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POLYPHENOLIC COMPOUNDS - A PROMISING LEADS FOR ANTIVIRAL THERAPY

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ABSTRACT

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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 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 plantderived 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 IC₅₀ 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 (EC₅₀-0.56µg/mL and IC₅₀-100µg/mL), with selectivity index values of 178, and moderate activity against influenza A virus, HSV-1 (EC₅₀-17.9µg/mL) and HSV-2, (EC₅₀-48.0µg/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 IC₅₀ 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 50μ g/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 EC₅₀ concentration for suppressing enterovirus-71 infection was 10.3 μ M, whereas its estimated CC₅₀ concentration was 79.0 μ M. Apigenin remarkably inhibits hepatitis C

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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 IC₅₀ 14.28 μ g/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 IC₅₀ 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 IC₅₀ 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 $2\mu g/ml$. 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 IC₅₀ of 15 μ g/ml and 38.4 \pm 2.4 μ M, 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 IC₅₀ of 13.86 μ M, whereas chrysin has an IC₅₀ of 24.12 μ M. 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 μ M but mild cytotoxicity at a concentration of 50 μ M. 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 μ M daidzein dose considerably reduced the feline calicivirus titer by 63.47±9.82%, while a 50 μ M 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

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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 (EC₅₀) 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 on the in-vitro evaluation, EGCG was found to have an EC50 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 μ g/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 IC₅₀ values ranging from 5.0 to 14.4 μ M. 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 (IC₅₀-65µM) against HIV-1

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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].





Figure 1. Polyphenolic compounds for antiviral therapy.

Kaempferol

Kaempferol is a yellow-coloredflavonol that occurs naturally in several fruits and vegetables. The kaempferol 3-Orobinobioside 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

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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 DENVinfected 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 (IC₅₀ - 2.3 μM), inhibits the 3amediated 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 μ M, 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 antiinflammatory 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 IC₅₀ 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 reduces inflammation 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 IC₅₀ value of 6.818μ M in chikungunya-infected hamster kidney cells [69]. Naringenin inhibits dengue virus replication in infected human-derived Huh7.5 hepatoma cells (In-vitro/250 μ M) 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

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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 phytocompounds inhibited papain-like protease dose-dependently, with an IC₅₀ 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 EC₅₀ 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), IC₅₀ values are 7.756±1.097, 6.225 ± 0.467 , and $2.738\pm1.931 \mu$ g/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 6th and 3rd positions of a flavone unit. Robustaflavone effectively suppresses the hepatitis B virus in-vitro (EC₅₀-0.25 μ M 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, EC₅₀-0.054 μ M& SI-894) and penciclovir (Ratio of robustaflavone and penciclovir is 1:1, EC₅₀-0.11 μ M& 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

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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 EC₅₀ 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 *invitro* and *in-vivo*. Researchers are increasingly turning their attention to 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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References

- Najafi ML. Evaluation of the effect of influential factors on the Aflatoxin levels of Medicinal Herbs in Different climate regions. J Adv Pharm Educ Res. 2020;10(3):30-3.
- 2. Niazi M, Yari F, Shakarami A. A Review of Medicinal Herbs in the Lamiaceae Family Used to Treat Arterial Hypertension. Entomol Appl Sci Lett. 2019;6(1):22-7.
- 3. Carocho M, Ferreira I. The role of phenolic compounds in the fight against cancer—A review. Anticancer Agents Med Chem. 2013;13(8):1236-58.
- Harborne JB. General procedures and measurement of total phenolics in Harborne JB (ed). Methods in plant biochemistry vol I Plant phenolics Academic London; 1989. 1-28 p.
- 5. Vuong QV. Utilization of bioactive compounds from agricultural and food production waste. CRC Press; 2017.

