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POLYPHENOLIC COMPOUNDS - A PROMISING LEADS FOR ANTIVIRAL THERAPY

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ABSTRACT

Medicinal plants consist of a wide range of phytochemicals, which are usually described as secondary metabolites. The production of secondary metabolites in medicinal plants affects different factors, like stress and defensive responses. Various factors, such as species differences, environmental variables, and so on, will influence the type and level of the presence of secondary metabolites. Phytochemicals are produced by these medicinal plants and have a range of biological effects on human health. Polyphenolic compounds are found throughout the plant kingdom that is highly effective in lowering or minimizing the risk of various chronic illnesses. Polyphenols are classified into two types: flavonoids and phenolic acids. Medicinal plants and plant-based foods have complex mixtures of bioactive polyphenolic compounds. Because of this complexation, we are unable to identify the specific phenolic compounds' health benefits. A variety of scientific publications have explored polyphenolic phytochemicals' biological activity and mechanisms of action. The relevant data were collected from peer-reviewed journals, accessed from different data resources like PubMed, Google Scholar, and Scopus. The current review article focuses on the study of the antiviral properties of polyphenolic compounds.

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Introduction

Medicinal plants have recently received a lot of interest, mainly because they contain pharmacologically active metabolites that are safe to use, low cost, and readily available [1, 2]. Plants have around eight thousand different phenolic compounds that have been determined in plants as secondary metabolites [3]. Secondary metabolites from plants are phenolics, and these are produced either from the shikimaic acid pathway or the polyketide acetate/malonate pathway, which have a multitude of physiological functions in plants [4]. Polyphenolic compounds are naturally occurring secondary metabolites of plants that contain phenolic groups and one or more hydroxyl groups in their structure. In their unbound state, they are attached to proteins or sugars. Polyphenols have varying degrees of pharmacological activity depending on their chemical composition. The three most common phenolic compounds present in human food are phenolic acids, flavonoids, and tannins. In addition, flavonoids are further divided into flavones, isoflavones, flavonols, anthocyanins, flavanols, flavanones, and phenolic acids into hydroxybenzoic and hydroxycinnamic acids. The antioxidant capabilities of polyphenolic compounds imply that they may have a vital role in preventing cancer, cardiovascular disease, and neurological disorders [5]. The primary objective of the current review article is to provide a summary of the antiviral properties of chemical entities derived from polyphenols.

Role of Polyphenols in Anti-Viral Therapy

Naturally occurring metabolites derived from plants have many biological effects. Chronic illnesses can be treated with plant-derived lead compounds. Food, fruits, nuts, and herbs contain polyphenols, a naturally occurring secondary metabolite. Various internal and external factors affect the biosynthesis of polyphenols in plants, notably weed growth, insect infestation, fungal and microbial infection, water shortages, elevated salt and toxic metal content, UV radiation, and temperature rise [6, 7]. Polyphenols are involved in a range of certain other functions in the plant system, including cell proliferation, photosynthesis, fertilization, hormone regulation, and nutrient mineralization systems, to name a few [8]. Thus, coumarins and tannins play a protective role against herbivores [9]. The use of physiologically active substances like polyphenols has recently been

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advocated as an alternative treatment due to its possible health benefits. Scientifically, more than five hundred different polyphenols have been documented. Extended supplementation of polyphenol-rich diets is the best defense against diseases like CVD, neurological disorders, diabetes, osteoporosis, and cancer. Several viruses can have varying degrees of impact on human health. In different replication stages of viral growth, polyphenols, notably flavonoids, will act on the virus to suppress its viral growth. Several polyphenolic compounds also restrain the development of the SARS Cov-19 virus efficiently. In COVID-19 therapy, formulations such as kabasurakudineer are utilized as a complementary therapy. While the antiviral effects of polyphenols are intriguing when examined *in-vitro* or in animal studies, there is inadequate convincing evidence from human studies, especially those involving larger populations. The chemical structures of promising leads are listed in **Figure 1**. Polyphenolic compounds are extensively used as antioxidants. Due to their antioxidative properties, they interfere with intracellular replication of viruses [10]. Various factors influence the antiviral activity of polyphenolic compounds, including their stability, reactivity, synergism, and bioavailability [6].

Acacetin

Acacetin is a naturally occurring flavonoid known as 5,7-dihydroxy-4-methoxy flavone and possesses many pharmacological activities [11]. A mixture of flavonoids called pectolinarin and acacetin-7-O-rutinoside was identified in ethanolic extracts of *Distictellaelongata* fruits. The mixture of the flavones is derived from chromatographic fractions, which show remarkable antiviral activity against DENV-2. Therefore, it could be due to the synergistic effect of the flavone mixture mentioned above, but the exact mechanism is unknown [12]. Acacetin was isolated from *Scoparia dulcis*, and the inhibitory effects of isolated flavonoids were tested against herpes simplex virus type 1. Among many flavonoids isolated from this plant, acacetin shows higher virucidal activity compared with others. The antiviral activity of acacetin is directly related to its concentration and incubation time. The proposed mechanism of action of acacetin is that it interrupts both steps of transcription and translation in the early stages of viral replication [13]. The ethyl acetate fraction of the ethanolic extract of *Moslascabra* was found to contain five different phytocompounds. It appears that the separated fractions have favorable antiviral properties against the influenza virus. A cytopathic inhibitory assay was conducted using MDCK cells to determine the antiviral properties of the extracts and the isolated compounds. *In-vitro* evaluation of isolated compounds has revealed better anti-influenza virus activities where ribavirin is the standard drug. Acacetin is one among those that showed good inhibition; the IC_{50} value is 1.671µg/ml. In addition, the ethanolic extract of *Moslascabra's* ethyl acetate fraction provided a significant antiviral effect in dose-dependent mannar, minimalized viral infection, and reduced toxicity in mice [14].

