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Flavonoids: promising natural compounds against viral infections

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Abstract

Flavonoids are widely distributed as secondary metabolites produced by plants and play important roles in plant physiology, having a variety of potential biological benefits such as antioxidant, anti-inflammatory, anticancer, antibacterial, antifungal and antiviral activity. Different flavonoids have been investigated for their potential antiviral activities and several of them exhibited significant antiviral properties in *in vitro* and even *in vivo* studies. This review summarizes the evidence for antiviral activity of different flavonoids, highlighting, where investigated, the cellular and molecular mechanisms of action on viruses. We also present future perspectives on therapeutic applications of flavonoids against viral infections.

Introduction

Throughout human history, thousands of biologically active plants have been identified and used in medicine. Virtually all cultures around the world continue to rely on medicinal plants for primary health care. According to the World Health Organization report, about 80% of the world's population depend on medicinal plants to satisfy their health requirements [30]. Furthermore, there are currently hundreds of modern drugs based on active compounds isolated from plants. Plants have the ability to produce a wide range of compounds including flavonoids, phytoalexins, lignans, and tannins, which are responsible for key functions in plant growth and development. Flavonoids or polyphenolics comprise the largest group of secondary metabolites found in vegetables, fruits, seeds, nuts, spices, stems as well as in red wine and tea (Table 1) [88]. These compounds are synthesized in response to various abiotic stress conditions such as ultraviolet radiation and play an important role as defense agents against plant pathogens and insects [9, 84]. The first evidence of a biological activity of flavonoids was reported by Albert Szent-Gyorgyii in 1938, who showed that citrus peel flavonoids prevent capillary bleeding and fragility associated with scurvy [109]. Since then, a broad spectrum of biological activities such as anti-inflammatory, antioxidant, antibacterial, antiviral, anticancer, and neuroprotective has been described

for flavonoids [40, 53, 65, 95, 137]. Research for antiviral agents isolated from plants started in 1950s, when the activity of 288 plants against influenza A virus was evaluated in embryonated eggs [14]. During the last 60 years, several plants and plant-derived compounds with antiviral properties were identified. In this article, we review the results of both *in vitro* and *in vivo* experiments demonstrating the antiviral activity of flavonoids, especially focusing on those classes of flavonoids that have been extensively investigated.

Table 1

Classification and sources of different flavonoids

Class	Flavonoid	Source(s)
Flavone	Apigenin	*Chamomile tea* (*Matricaria chamomilla*), leaves of parsley (*Petroselinum crispum*), celery (*Apium graveolens*) and spinach (*Spinacia oleracea*)
	Baicalein	Roots of baical skullcap (*Scutellaria baicalensis*) and blue skullcap (*Scutellaria lateriflora*)
	Luteolin	Leaves of basil (*Ocimum basilicum*), parsley (*Petroselinum crispum*) and spinach (*Spinacia oleracea*), seeds of pepper (*Capsicum annuum*)
Flavonol	Quercetin	Red (grape) wines, leaves of radish (*Raphanus raphanistrum* subsp. *sativus*) and fennel (*Foeniculum vulgare*), seeds of pepper (*Capsicum annuum*)
	Kaempferol	Raspberry (*Rubus idaeus*), capers (*Capparis spinosa*), Brussels sprout (*Brassica oleracea*), black bean (*Phaseolus vulgaris*) and fruit of grapes
	Rutin	Seeds of Tartary buckwheat (*Fagopyrum tataricum*), leaves and petioles of rhubarb (*Rheum rhabarbarum*), fruits of orange (*Citrus aurantium*) and lemon (*Citrus limon*)
	Fisetin	Leaves of acacias (*Acacia greggii* and *Acacia berlandieri*), fruits of strawberry (*Fragaria ananassa*) and grapes
Flavan	Catechin	Cocoa bean (*Theobroma cacao*), argan oil (*Argania spinosa*), leaves of tea plant (*Camellia sinensis*)
	Epigallocatechin gallate	Leaves of tea plant (*Camellia sinensis*), skin of apple (*Malus pumila*) and plums
Isoflavone	Genistein, glycitein, daidzein, puerarin, ononin	Seeds of fava beans (*Vicia faba*) and soybeans (*Glycine max*)
Anthocyanidin	Cyanidin, peonidin, apigenidin	Seeds and skin of cherry (*Prunus avium*), blackberry (*Rubus* genus), bilberry (*Vaccinium* genus).