Pharmacophore, 13(1) 2021, Pages 36-47

- 6. Montenegro-Landívar MF, Tapia-Quirós P, Vecino X, Reig M, Valderrama C, Granados M, et al. Polyphenols and their potential role to fight viral diseases: An overview. Sci Total Environ. 2021;801:149719.
- 7. Tuladhar P, Sasidharan S, Saudagar P. Role of phenols and polyphenols in plant defense response to biotic and abiotic stresses. In Biocontrol Agents and Secondary Metabolites Woodhead Publishing; 2021. pp.419-41.
- 8. Sharma A, Shahzad B, Rehman A, Bhardwaj R, Landi M, Zheng B. Response of phenylpropanoid pathway and the role of polyphenols in plants under abiotic stress. Molecules. 2019;24(13):2452.
- 9. Lattanzio V. Phenolic Compounds: Introduction 50. Nat Prod. 2013:1543-80.
- 10. Sundararajan A, Ganapathy R, Huan L, Dunlap JR, Webby RJ, Kotwal GJ, et al. Influenza virus variation in susceptibility to inactivation by pomegranate polyphenols is determined by envelope glycoproteins. Antiviral Res. 2010;88(1):1-9.
- 11. Semwal RB, Semwal DK, Combrinck S, Trill J, Gibbons S, Viljoen A. Acacetin—A simple flavone exhibiting diverse pharmacological activities. Phytochem Lett. 2019;32:56-65.
- 12. Simões LR, Maciel GM, Brandão GC, Kroon EG, Castilho RO, Oliveira AB. Antiviral activity of Distictella elongata(Vahl) Urb.(Bignoniaceae), a potentially useful source of anti-dengue drugs from the state of Minas Gerais, Brazil. Lett Appl Microbiol. 2011;53(6):602-7.
- 13. Hayashi K, Hayashi T, Arisawa M, Morita N. Antiviral agents of plant origin. Antiherpetic activity of acacetin. Antiviral Chem Chemother. 1993;4(1):49-53.
- 14. Wu Q, Yu C, Yan Y, Chen J, Zhang C, Wen X. Antiviral flavonoids from Moslascabra. Fitoterapia. 2010;81(5):429-33.
- 15. Yu S, Yan H, Zhang L, Shan M, Chen P, Ding A, et al. A review on the phytochemistry, pharmacology, and pharmacokinetics of amentoflavone, a naturally-occurring biflavonoid. Molecules. 2017;22(2):299.
- 16. Li F, Song X, Su G, Wang Y, Wang Z, Jia J, et al, Amentoflavone inhibits HSV-1 and ACV-resistant strain infection by suppressing viral early infection. Viruses. 2019;11(5):466.
- 17. Lin YM, Flavin MT, Schure R, Chen FC, Sidwell R, Barnard DI, et al. Antiviral activities of biflavonoids. Planta Med. 1999;65(02):120-5.
- Yin D, Li J, Lei X, Liu Y, Yang Z, Chen K. Antiviral activity of total flavonoid extracts from Selaginella moellendorffii Hieron against coxsackievirus B3 in-vitro and in-vivo. J Evidence-Based Complementary Altern Med. 2014;2014.
- 19. Wilsky S, Sobotta K, Wiesener N, Pilas J, Althof N, Munder T, et al. Inhibition of fatty acid synthase by amentoflavone reduces coxsackievirus B3 replication. Arch Virol. 2012;157(2):259-69.
- Ryu YB, Jeong HJ, Kim JH, Kim YM, Park JY, Kim D, et al. Biflavonoids from Torreya nucifera displaying SARS-CoV 3CLpro inhibition. Bioorg Med Chem. 2010;18(22):7940-7.
- 21. Salehi B, Venditti A, Sharifi-Rad M, Kręgiel D, Sharifi-Rad J, DurazzoA, et al. The therapeutic potential of apigenin. Int J Mol Sci. 2019;20(6):1305.