Amentoflavone

Amentoflavone is a familiar biflavonoid that occurs in large numbers of medicinal plants. It is a popular polyphenolic component due to its pharmacological importance, such as inflammation reduction, free radical scavengers, and blood glucose control. Experts in pharmacognosy have isolated and identified this biflavonoid from many medicinal plants, many of which play an essential role in the traditional treatment system in many parts of the world [15]. Acyclovir is the available drug for treating viral infections, and Acyclovir-resistant strains have emerged due to continuous treatment. In addition to its inhibition of HSV-1 (F strain), amentoflavone has also demonstrated good activity against several ACV-resistant strains. Increased amentoflavone concentration significantly inhibited HSV-1 (F strain) infection and many ACV-resistant strains, possibly by inhibiting early gene expression, suppressing NF-kB-mediated inflammation, and inducing autophagy [16]. Amentoflavone isolated from *Rhus succedanea* and *Garcinia multiflora*. Amentoflavone has significant antiviral activity against influenza B virus (EC_{50}-0.56µg/mL and IC_{50}-100µg/mL), with selectivity index values of 178, and moderate activity against influenza A virus, HSV-1 (EC_{50}-17.9µg/mL) and HSV-2, (EC_{50}-48.0µg/mL) [17]. Coxsackievirus B3 is one of the Group B coxsackieviruses which cause viral myocarditis [18]. In another study, amentoflavone was also known for minimizing Coxsackievirus B3 cell division by hindering fatty acid synthase expression [19]. The leaves of *Torreyanucifera* contain twelve phytochemicals, including eight diterpenoids and four biflavonoids, including amentoflavone. Biflavoneamentoflavone has shown the greatest potency against SARS-CoV 3CLpro, with an IC_{50} of 8.3µM [20].

Apigenin

Apigenin is widely distributed in plants, and it is considered one of the most studied phenolics. In contrast to glycosidic molecules, this non-glycosidic particle seems to have antiviral activity against the hydroxylation of the 3-position [21]. The flavonoids apigenin and luteolin are abundant in ethanolic fractions of the entire plant of *Cynodon dactylon*. Further chromatographic studies confirmed the presence of flavonoids. Flavonoid fraction are shown potential anti-CHIKV activity at minimal concentrations ie. 25 to 50µg/mL. The treatment of the flavonoidal rich fraction has a greater ability to reduce viral mRNA synthesis reduction [22]. Apigenin was shown to exert a strong *in-vitro* and *in-vivo* antiviral activity against the buffalopox virus. The hypothesized mechanism of action may impede viral protein translation and hence directly inhibit viral polymerase activity [23]. Apigenin's early treatment of the African swine fever virus showed promising results. The inhibitory activity in-vitro is primarily due to a dose-dependent mechanism. Furthermore, apigenin can prevent the African swine fever virus from replicating, interfering with the virus's early stages of the disease [24]. Apigenin possesses significant antiviral efficacy against infection with enterovirus 71. Apigenin's estimated EC_{50} concentration for suppressing enterovirus-71 infection was 10.3 µM, whereas its estimated CC_{50} concentration was 79.0 µM. Apigenin treatment decreased enterovirus-71 disease by inhibiting the expression of hnRNP A1 and A2 [25]. In-vitro treatment of apigenin remarkably inhibits hepatitis C

virus (HCV) replication. In the liver, hepatitis C virus replication is managed by a liver enzyme, namely MicroRNA122 (miR122). Apigenin's ability to inhibit HCV replication appears to be based on a lowering in miR122 expression levels, which is achieved through inhibiting TRBP phosphorylation [26].

Baicalein

The flavonoid baicalein shows antiviral activity and could potentially treat herpes viruses, adenoviruses, and respiratory syncytial viruses. Mosquito bites spread the infectious disease Japanese encephalitis, and the infection affects the brain cells. Baicalein had an IC_{50} 14.28 µg/mL against the Japanese encephalitis virus, and it was proven to have a substantial inhibitory effect [27]. Chikungunya virus causes painful arthritis in humans and is transmitted by mosquitoes. Baicalein was studied for its inhibitory action against CHIKV. Baicalein showed significant inhibition of CHIKV infection, having an IC_{50} value of 1.891 µg/ml with low cytotoxicity. The inhibitory effect of Baicalein may induce the inhibition of CHIKV mRNA synthesis or genome replication [28]. Baicalein has been proven *in-vitro* to cause cell death in HIV-infected cells and to be an antagonist of HIV-RT reverse transcriptase, an inhibitor of viral RNA replication, and a virus antagonist [29]. Cytomegalovirus is a common virus that affects people with weaker immune systems, such as pregnant women, recipients of organ transplants, and AIDS patients. Human cytomegalovirus is most effectively inhibited by baicalein, which has an IC_{50} of 0.40±04 µm in the colorimetric assay and 1.2±0.8µm in the titer reduction assay. In addition to reducing HCMV early and late proteins, it also reduces viral DNA [30]. Both *in-vitro* and *in-vivo* studies have shown that baicalein has a stronger inhibitory effect on influenza viruses. By using the cytopathic effect (CPE) assay, baicalin showed significant activity against the influenza virus at a dose of 1.2µg/ml, whereas using the plaque inhibition assay; baicalin demonstrated significant activity against the virus at a dosage of 2µg/ml. Oral administration of baicalein is more effective than baicalin. The suggested mechanism may be the inhibition neuraminidase enzyme [31].

