CHIKV chikungunya virus, ZIKV Zika virus, EV Enterovirus.. HN type of influenza viruses the half maximal inhibitory concentration (IC50) is a measure of the potency of a substance in inhibiting a specific biological or biochemical function. Half maximal effective concentration (EC50) is a toxic unit, which measures the concentration of a drug, antibody or toxicant which induces a response halfway between the baseline and maximum after a specified exposure time.

Table 4: Phenolics with anti-COVID-19 activity

No	Compund	IC_{50}	Ref
8	Curcumin,	20	[70]
14	Herbacetin,	33.17	[71]
21	Quercetin	23.8	[73]
22	Myricetin	43	[72]
23	Rhoifolin,	27.45	[71]
24	Pectolinarin	37.78	[71]
25	Tannic acid	13.4	[74]
26	Puerarin	42	[72]
27	Diadzein	56	[72]
28	Xanthoangelol E	11.4	[75]
29	Amentoflavone,	8.3	[76]
30	Kaempferol	16.3	[77]
31	Papyriflavonol A	3.7	[77]

Viral infection is one of the main hazards for public health, and caused considerable damage to human population. A number of medicinal plants rich in phenolics have been used against viral infection. Recently, the role of phenolics in the prevention and treatment of many diseases has been investigated [78]. So far, antiviral activity of these compounds has been reported using both in vitro and in vivo model of the investigations.

Viruses are infectious microbes made up of nucleic-acid genome (RNA or DNA) surrounded by a protective protein envelope. They can't propagate alone. The obligate intracellular parasites aim to deliver their genetic material to the host cell to permit the transcription by the host cell and continue to survive. Phenolic compounds have promising antiviral properties through various mechanisms. They could act as a treatment or prevention strategy during virus life cycle stages [79-81].

Phenolics can attach themselves to the viruses' surface proteins prohibiting their penetration into the host cells. They act as a transcription blocker to hamper viral DNA replication. They hinder protein translation and poly-protein processing. They can also inhibit virion release to invade other healthy host cells. Indirectly, they reduce the ubiquitin molecule level that the virus uses for its replication in the host cell. Moreover, phenolics can also modify the immune system and decrease the viral load [82].

Gallic acid (**1**), one of the most widely distributed phenolics of tea, exhibited great anti-HIV potency (IC_{50}=23.9 μM), while its methylgallate derivatives (**2**) was more active ($1C_{50}$=0.2 μM) [35,36].

Chlorogenic (**3**) and caffeic acids (**4**) isolated from coffee showed inhibition to HSV (EC_{50}=47.6; 15.3 μM), adenovirus (EC_{50}=13.3; 14.20 μM), HBV (IC_{50}=1.30;0.70 μM) and influenza virus (IC_{50}=84.0; 24.3 μM) [37-40]. Also, from coffee, Ferulic acid (4-hydroxy-3-methoxy cinnamic acid (**5**) exhibited antiviral activity against HSV (EC_{50}> 100mM) and canine distemper virus (CDV, IC_{50}=3.6 μM) [41,42]. Resveratrol (3, 5, 4-trihydroxystilbene, (**6**), showed activities against EBV, HCMV, VZV and HIV viruses (EC_{50}=52.20 μM, IC_{50}=1.7 μM, EC_{50}= 19.0 Mm, EC50>2.5 μM). Also, it showed antiviral activity against vaccinia virus (VACV), monkeypox virus (MPXV) with IC_{50} = 3.5 and 15.23μM [43-48].

Epicatechin (**7**), isolated from green tea, demonstrated relatively more potent activity against HSV (EC_{50} = 2.5 μM), rabies virus (EC_{50} = 85.4 μM) and influenza virus (IC_{50} > 145.1 μM, EC50 > 600.0 μM) [50]. Curcumin (**8**), isolated from turmeric, showed great and diverse antiviral potencies against HSV (IC50= 33.0 μM), HBV (IC_{50}=150), HIV (IC_{50}= 40.0 μM) [49-52].