- 22. Murali KS, Sivasubramanian S, Vincent S, Murugan SB, Giridaran B, Dinesh S, et al. Anti—chikungunya activity of luteolin and apigenin rich fraction from Cynodon dactylon. Asian Pac J Trop Med. 2015;8(5):352-8.
- 23. Khandelwal N, Chander Y, Kumar R, Riyesh T, Dedar RK, Kumar M, et al. Antiviral activity of Apigenin against buffalopox: Novel mechanistic insights and drug-resistance considerations. Antiviral Res. 2020;181:104870.
- 24. Hakobyan A, Arabyan E, Avetisyan A, Abroyan L, Hakobyan L, Zakaryan H. Apigenin inhibits African swine fever virus infection in-vitro. Arch Virol. 2016;161(12):3445-53.
- 25. Zhang W, Qiao H, Lv Y, Wang J, Chen X, Hou Y, et al. Apigenin inhibits enterovirus-71 infection by disrupting viral RNA association with trans-acting factors. PloS One. 2014;9(10):e110429.
- 26. Shibata C, Ohno M, Otsuka M, Kishikawa T, Goto K, Muroyama R, et al. The flavonoid apigenin inhibits hepatitis C virus replication by decreasing mature microRNA122 levels. Virology. 2014;462:42-8.
- 27. Johari J, Kianmehr A, Mustafa MR, Abubakar S, Zandi K. Antiviral activity of baicalein and quercetin against the Japanese encephalitis virus. Int J Mol Sci. 2012;13(12):16785-95.
- 28. Lani R, Hassandarvish P, Shu MH, Phoon WH, Chu JJ, Higgs S, et al. Antiviral activity of selected flavonoids against Chikungunya virus. Antiviral Res. 2016;133:50-61.
- 29. Ono K, Nakane H, Fukushima M, Chermann JC, Barré-Sinoussi F. Inhibition of reverse transcriptase activity by a flavonoid compound, 5, 6, 7-trihydroxyflavone. Biochem Biophys Res Commun. 1989;160(3):982-7.
- 30. Evers DL, Chao CF, Wang X, Zhang Z, Huong SM, Huang ES. Human cytomegalovirus-inhibitory flavonoids: studies on antiviral activity and mechanism of action. Antiviral Res. 2005;68(3):124-34.
- 31. Xu G, Dou J, Zhang L, Guo Q, Zhou C. Inhibitory effects of baicalein on the influenza virus in vivo is determined by baicalin in the serum. Biol Pharm Bull. 2010;33(2):238-43.
- 32. Kim DW, Seo KH, Curtis-Long MJ, Oh KY, Oh JW, Cho JK, et al. Phenolic phytochemical displaying SARS-CoV papain-like protease inhibition from the seeds of Psoralea corylifolia. J Enzyme Inhib Med Chem. 2014;29(1):59-63.
- Cirone M, Zompetta C, Tarasi D, Frati L, Faggioni A. Infection of human T lymphoid cells by human herpesvirus 6 is blocked by two unrelated protein tyrosine kinase inhibitors, biochanin A and herbimycin. AIDS Res Hum Retroviruses. 1996;12(17):1629-34.
- 34. Sithisarn P, Michaelis M, Schubert-Zsilavecz M, Cinatl Jr J. Differential antiviral and anti-inflammatory mechanisms of the flavonoids biochanin A and baicalein in H5N1 influenza A virus-infected cells. Antiviral Res. 2013;97(1):41-8.
- 35. Michaelis M, Sithisarn P, Cinatl Jr J. Effects of flavonoid-induced oxidative stress on anti-H5N1 influenza a virus activity exerted by baicalein and biochanin A. BMC Res Notes. 2014;7(1):1-6.