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Chemistry of flavonoids

There are now more than 6000 varieties of flavonoids that have been structurally identified [35]. All these compounds comprise a flavan nucleus and a fifteen-carbon skeleton consisting of two benzene

rings (A- and B-rings, as shown in Fig. 1) connected via a heterocyclic pyrene ring (C-ring, as shown in Fig. 1). Flavonoids are divided into several classes such as anthocyanidins, flavones, flavonols, flavanones, flavan, isoflavanoids, biflavanoids, etc (Table 1) [24]. The various classes of flavonoids differ in the level of oxidation and pattern of substitution of the pyrene ring, whereas individual compounds within the classes differ in the pattern of substitution of benzene rings. While in flavonoids the B-ring links to the C-ring at the C2 position, the B-ring of isoflavonoids is substituted at position C3 (Fig. 1). Biflavonoids comprise of two identical or non-identical flavonoid units conjoined through an alkyl- or alkoxy-based linker (Fig. 1).

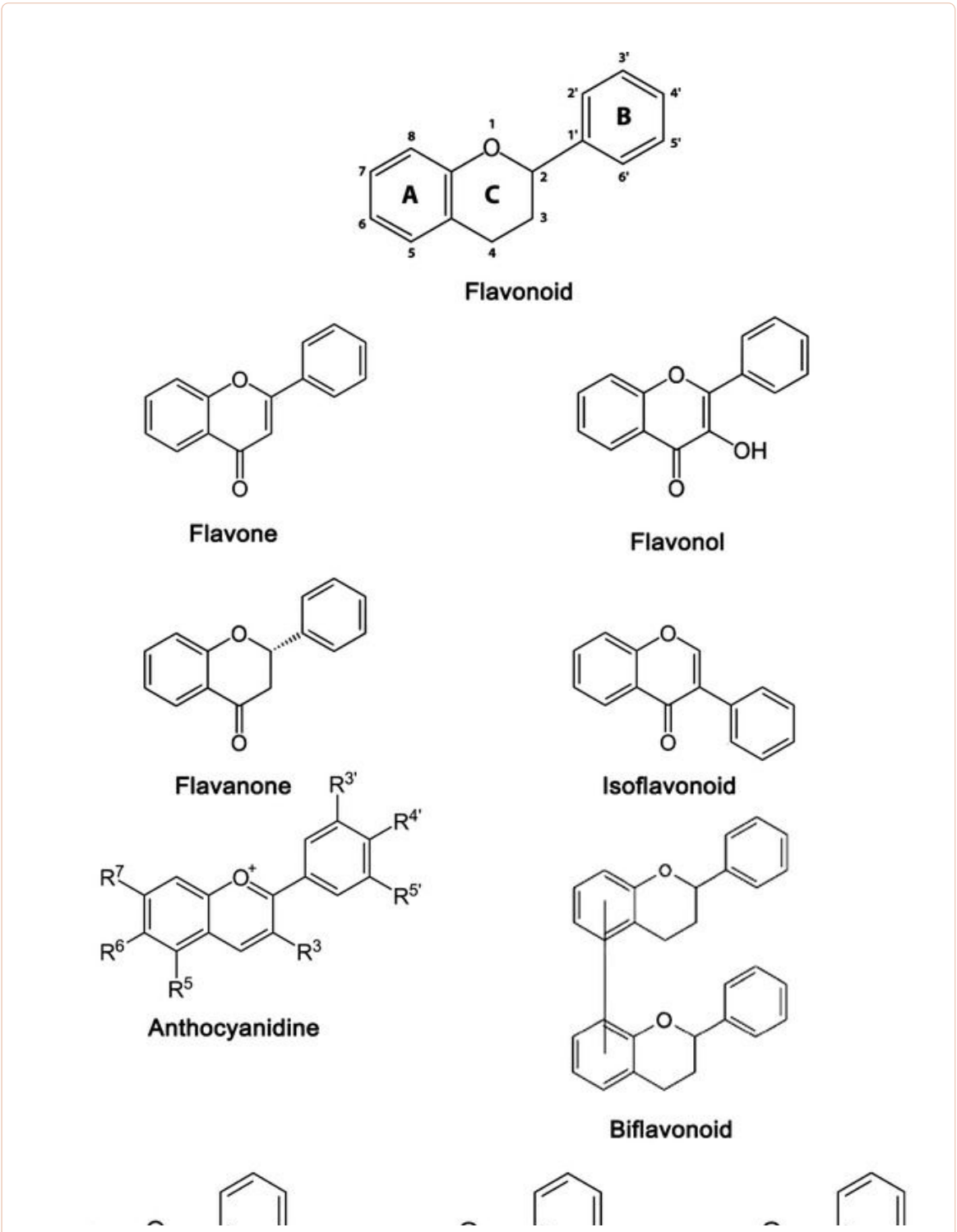

Fig. 1

Basic structure of various flavonoids

In plants, flavonoids generally occur as aglycones, glycosides and methylated derivatives. They are biosynthesized through the phenylpropanoid pathway, transforming phenylalanine into 4-coumaroyl-CoA, which then enters the flavonoid biosynthesis pathway [32]. Depending on the plant species, a group of enzymes, such as hydroxylases and reductases, modify the basic flavonoid skeleton, resulting in the different flavonoid classes. Finally, transferases modify the flavonoid skeleton with sugar, methyl groups and acyl moieties. These modifications alter the solubility and reactivity of flavonoids [6]. A large body of evidence supports the role of light in the regulation of flavonoid biosynthesis [156].

Antiviral activity of flavones

Flavones constitute a major class in the flavonoid family based on a 2-phenyl-1-benzopyran-4-one backbone. Natural flavones include apigenin, baicalein, chrysin, luteolin, scutellarein, tangeritin, wogonin and 6-hydroxyflavone. The antiviral activity of flavones is known from the 1990s, when it was showed that the simultaneous application of apigenin with acyclovir resulted in an enhanced antiviral effect on herpes simplex virus types 1 and 2 (HSV-1 and HSV-2) in cell culture [92]. Apigenin is most commonly isolated in abundance from the family *Asteraceae*. The organic and aqueous extracts from Asteraceae plants with apigenin as a major compound were found to be active against HSV-1, poliovirus type 2 and hepatitis C virus (HCV) [85, 127]. Apigenin isolated from sweet basil (*Ocimum basilicum*) showed a potent antiviral activity against adenoviruses (ADV) and hepatitis B virus *in vitro* [17]. Besides these DNA viruses, apigenin was found to exert antiviral effect against African swine fever virus (ASFV), by suppressing the viral protein synthesis and reducing the ASFV yield by 3 log [46]. Apigenin is also active against RNA