Bavachinin

Psoralea corylifolia L. seeds were extracted with ethanol and six bioactive components were isolated, bavachinin is one of them. Bavachinin and seed extracts are significantly more effective at inhibiting SARS-CoV-PLpro, with an IC_{50} of 15 µg/ml and 38.4 ± 2.4µM, respectively [32].

Biochanin A

Biochanin A is an isoflavone and is found naturally in the legumes of several clover species, most notably red clover, as well as in a variety of herbal dietary supplements. Biochanin A decreased human herpesvirus 6 (HHV-6) antigen expressions by reducing protein tyrosine kinase phosphorylation [33]. The advantage of biochanin A is hindering the multiplication of two dissimilar H5N1 strains. In macrophages and lung epithelial cells, pro-inflammatory gene expression initiated by H5N1 is inhibited by biochanin A. The antiviral benefits of the neuraminidase inhibitor zanamivir were increased by the use of biochanin A, which has been revealed to disrupt critical processes within the viral replication cycle. As part of cellular signaling pathways, biochanin A inhibits AKT, ERK 1/2, and NFjB activation. It produces cytokines that stimulate cellular inflammatory responses in response to influenza virus replication. In H5N1-infected A549 cells, biochanin A inhibited the production of IL6, IL8, and CXCL10 [34]. As H5N1 infects human alveolar basal epithelial cells, biochanin A increases ROS generation, but antioxidants suppress ROS formation and enhance anti-H5N1 activity [35].

Chrysin

Chrysin is found in a wide range of medicinal plant extracts, such as propolis, passionflower (*Passifloracaerulea*), and honey, all of which possess a high source of trade value and are highly effective therapeutic agents. *In-vitro* antiviral activity of chysin and synthesized di-isopropyl chrysin-7-yl phosphate against infectious Enterovirus 71 was improved. Even at low concentrations, the flavone shows more significant inhibitory activity while causing low cytotoxicity. It has been shown that di-isopropyl chrysin-7-yl phosphate has an IC_{50} of 13.86 µM, whereas chrysin has an IC_{50} of 24.12 µM. A synthetic di-isopropyl chrysin-7-yl phosphate was more effective than chrysin at inhibiting EV71 replication [36]. Coxsackievirus B3 is a member of the same genus (Enterovirus) as EV71. CVB3 induces a range of illnesses in humans, including viral myocarditis. Furthermore, *in-vivo* and *in-vitro* studies of both chysin and its derivatives have shown effective inhibition of CVB3 infections. In *in-vitro*, chrysine alone exhibited antiviral activity against CVB3 at a concentration of 10 µM but mild cytotoxicity at a concentration of 50 µM. In animal studies, the 4-substituted benzyl derivatives show the strongest activity against CVB3 and also lesser cytotoxicity, unlike chrysin. The decrease in serum CXCL1 levels seen with the chrysin derivative could be a result of a reduction in viral replication [37].

Daidzein

Daidzein is a naturally occurring isoflavonic phytoestrogen that is predominantly found in leguminous plants such as soybeans and mung beans. Daidzein shows a promising antiviral effect against feline calicivirus and murine norovirus. A 200 µM daidzein dose considerably reduced the feline calicivirus titer by 63.47±9.82%, while a 50 µM daidzein dose significantly lowered the murine norovirus titer by 46.32±8.70% [38]. Daidzein's antiviral efficacy was attributed to the ability to prevent the ingress of viruses by blocking the neuraminidase enzyme [39]. Recent research suggests that daidzein's antiviral activity

is not dependent on its ability to inhibit viral enzymes such as neuraminidase and cap-dependent endonuclease. Daidzein regulates virus replication via signal transduction via 5-lipoxygenase products [40].

Epigallocatechin Gallate

Green tea contains high amounts of catechins. Green tea is derived from *Cameliasinesis* leaves. Green tea is the primary source of epigallocatechin gallate (EGCG), a polyphenol. In MDCK cell culture, the polyphenolic chemicals epigallocatechin gallate (EGCG) and epicatechin gallate (ECG) were shown to be effective inhibitors of influenza virus replication. EGCG and ECG exhibited 50% effective inhibitory concentrations (EC_{50}) of 22–28 and 22–40µM, respectively. EGCG is much more productive than ECG in reducing hemagglutination. Based on the fact that the whole tea extract was significantly more efficient than any isolated polyphenol. EGCG and ECG effectively inhibit viral RNA production in MDCK cells at high concentrations. The neuraminidase activity further supports the inhibitory activity of green tea. Green tea's antiviral effect is significantly enhanced by the presence of the catechin skeleton's 3-galloyl group [41]. In another investigation, Epigallocatechin gallate (EGCG) and gallocatechingallate (GCG) wasfound to suppress enterovirus-71 (EV71) replication in Vero cells. The antiviral effect of polyphenols was found to be associated with their antioxidant capacity. The treatment with EGCG greatly diminished the production of reactive oxygen species. Cells lacking glucose-6-phosphate dehydrogenase are extremely vulnerable to viral infection. Glucose-6-phosphate dehydrogenase (G-6-PD) deficiency accelerated the replication of EV71 and such acceleration was largely undone by EGCG. EGCG may inhibit viral replication by altering the cellular redox environment [42]. Porcine circovirus type 2 (PCV2) infections induced an inhibitory effect from EGCG at 100 µM, without causing cytotoxicity in the host cell. Based onthe *in-vitro* evaluation, EGCG was found to have an EC_{50} value of 37.79±1.64 µM against PCV2. PCV2's capsid binds to the EGCG molecule. EGCG may bind competitively to the PCV2 capsid, preventing the virus from attaching to host cells. EGCG may form hydrogen bonds with positively charged amino acids in the capsid, such as ARG51 and ARG73. The newly developed connection between the capsid and heparan sulfate might disturb the electrostatic interaction, leadingto impairing virus adhesion to the cell surface [43]. Epigallocatechin Gallate is has been found to have an encouraging inhibitory effect against the West Nile Virus, Zika Virus, and Dengue Virus. According to the proposed mechanism, EGCG's ability to inhibit viral replication is that it binds directly to viral particles and inhibits host cell attachment [44]. An Alphavirus called chikungunya virus (CHIKV) causes chikungunya fever and is spread by mosquitoes. *In-vitro*, EGCG decreased CHIKV infection, but not the viral replication [45]. EGCG inhibits HIV-1–glycoprotein 120 binding to the CD4 molecule and limiting the virus's anchoring and penetration into the host. The effect of EGCG on HIV-1 infection is dose-dependent. Inhibition of HIV-1 infection by EGCG through cell growth inhibition or apoptosis [46]. EGCG at a dose of 1.6 and 2.0 µM was 50% effective at inhibiting HIV-1 and HIV-2 in HeLa-CD4-LTR-gal cells. Additionally, EGCG has been shown to block reverse transcription and function synergistically with another reverse transcription inhibitor, azidothymidine [47].