Pharmacophore, 13(1) 2021, Pages 36-47

- 36. Wang J, Zhang T, Du J, Cui S, Yang F, Jin Q. Anti-enterovirus 71 effects of chrysin and its phosphate ester. PLoS One. 2014;9(3):e89668.
- 37. Song JH, Kwon BE, Jang H, Kang H, Cho S, Park K, et al. Antiviral activity of chrysin derivatives against coxsackievirus B3 in vitro and in-vivo. Biomol Ther. 2015;23(5):465.
- Seo DJ, Jeon SB, Oh H, Lee BH, Lee SY, Oh SH, et al. Comparison of the antiviral activity of flavonoids against murine norovirus and feline calicivirus. Food Control. 2016;60:25-30.
- 39. Liu AL, Wang HD, Lee SM, Wang YT, Du GH. Structure activity relationship of flavonoids as influenza virus neuraminidase inhibitors and their in vitro anti-viral activities. Bioorg Med Chem. 2008;16(15):7141-7.
- 40. Horio Y, Sogabe R, Shichiri M, Ishida N, Morimoto R, Ohshima A, et al. Induction of a 5-lipoxygenase product by daidzein is involved in the regulation of influenza virus replication. J Clin Biochem Nutr. 2020;66(1):36-42.
- 41. Song JM, Lee KH, Seong BL. Antiviral effect of catechins in green tea on influenza virus. Antiviral Res. 2005;68(2):66-74.
- 42. Ho HY, Cheng ML, Weng SF, Leu YL, Chiu DT. Antiviral effect of epigallocatechin gallate on enterovirus 71. J Agric Food Chem. 2009;57(14):6140-7.
- 43. Li J, Song D, Wang S, Dai Y, Zhou J, Gu J. Antiviral effect of epigallocatechin gallate via impairing porcine circovirus type 2 attachment to host cell receptor. Viruses. 2020;12(2):176.
- 44. Vázquez-Calvo Á, Jiménez de Oya N, Martín-Acebes MA, Garcia-Moruno E, Saiz JC. Antiviral properties of the natural polyphenols delphinidin and epigallocatechin gallate against the flaviviruses West Nile virus, Zika virus, and dengue virus. Front Microbiol. 2017;8:1314.
- 45. Weber C, Sliva K, von Rhein C, Kümmerer BM, Schnierle BS. The green tea catechin, epigallocatechin gallate inhibits chikungunya virus infection. Antiviral Res. 2015;113:1-3.
- 46. Nance CL, Siwak EB, Shearer WT. Preclinical development of the green tea catechin, epigallocatechin gallate, as an HIV-1 therapy. J Allergy Clin Immunol. 2009;123(2):459-65.
- 47. Li S, Hattori T, Kodama EN. Epigallocatechin gallate inhibits the HIV reverse transcription step. Antiviral Chem. Chemother. 2011;21(6):239-43.
- 48. Meyer JJ, Afolayan AJ, Taylor MB, Erasmus D. Antiviral activity of galangin isolated from the aerial parts of Helichrysum aureonitens. J Ethnopharmacol. 1997;56(2):165-9.
- 49. Lyu SY, Rhim JY, Park WB. Antiherpetic activities of flavonoids against herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2) in vitro. Arch Pharmacal Res. 2005;28(11):1293-301.
- 50. Barron D, Ibrahim RK. Isoprenylated flavonoids-a survey. Phytochemistry. 1996;43(5):921-82.