Catechin (**9**) was isolated from green tea and displayed antiviral potency against herpes simplex virus [HSV, 50% maximal effective concentration (EC_{50}) = 4.0 μM], HIV (IC_{50} = 5.3 μM), rabies virus (EC_{50} = 36.5 μM) and influenza virus (IC_{50} > 144.6 μM), while Theaflavin (**10**) showed potent inhibitory activity against adenovirus (ADV), HIV, respiratory syncytial virus (RSV) and influenza virus with a mean 50% inhibitory concentration (IC_{50}) of 13.6, 5.3, 68.5 and 16.2 μM, respectively [53]. Also, from green tea, epigallocatechin 3-gallate (**11**) showed different modes of action in combating important human pathogens like HSV (IC_{50} = 38.6 μM, EC_{50} = 2.5 μM), Epstein-Barr virus (EBV, EC50 = 5.7 μM), adenovirus (IC_{50} > 57.6 μM), hepatitis B virus (HBV, IC_{50} = 39.4 μM), HIV (IC_{50} = 9.9 μM), RSV (IC_{50} = 57.6 μM), influenza virus (IC_{50} = 56.5 μM, EC_{50} = 28.4 μM), enterovirus (IC_{50} = 10.0 μM) and hepatitis C virus (HCV, IC_{50} = 2.5 μM, EC_{50} = 17.9 μM) [54]. Luteolin (**12**) exhibits inhibitory effects on Epstein-Barr Virus, Japanese encephalitis virus and influenza A virus (H3N2) [55,56].

In vitro antiviral experiments, baicalein (**13**) inhibited Influenza A virus subtype H3N2 virus with IC_{50} = 13.5. It also exhibited significant effects against DENV (Dengue virus), coxsackievirus B3 (CVB3) and JEV (Japanese encephalitis virus) with IC_{50}= 13.5, 42.90, 7.27. [57-60]. Hesperetin {**14**) with IC_{50} = 8.500 μM and naringenin (**15**) with IC_{50} = 6.818 μM inhibited the post entry stages of CHIKV (Chikungunya virus) replication activity. Also, naringenin showed antiviral activity against ZIKV (Zika virus) and HCV (Hepatitis C virus) with IC_{50}=58.7 and EC_{50}=200 [61,62]. As a flavone type, apigenin (**16**) showed high activity against HSV-2 (Herpes simplex virus) (EC_{50} = 9.7 mg/L), ADV-3 (adenoviruses type 3) (EC50 = 11.1 mg/L), hepatitis B surface antigen (EC50 = 7.1 mg/L). Its activity against HCMV (Human Cytomegalovirus) was reported (IC_{50} = 22±3) [63, 64]. Geraniin (**17**) have also been reported against enterovirus 71 (EV71) (IC_{50}=10 μg/mL), herpes simplex virus type 2 (HSV-2) (IC_{50}=18.4 ±2.0 μM), human immunodeficiency virus (HIV) (IC_{50}= 6.28 μg/mL, Epstein–Barr virus (EBV) (IC_{50}=15.7 μM,), and hepatitis C virus (HCV) (IC_{50}= 8.91 μM) [65]. Nordihydroguaiaretic acid (**18**) can inhibit HIV (IC_{50} = 20 μM), and lipid metabolic pathways necessary for HCV replication in Huh7.5.1 cells (EC_{50}= 30 μM) [65].

The antiviral effect of salidroside (**19**) has also been reported against RSV (IC_{50}= 10.3) and CVB3 in vitro in myocytes and in vivo in BALB/c mice (IC_{50}=39.0 1.2 mg/L; 20 and 40 mg/kg at days 7 and 14) [65]. Genistein (**20**) prevented plaque formation of B virus and reduced virus production with an IC_{50} = 33 and HSV-1 by 10.04±0.97 [66, 67]. Quercetin showed potent anti-ZIKV activity by targeting the replication process of the virus. Quercetin (**21**) showed strong inhibitory effect on different viral strains of Influenza-A Virus. The IC_{50} values of quercetin against (H1N1) was.756 ± 1. [60] with the virus at a concentration of IC_{50} = 28.9 μg/ml. Quercetin exhibited inhibitory effect against DENV-2. [62]. Quercetin showed potent anti-ZIKV activity by targeting the replication process of the virus. Quercetin nearly obtained complete inhibition on the process of zika virus viral RNA production. The IC_{50} quercetin was 2.30 ± 0.50 μM. for quercetin [69] Quercetin tested against the HSV-1 and showed strong inhibitory effects and reduced the CPE (cytopathic effect) in the virus infected cells. quercetin at EC_{50} = 1.69 μg/ml [71], Myricetin (**22**) was analyzed for its anti-ZIKV activity, it showed potent anti-ZIKV activity by targeting the replication process of the virus. The IC_{50} value for myricetin was 0.58 ± 0.17 μM, [62].