Galangin

Galangin is a 7-hydroxy flavonol isolated from aerial parts of *Helichrysumaureonitens*. At doses ranging from 12 to 47 µg/ml, galangin showed significant antiviral activity against HSV-1 and CoxB1 [48]. Eighteen different flavonoids were evaluated *in-vitro* for their ability to prevent herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2). Flavanols and flavonolswere found to be more active than flavones. Administering galangin before adsorption of the virus exhibited minimal improvement of inhibition, implying that the galangin may also act intracellularly [49].

C- Geranylated Flavonoids (Tomentin A-E)

Flavonoids containing a terpene side chain are known as C-geranylated flavonoids [50] thereby adding the chain to the flavonoid skeleton. Methanolic extracts of *Paulownia tomentosa* fruit contain five novel C-geranylated flavonoids. A total of twelve C-geranylated flavanones were selected to evaluate their antiviral activity against the SARS-CoV papain-like protease (PLpro). A multitude of viral life cycle phases requires protease enzymes [51]. The majority of the isolated compounds are SARS-CoVPLpro inhibitors. The inhibitory effect of isolated compounds is completely dose-dependent, with IC_{50} values ranging from 5.0 to 14.4 µM. These five novel C-geranylated flavanones with a 3,4 -dihydro-2H-pyran moiety are inhibited more effectively than their parent compounds [52].

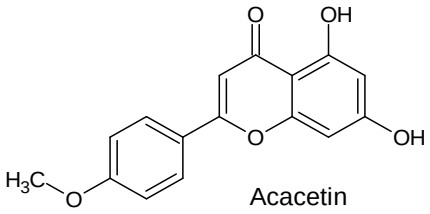
Hesperetin

Hesperitin is a flavonoid that is widespread in citrus fruit. In comparison to Hesperedin, Hesperetin has greater bioavailability. Hesperetin exerts a significant inhibitory impact on the Sindbisneurovirulent strain *in-vitro*. The results of the plaque test indicated that Hesperetin had a 50% inhibitory concentration of 20.5 g/ml against Sindbisneurovirulent strain infection. Their glycoside, hesperidin possessing lacked inhibitory action. Flavavones exhibit antiviral activity, mostly due to the presence of the rutinoside moiety [53, 54]. Hesperetin exhibits strong antiviral efficacy against CHIKV by dose-dependent mechanisms, limiting viral replication and down-regulating viral protein synthesis, which is required in viral replication [55].

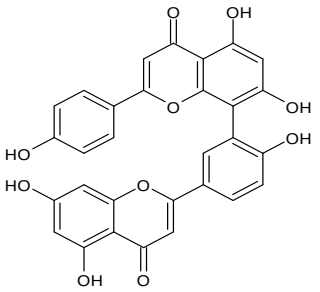
Hinokiflavone

Eleven biflavonids have been isolated from both the plants of seed kernels of *Rhus succedanea* and heartwood of *Garcinia multiflora.* Hinokiflavone is a biflavone isolated from the seeds of *Rhus succedanea*. According to the experimental observations, the biflavonidshinokiflavone and robustaflavone have similar inhibitory activities (IC_{50}-65µM) against HIV-1

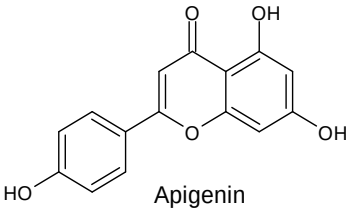
reverse transcriptase. Morelloflavone is one of the biflavonoids found in *Garcinia multiflora* that has promising antiviral action against HIV-1 when compared to all other biflavonoids (strain LAV-1). Morelloflavone is a flavanone (naringenin) and a flavone (luteolin) molecule linked together by an I-3-II-8 bond, which is responsible for promising antiviral activity [56].