viruses. For picronaviruses, it has been shown that apigenin is able to inhibit viral protein synthesis through suppressing viral IRES activity [82, 107]. Furthermore, apigenin affects enterovirus-71 (EV71) translation by disrupting viral RNA association with trans-acting factors regulating EV71 translation [153]. Shibata et al. [115] showed that apigenin has antiviral effect on HCV through the reduction of mature microRNA122, a liver-specific microRNA which positively regulates HCV replication.

Among flavones, baicalein and luteolin have been also extensively investigated with respect to their antiviral activity. Baicalein significantly reduced the levels of human cytomegalovirus (HCMV) early and late proteins, as well as viral DNA synthesis, although it had no effect on viral polymerase activity [23, 31]. Baicalein impaired avian influenza H5N1 virus replication in both human lung epithelial cells and monocyte-derived macrophages by interfering with neuraminidase activity [116]. Other studies showed that oral administration of baicalein to BALB/c mice infected with influenza H1N1 virus decreased the lung virus titer and increased the mean time to death [139]. Similar effects were recorded on mice infected with Sendai virus [28]. These inhibitory effects *in vivo* were mediated by serum baicalin, a metabolite of baicalein which has a glucose residue [26]. Baicalin alone exerts its anti-influenza activity by modulating the function of NS1 protein, which down-regulates IFN induction [99]. Further studies indicated that baicalin can directly induce IFN-γ production in human $CD4^+$ T cells and $CD8^+$ T cells and act as a potent inducer of IFN-γ during influenza virus infection [19]. Recently, novel baicalein analogs with B-rings substituted with bromine atoms demonstrated extremely potent activity against influenza H1N1 Tamiflu-resistant virus, indicating that baicalein and its analogs can be favorable alternatives in the management of Tamiflu-resistant viruses [21]. *In vitro* replication of HIV-1 was suppressed by baicalin when infected cells were treated during the early stage of the virus replication cycle [66]. HIV-1 envelope protein was found to be the target site of baicalin's antiviral action via the interference of interactions between the virus structural protein and specific host immune cells [75]. Baicalein and baicalin were also investigated against dengue virus (DENV). They exerted a significant virucidal effect on extracellular viral particles and interfered with different steps of DENV-2 replication [91, 148, 150]. *In silico* studies revealed that baicalein has strong binding affinity with DENV NS3/NS2B protein (-7.5 kcal/mol), and baicalin may interact closely with the virus NS5 protein at a binding affinity of -8.6 kcal/mol [47]. For baicalin, computational studies also showed a high binding affinity (-9.8 kcal/mol) against chikungunya virus (CHIKV) nsP3 protein, suggesting that baicalin can potentially interfere with CHIKV infection [114].