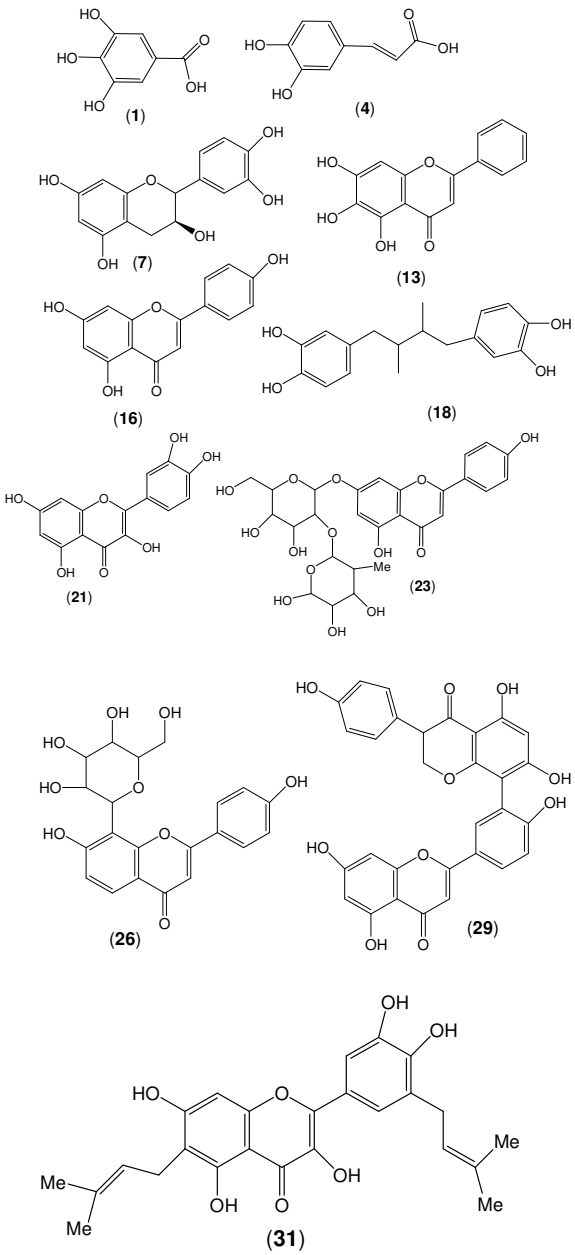

Figure 1: Structure of some phenolic compounds with anti-viral activity

Concerning COVID-19, the highly contagious novel disease caused by SARS-CoV-2, has become a major international concern as it has spread quickly all over the globe. Numerous phenolics were found to have antiviral effects against SARS.

Curcumin, (8) being already explored *in vitro* as a potent inhibitor of SARS-CoV Mpro with an IC_{50} value of 20 M[70]. The flavonoids Herbacetin, rhoifolin, and pectolinarin (**14**, **23**, 24) were found to be effective inhibitors of Mpro of SARS-CoV. Using FRET-based assay, IC_{50} values were determined and were 33.17, 27.45, and 37.78 M, respectively [71]. Isoflavones puerarin and daidzein (**26**, **27**) and flavonol myricetin (**22**) were found to be potent inhibitors with IC_{50} values of 42, 56, and 43 M, respectively [72]. Quercetin (21) was the most promising flavonoids with anti-CoV potential with IC_{50} = 23.8 [73]. Tannic acid (**25**) was revealed to be another potential natural drug against SARS-CoV-2. The concentration of tannic acid required to inhibit 50% of the proteases activity, IC_{50}, was 13.4 M [74]. An chalcone, isolated from *Angelica keiskei,* named xanthoangelol E (**28**), was shown to be an effective inhibitor of SARS-CoV with IC_{50} values of 11.4 M [75]. Amentoflavone, (**29**) a biflavone isolated from *Torreya nucifera,* demonstrated a prominent inhibitor of SARS-CoV with IC_{50} = 8.3 lM [76]. Kaempferol (**30**) exhibited anti-SARS activity with IC_{50}=16.3, while the papyriflavonol A (**31**), a double prenylated flavone derivative, presents one of the most significant inhibitors of SARS with IC_{50} value of 3.7 [77].

3. CONCLUSION

Literature search has led to the identification of numerous phenolics exerting antiviral activity. Medicinal plants are a rich source of phenolic compounds with potential antiviral activity. They are found both in underground and above-ground plant organs. The bioactive phenlic compounds in plants and their extracts have antiviral activity and can be used preventively or to fight infections.

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5. Conflicts of Interest:

The author declares no conflict of interest.

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