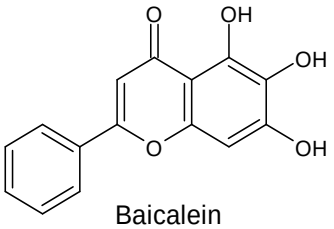
Acacetin



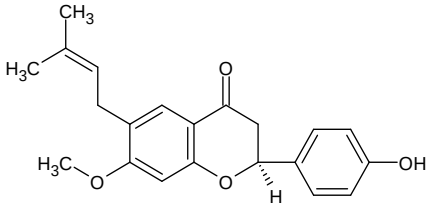
Amentoflavone



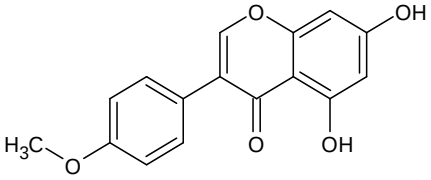
Apigenin



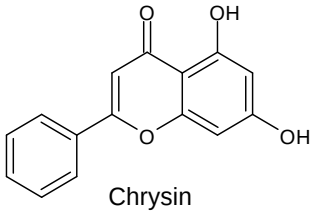
Baicalein



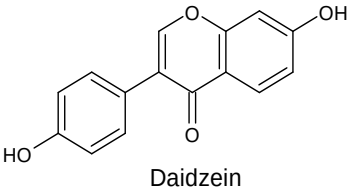
Bavachinin



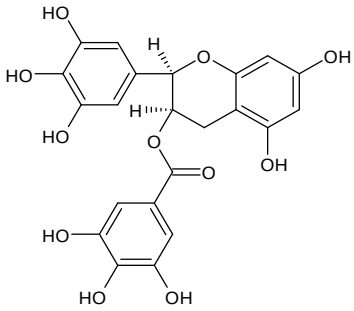
Biochanin A



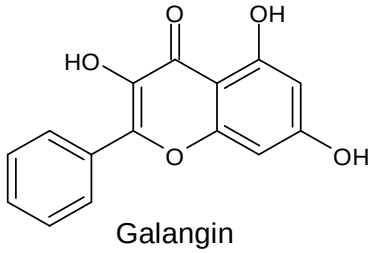
Chrysin



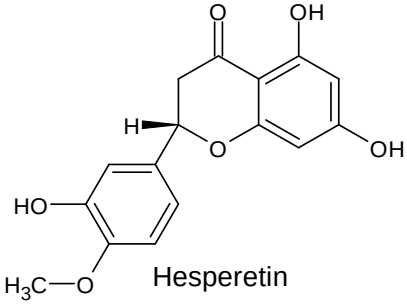
Daidzein



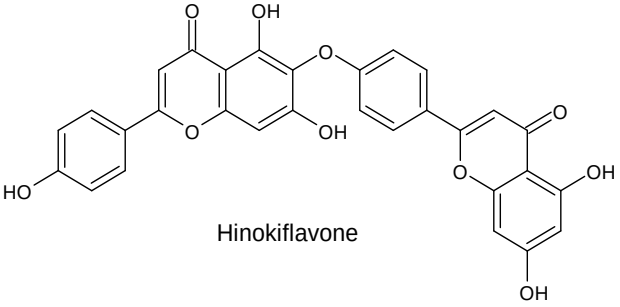
Epigallocatechin gallate



Galangin



Hesperetin



Hinokiflavone

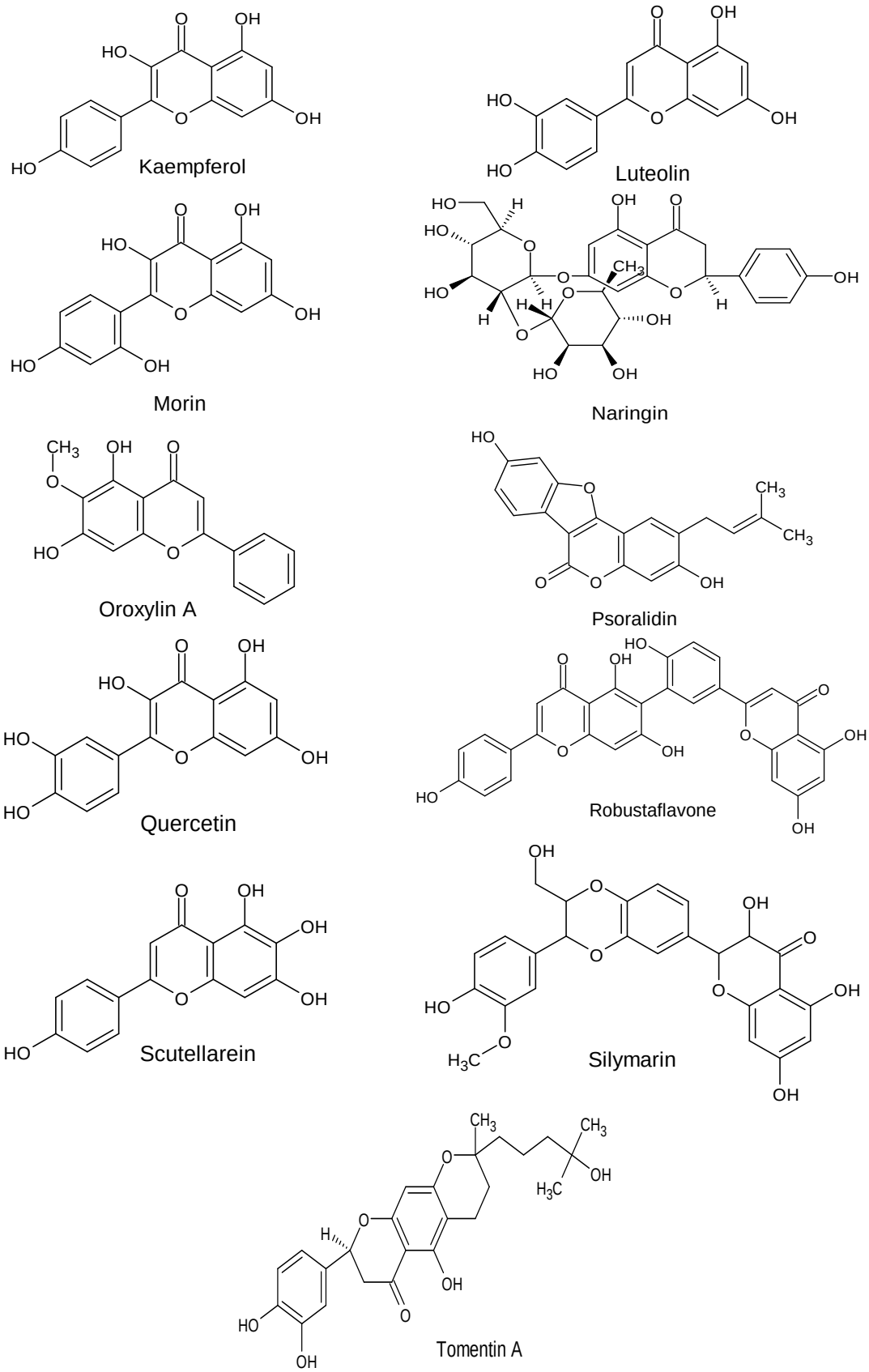


Figure 1. Polyphenolic compounds for antiviral therapy.

Kaempferol

Kaempferol is a yellow-coloredflavonol that occurs naturally in several fruits and vegetables. The kaempferol 3-O-robinobioside is obtained from an ethanolic extract of *Ficusbenjamina* leaves. The isolated flavone was found to have a considerable inhibitory effect on Herpes Simplex Viruses 1 and 2. However, it does not have a more robust antiviral

effectiveness against Varicella Zoster Virus [57]. Cytomegalovirus is a member of the Betehepes virus family. In HIV/AIDS and organ transplantation patients, human cytomegalovirus replication produces significant infections such as hepatic complications and pneumonia. Five different flavonoids are isolated from buds of *plantanusorientalis*. Kaempferol and its acyl-substituted derivatives possess better effect than others to reduce Human Cytomegalovirus replication [58]. In another study, Kaempferol's antiviral activity was evaluated in BHK-21 cells against Japanese encephalitis and Dengue viruses. Against the Japanese encephalitis virus, Kaempferol inhibits the virus replication significantly but does not show inhibition positively when tested against the Dengu virus. Kaempferol treatment enhanced the level of the protein GRP78 in DENV-infected cells but not in JEV-infected cells. Treatment with kaempferol, which causes cellular modification, can have conflicting effects on viruses from the same family, indicating that the two viruses have different replication methods [59]. Coronavirus 3a Channel Protein is crucial to the replication of the virus. Developing antiviral medications targeting viral ion channels is a promising target. Juglanin, a kaempferol glycoside with an arabinose residue (IC_{50} - 2.3 μM), inhibits the 3a-mediated current significantly. Kaempferol glycosides containing rhamnose residues, such as afzelin, also appear to be effective [60]. Five flavonols were isolated from *Rhodiolarosea*, with kaempferol being one of them. In an *in-vitro* investigation, the neuraminidase inhibitory effects of isolated compounds in MDCK cells against two influenza virus strains, H1N1 and H9N2, were explored for their ability to reduce viral-induced cytotoxicity. Kaempferol exhibited the most significant antiviral activity against both H1N1 and H9N2 influenza virus strains, with EC_{50} values of 30.2 and 18.5 μM, respectively. The number and location of hydroxyl groups on their backbones affected the antiviral activity of flavonoids [61].