- 51. Cheng CL, Jia XH, Xiao CM, Tang WZ. Paulownia C-geranylated flavonoids: their structural variety, biological activity, and application prospects. Phytochem Rev. 2019;18(3):549-70.
- 52. Cho JK, Curtis-Long MJ, Lee KH, Kim DW, Ryu HW, Yuk HJ, et al. Geranylated flavonoids displaying SARS-CoV papain-like protease inhibition from the fruits of Paulownia tomentosa. Bioorg Med Chem. 2013;21(11):3051-7.
- Paredes A, Alzuru M, Mendez J, Rodríguez-Ortega M. Anti-Sindbis activity of flavanones hesperetin and naringenin. Biol Pharm Bull. 2003;26(1):108-9.
- 54. Dong W, Wei X, Zhang F, Hao J, Huang F, Zhang C, et al. A dual character of flavonoids in influenza A virus replication and spread through modulating cell-autonomous immunity by MAPK signaling pathways. Sci Rep. 2014;4(1):1-2.
- 55. Ahmadi A, Hassandarvish P, Lani R, Yadollahi P, Jokar A, Bakar SA, et al. Inhibition of chikungunya virus replication by hesperetin and naringenin. RSC Adv. 2016;6(73):69421-30.
- 56. Lin YM, Anderson H, Flavin MT, Pai YH, Mata-Greenwood E, Pengsuparp T, et al. In vitro anti-HIV activity of biflavonoids isolated from Rhus succedanea and Garcinia multiflora. J Nat Prod. 1997;60(9):884-8.
- 57. Yarmolinsky L, Huleihel M, Zaccai M, Ben-Shabat S. Potent antiviral flavone glycosides from Ficus benjamina leaves. Fitoterapia. 2012;83(2):362-7.
- 58. Mitrocotsa D, Mitaku S, Axarlis S, Harvala C, Malamas M. Evaluation of the antiviral activity of kaempferol and its glycosides against human cytomegalovirus. Planta Med. 2000;66(04):377-9.
- 59. Care C, Sornjai W, Jaratsittisin J, Hitakarun A, Wikan N, Triwitayakorn K, et al. Discordant activity of kaempferol towards dengue virus and Japanese Encephalitis virus. Molecules. 2020;25(5):1246.
- 60. Schwarz S, Sauter D, Wang K, Zhang R, Sun B, Karioti A, et al. Kaempferol derivatives as antiviral drugs against the 3a channel protein of coronavirus. Planta Med. 2014;80(02/03):177-82.
- 61. Jeong HJ, Ryu YB, Park SJ, Kim JH, Kwon HJ, Kim JH, et al. Neuraminidase inhibitory activities of flavonols isolated from Rhodiola rosea roots and their in vitro anti-influenza viral activities. Bioorg Med Chem. 2009;17(19):6816-23.
- 62. Manzoor MF, Ahmad N, Ahmed Z, Siddique R, Zeng XA, Rahaman A, et al. Novel extraction techniques and pharmaceutical activities of luteolin and its derivatives. J Food Biochem. 2019;43(9):e12974.
- 63. Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol. 2004;78(20):11334-9.
- 64. Mehla R, Bivalkar-Mehla S, Chauhan A. A flavonoid, luteolin, cripples HIV-1 by abrogation of tat function. PLos One. 2011;6(11):e27915.
- 65. Murali KS, Sivasubramanian S, Vincent S, Murugan SB, Giridaran B, Dinesh S, et al. Anti—chikungunya activity of luteolin and apigenin rich fraction from Cynodon dactylon. Asian Pac J Trop Med. 2015;8(5):352-8.