Luteolin

Luteolin is a yellow-colored bioflavonoid and is found in a variety of vegetables and fruits. Its chemical formula is 3′, 4′, 5, 7, tetra-hydroxyl flavonoid [62]. Luteolin and tetra-O-galloyl-ß-d-glucose (TGG) are two small compounds that prevent the coronavirus from infecting host cells and triggering severe acute respiratory syndrome. Defeating SARS-CoV entry into Vero E6 cells is especially effective with TGG and luteolin. A critical component of the virus-cell fusion process is the transmembrane S2 subunit of the S protein. When frontal affinity chromatography-mass spectrometry was used to compare the outcomes, TGG and luteolin were observed to have the highest affinity for the S2 protein. According to a proposed mechanism, the antiviral effect of luteolin may be achieved by disrupting the virus-cell fusion process [63]. Flavones, a type of flavonoids with a distinctive 2-phenylchromene-4-one ring structure, have been found to have antiviral and anti-inflammatory activities [64]. *Cynodondactylon* L. Pers contains luteolin and apigenin as major phytocompounds. Further evidence of flavonoid presence is confirmed by RP-HPLC and GC-MS studies, and flavonoids demonstrate anti-chikungunya properties in Vero cells. By achieving a very high degree of viral inhibitory activity (nearly 98%) at a concentration of 50μg/mL., the fraction was found to be less cytotoxic. It has been shown that fraction-treated infected cells show a significant reduction in viral mRNA production in comparison with virus-infected control cells [65]. The Japanese encephalitis virus is a neurotropic flavivirus that causes Japanese encephalitis. Human viral encephalitis caused by the Japanese encephalitis virus has a significant mortality rate. Luteolin was an antiviral bioflavonoid that was very effective at blocking JEV from growing in A549 cells. It had an IC_{50} value of 4.56μg/mL.Luteolin was also found to have extracellular virucidal action against the Japanese encephalitis virus. The time-of-drug addition assay shows that luteolin halts Japanese encephalitis virus infection after the virus has entered the body [66]. The acute respiratory viral disease, influenza causes considerable mortality and morbidity. In an *in-vitro* investigation, luteolin reduced influenza-A virus replication. A time-of-drug addition experiment revealed that this drug inhibited viral reproduction early in the infection. Luteolin inhibited coat protein I complex production, associated with influenza virus invasion and the endocytic process [67].

Morin

Globally, millions of people are affected by the influenza virus, which causes the flu. An influenza infection with morin hydrate inhibits viral entry into host cells as well as reducesinflammation in mice. Combining Morin and oseltamivir phosphate therapy effectively lowers viral titers and reduces pulmonary inflammation, which is suppressed through lower levels of cytokines and chemokines that promote inflammation. This suggests that morin hydrate has antiviral properties because it prevents the virus from entering the body [68].

Naringenin

Citrus fruits contain vast amounts of naringenin, a flavone subclass molecule. Both hesperetin and naringenin are capable of preventing Chikungunya virus intracellular proliferation. Naringenin suppresses virus replication in vitro with an IC_{50} value of 6.818μM in chikungunya-infected hamster kidney cells [69]. Naringenin inhibits dengue virus replication in infected human-derived Huh7.5 hepatoma cells (In-vitro/250 μM) in a dose-dependent manner [70].

Oroxylin A

Oroxylin A is a flavonoid found in the roots of *Scutellariabaicalensis*Georgi, an indigenous plant to China. Oroxylin A exhibits a wide range of pharmacological actions, including antioxidant, anti-inflammatory, neuroprotective, and antiviral activity, and is particularly effective against cancer [71]. Oroxylin A and two more flavonoids are isolated and purified from the aerial parts of *Scutellariabaicalensis*Georgi. Oroxylin A protects mice against Coxsackievirus B3, which causes acute pancreatitis. It also lessens the damage caused by the virus. Oroxylin A treated mice showed a smaller viral titer in the pancreas as well as a

decreased level of proinflammatory cytokines such as interleukin-6 and tumour necrosis factor-alpha in the blood. Furthermore, oroxylin A treatment reduced the histological pancreatic lesions and apoptotic cell death caused by coxsackievirus B3 infection [72]. Enterovirus 71 is one of the most common causes of newborn death, and Oroxylin A has been shown to have an inhibitory effect on the virus. The primary mechanism of action of oroxylin A is the inhibition of viral replication and viral VP2 protein expression, which eventually leads to the inhibition of virus capsid protein production [73].

Psoralidin

The seeds of *Psoralea corylifolia* L. play a significant role in traditional medicines like Ayurveda and the Chinese medication system to treat various skin diseases like psoriasis, Hansen's disease, and vitiligo [74]. From ethanolic extracts of *Psoralea corylifolia* seeds, bioassay-guided fractions isolated six different phytocompounds namely bavachinin, neobavaisoflavone, isobavachalcone, 4′-O-methylbavachalcone, psoralidin, and corylifol A. Most of the isolated phytocompouds inhibited papain-like protease dose-dependently, with an IC_{50} ranging between 4.2 and 38.4 μM. All six polyphenolic compounds have good inhibitory effects, but isobavachalcone and psoralidin are the most potent. SARS-CoV-2 is an example of a type I mechanism, because of the selective binding of psoralidin to the free enzyme instead of the enzyme-substrate [32].

Quercetin

Quercetin is the most abundant flavonoid found in foods and fruits. Quercetin is well-known for its antioxidant, antifungal, anticarcinogenic, and cytotoxic activity [75]. The ethyl acetate fraction of the 70% ethanol extract of *Elaeocarpus sylvestris* comprises quercetin, penta-O-galloyl-D-glucose, and isoquercitrin. The isolated phytocomponents were powerful antiviral agents against varicella-zoster and human cytomegalovirus. The phyocompounds quercetin and isoquercitrin were found to be effective in inhibiting the replication of the varicella-zoster virus and human cytomegalovirus in the early stages of their development [76]. Quercetin was obtained from an aqueous extract of *Embelia ribes*. The isolated phytocompounds have a dose-dependent inhibitory effect on the viral protease non-structural protein 3, causing a reduction in HCV replication [77]. SARS-CoV entry is hindered by quercetin, which exhibits structural similarities with luteolin. The EC_{50} for quercetin antiviral activity against HIV-Luc/SARS pseudotyped virus was 83.4 μM in an MTT experiment conducted in Vero E6 cells containing HIV-Luc/SARS pseudotyped virus. Quercetin has very low cytotoxicity, with a 50% cytotoxic concentration of 3.32 mM [63]. In another study, because of their similar antiviral and immunomodulatory activities and the capacity of ascorbate to recycle quercetin, co-administration of both quercetin and vitamin-C for the prevention and treatment of SARS-CoV-2 exhibits a more significant synergistic antiviral effect [78]. Quercetin has a more potent antiviral effect against three influenza-A virus strains namely A/Puerto Rico/8/34 (H1N1), A/FM-1/47/1 (H1N1), and A/Aichi/2/68 (H3N2), IC_{50} values are 7.756±1.097, 6.225±0.467, and 2.738±1.931 μg/mL, respectively. An important role played by the glycoprotein hemagglutinin during the early stages of influenza virus infection makes it a potential target for influenza therapy. Quercetin targets the HA2 subunit of hemagglutinin, which offers new insight into influenza fusion inhibitors [79].

Robustaflavone

Robustaflavone is a biflavanoid that naturally exists in the seed kernel extract of *Rhus succedanea*. Robustaflavone is composed of two apigenin units (5, 7, 4-trihydroxyflavone) bonded at the 6^{th} and 3^{rd} positions of a flavone unit. Robustaflavone effectively suppresses the hepatitis B virus in-vitro (EC_{50}-0.25μM and SI-153) by inhibiting the hepatitis B virus DNA polymerase [80]. Drug resistance is a serious problem in antiviral therapy. Robustaflavone is a new non-nucleoside natural entity with anti-HBV replication activity. In another investigation, robustaflavone showed a more synergistic impact when combined with two anti-HBV medicines, lamivudine (Ratio of robustaflavone and lamivudine is 10:1, EC_{50}-0.054 μM& SI-894) and penciclovir (Ratio of robustaflavone and penciclovir is 1:1, EC_{50}-0.11 μM& SI-684) [81]. Robustaflavone also suppresses HIV-1 reverse transcriptase activity [82].