Pharmacophore, 13(1) 2021, Pages 36-47

- Fan W, Qian S, Qian P, Li X. Antiviral activity of luteolin against Japanese encephalitis virus. Virus Res. 2016;220:112-6.
- 67. Yan H, Ma L, Wang H, Wu S, Huang H, Gu Z, et al. Luteolin decreases the yield of influenza A virus in vitro by interfering with the coat protein I complex expression. J Nat Med. 2019;73(3):487-96.
- 68. Hong EH, Song JH, Kim SR, Cho J, Jeong B, Yang H, et al. Morin Hydrate Inhibits Influenza Virus entry into Host Cells and Has Anti-inflammatory Effect in Influenza-infected Mice. Immune Netw. 2020;20(4):e32
- 69. Ahmadi A, Hassandarvish P, Lani R, Yadollahi P, Jokar A, Bakar SA, et al. Inhibition of chikungunya virus replication by hesperetin and naringenin. RSC Adv. 2016;6(73):69421-30.
- 70. Frabasile S, Koishi AC, Kuczera D, Silveira GF, Verri WA, Dos Santos CN, et al. The citrus flavanone naringenin impairs dengue virus replication in human cells. Sci Rep. 2017;7(1):1-1.
- 71. Lu L, Guo Q, Zhao L. Overview of oroxylin A: a promising flavonoid compound. Phytother Res. 2016;30(11):1765-74.
- 72. Kwon BE, Song JH, Song HH, Kang JW, Hwang SN, Rhee KJ, et al. Antiviral activity of oroxylin A against coxsackievirus B3 alleviates virus-induced acute pancreatic damage in mice. PLoS One. 2016;11(5):e0155784. doi:10.1371/journal.pone.0155784
- 73. Choi HJ, Song HH, Lee JS, Ko HJ, Song JH. Inhibitory effects of norwogonin, oroxylin A, and mosloflavone on enterovirus 71. Biomol Ther. 2016;24(5):552.
- 74. Sah P, Agarwal D, Garg SP. Isolation and identification of furocoumarins from the seeds of Psoralea corylifolia Linn. Indian J Pharm Sci. 2006;68(6):768.
- 75. Batiha GE, Beshbishy AM, Ikram M, Mulla ZS, El-Hack ME, Taha AE, et al. The pharmacological activity, biochemical properties, and pharmacokinetics of the major natural polyphenolic flavonoid: quercetin. Foods. 2020;9(3):374.
- 76. Kim CH, Kim JE, Song YJ. Antiviral activities of quercetin and isoquercitrin against human herpesviruses. Molecules. 2020;25(10):2379.
- 77. Bachmetov L, Gal-Tanamy M, Shapira A, Vorobeychik M, Giterman-Galam T, Sathiyamoorthy P, et al. Suppression of hepatitis C virus by the flavonoid quercetin is mediated by inhibition of NS3 protease activity. J Viral Hepatitis. 2012;19(2):e81-8. doi:10.1111/j.1365-2893.2011.01507.x
- 78. Colunga Biancatelli RM, Berrill M, Catravas JD, Marik PE. Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Front Immunol. 2020;11:1451.
- 79. Wu W, Li R, Li X, He J, Jiang S, Liu S, et al. Quercetin as an antiviral agent inhibits influenza-A virus (IAV) entry. Viruses. 2016;8(1):6.
- Lin YM, Zembower DE, Flavin MT, Schure RM, Anderson HM, Korba BE, et al. Robustaflavone, a naturally occurring biflavanoid, is a potent non-nucleoside inhibitor of hepatitis B virus replication in vitro. Bioorg Med Chem Lett. 1997;7(17):2325-8.
- 81. Zembower DE, Lin YM, Flavin MT, Chen FC, Korba BE. Robustaflavone, a potential non-nucleoside anti-hepatitis B agent. Antiviral Res. 1998;39(2):81-8.
- Lin YM, Anderson H, Flavin MT, Pai YH, Mata-Greenwood E, Pengsuparp T, et al. In vitro anti-HIV activity of biflavonoids isolated from Rhus succedanea and Garcinia multiflora. J Nat Prod. 1997;60(9):884-8.
- Liu H, Ye F, Sun Q, Liang H, Li C, Li S, et al. Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in-vitro. J Enzyme Inhib Med Chem. 2021;36(1):497-503.
- 84. Zannella C, Giugliano R, Chianese A, Buonocore C, Vitale GA, Sanna G, et al. Antiviral Activity of Vitis vinifera Leaf Extract against SARS-CoV-2 and HSV-1. Viruses. 2021;13(7):1263.
- 85. Yu MS, Lee J, Lee JM, Kim Y, Chin YW, Jee JG, et al. Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13. Bioorg Med Chem Lett. 2012;22(12):4049-54.
- Spedding G, Ratty A, Middleton Jr E. Inhibition of reverse transcriptases by flavonoids. Antiviral Res. 1989;12(2):99-110.
- 87. Lani R, Hassandarvish P, Chiam CW, Moghaddam E, Chu JJ, Rausalu K, et al. Antiviral activity of silymarin against chikungunya virus. Sci Rep. 2015;5(1):1-0.
- Camini FC, da Silva TF, da Silva Caetano CC, Almeida LT, Ferraz AC, Vitoreti VM, et al. Antiviral activity of silymarin against Mayaro virus and protective effect in virus-induced oxidative stress. Antiviral Res. 2018;158:8-12.
- Low ZX, OuYong BM, Hassandarvish P, Poh CL, Ramanathan B. Antiviral activity of silymarin and baicalein against dengue virus. Sci Rep. 2021;11(1):1-3.
- 90. Lalani SS, Anasir MI, Poh CL. Antiviral activity of silymarin in comparison with baicalein against EV-A71. BMC Complementary Med Ther. 2020;20(1):1-2.
- 91. da Silva TF, Ferraz AC, Almeida LT, da Silva Caetano CC, Camini FC, Lima RL, et al. Antiviral effect of silymarin against Zika virus in-vitro. Acta Trop. 2020;211:105613.