Scutellarein

A flavonoid called scutellarein has been found in *Scutellariabaicalensis*Georgi. It is known chemically as 5, 6, 7, 4'-Tetrahydroxyflavone. The roots are an essential part of traditional Chinese medicine for treating heat-clearing, fire purification, detoxification, and hemostasis. Recently, *Scutellariabaicalensis* (黃芩HuángQín) has been officially included in the Chinese and European pharmacopoeias. Several biological activities of *Scutellariabaicalensis* extract are known and reported, including anti-inflammatory, anti-microbial, anti-tumor, and anti-viral effects. Surprisingly, *S. baicalensis* extracts displayed potent antiviral properties against different strains of viruses [83]. It has been revealed that the leaves of *Vitis vinifera* contain nearly forty distinct phenolic compounds. Scutellarein, a flavone, is one of them. Leaf extract is the most effective inhibitor of HSV-1 and SARS-CoV-2 replication. By blocking the proteins enriched on the surface of the virus by phenolic compounds in the extracts at very low concentrations (10 μg/mL) the extracts effectively inhibit the spread of the virus during the early stages of infection [84, 85]. The enzyme reverse transcriptase is essential for retrovirus replication within infected cells. Scutellarein and two other flavonoids, amentoflavone and quercetin, inhibited three reverse transcriptases, namely avian myeloblastosis RT, Rous-associated virus-2 RT, and Maloney murine leukaemia RT by dose-dependent mannar [86].

Silymarin

Silymarin is flavonolignans derived from *Silybum marianum* and is used to treat cirrhosis, hepatocellular carcinoma, and chronic liver inflammation. It also reduces oxidative damage to liver cells and prevents fibrosis. An *in-vitro* assessment of silymarin's antiviral activity against mosquito-borne chikungunya virus (CHIKV) was conducted with CHIKV replicon cell lines and a clinical isolate of this virus. In two days of treatment with Vero cells and BHK-21 cells, silymarin at 800 µg/ml caused no detectable toxicity, and 95% of cells survived. The antiviral properties of silymarin were demonstrated in studies of the CHIKV virus, where it inhibited both viral replication efficiency and the generation of replication-related viral proteins [87]. The Mayaro virus causes Mayaro fever. In addition to fever, arthralgia, vomiting, and diarrhea, mayaro fever can also result in headaches and a rash. Persistent arthritis and arthralgia are more common in individuals who are infected by infection. The antiviral action of silymarin is observed in HepG2 cells infected with the Mayaro virus. Silymarin was notable for its antiviral activity against the Mayaro virus and its reduction of the formation of reactive oxygen species (ROS) and oxidative stress markers, malondialdehyde (MDA), and carbonyl protein [88]. An *in-vitro* study found that silymarin suppressed dengue virus production in Vero cells. Virucidal effects of silymarin were found against DENV-3 with a half-maximal cytotoxic dose of 749.70 µg/mL and a selective index of 10.87. Silymarin decreased the virus's infectivity by 72.46% after it inhibited the virus's entry into the cells. According to an *in-silico* molecular docking study, silymarin could bind to viral envelope (E) proteins, indicating antiviral activity [89]. In another study, silymarin inhibited Enterovirus-A71 (EV-A71) more effectively than baicalein. Silymarin purportedly provides direct extracellular virucidal effects against EV-A71 with a SI of 10.53 at a 50% inhibitory dose of 15.2± 3.53 µg/mL. Additionally, it was proven that it inhibits infection in Vero cells by interfering with both viral attachment and entry into cells [90]. A dose of silymarin that inhibited Zika virus (ZIKV) infection significantly, with an EC_{50} of 34.17µg/mL, a selectivity index greater than 17, and potency fourfold that of the positive control ribavirin, was significantly more potent than ribavirin. In an *in-vitro* study, silimarin showed strong antiviral activity against ZIKV, exerting its activity at all phases of the viral replication cycle, but especially at earlier stages of viral replication. Simlymarin may act synergistically to reduce viral load at all stages due to its complex structure of phytocompounds [91].

Conclusion

Natural products have grown in popularity among consumers in recent years due to increased public knowledge of their benefits. Polyphenols are widely recognized as one of the most diverse classes of phytochemicals, containing a large variety of biologically active substances. Recent research indicates that their use may be associated with diseases like cancer, diabetes, and CVD. A phenolic compound consists of at least one aromatic ring with at least one or more hydroxyl substituents. The number and position of hydroxyl groups in its chemical structure significantly affect its ability to scavenge oxygen radicals and other reactive species. The wide range of biological functions of polyphenolic chemicals has made them useful in treating viral infections. Polyphenols are potent antioxidants. In addition, polyphenols were also shown to inhibit viral growth both *in-vitro* and *in-vivo*. Researchers are increasingly turning their attention to polyphenolic compounds due to their antiviral properties and ability to target various phases of viral infection. The main benefit of polyphenols is their non-toxicity to human cells. Most of the polyphenols have limited their bioavailability, which is addressed by developing novel drug delivery systems. Once their mechanisms of action and therapeutic effects are understood, polyphenols can be used as potential lead molecules for developing antiviral medications. This review provides information on the antiviral potential of natural phenolics and their mechanisms of action, which may assist researchers in investigating phenolic compounds and their role as potential antiviral agents.

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