It was found that luteolin has antiviral effect on HIV-1 reactivation by blocking both clade B- and

C-Tat-driven LTR transactivation [87]. Luteolin also showed significant inhibition of Epstein-Barr virus (EBV) reactivation in cells [133]; it suppressed the activities of the immediate-early genes Zta and Rta by deregulating transcription factor Sp1 binding. Xu et al. [142] tested 400 highly purified natural compounds for inhibition of EV71 and coxsackievirus A16 infections and found that luteolin exhibited the most potent inhibition through disruption of viral RNA replication. Besides these antiviral activities, luteolin or luteolin-rich fractions showed antiviral effects against severe acute respiratory syndrome coronavirus (SARS-CoV), rhesus rotavirus, CHIKV and Japanese encephalitis virus (JEV) [33, 67, 94, 146].

Antiviral activity of flavonols

Flavonols are characterized by a 3-hydroxy-2-phenylchromen-4-one backbone. Among flavonols the antiviral effect of quercetin was the most extensively investigated. Early *in vivo* studies showed that oral treatment with quercetin protected mice from lethal Mengo virus [44, 125]. Furthermore, an enhanced protection was observed when quercetin was administered in combination with murine type I interferon (IFN) [125]. Quercetin also demonstrated a dose-dependent antiviral activity against poliovirus type 1, HSV-1, HSV-2, and respiratory syncytial virus (RSV) in cell cultures [60, 83]. *Epimedium koreanum* Nakai, which contains quercetin as the major active component, has been shown to induce secretion of type I IFN, reducing the replication of HSV, Newcastle disease virus (NDV), vesicular stomatitis virus (VSV) *in vitro*, as well as influenza A subtypes (H1N1, H5N2, H7N3 and H9N2) in *vivo* [18]. Hung et al. [51] have suggested possible mechanisms whereby quercetin may exert its anti-HSV activity. They revealed that quercetin inhibits the infection of HSV-1, HSV-2 and acyclovir-resistant HSV-1 mainly by blocking viral binding and penetration to the host cell. They also reported that quercetin suppresses NF-κB activation, which is essential for HSV gene expression. Recent investigations also pointed out the antiviral activity of quercetin against a wide spectrum of influenza virus strains. It interacts with influenza hemagglutinin protein, thereby inhibiting viral-cell fusion [136]. In addition, *in silico* analysis revealed that quercetin may be a potential inhibitor of the neuraminidase of influenza A H1N1 and H7N9 viruses [79, 80]. Molecular docking analysis also found that quercetin may interact with HCV NS3 helicase, NS5B polymerase and p7 proteins [34, 86]. These results correlate with experimental studies showing the anti-HCV activity of quercetin through inhibition of NS3 helicase and heat shock proteins [4, 81]. Besides these viruses, the inhibitory activity of quercetin and its derivatives have been reported for other viruses, including ADVs, arthropod-borne Mayaro virus, porcine reproductive and respiratory syndrome virus, canine distemper virus, JEV, DENV-2, porcine epidemic diarrhea virus, and equid herpesvirus 1 [11, 16, 27, 38, 41, 59, 118, 149]. Quercetin also possesses anti-rhinoviral effects by inhibiting endocytosis, transcription of the viral genome and viral protein synthesis [37]. In mice infected with rhinovirus, quercetin treatment decreased viral replication and attenuated virus-induced airway cholinergic hyper-responsiveness [37].

Kaempferol is another flavonol extracted from different medicinal herbs. Kaempferol and its derivatives bearing acyl substituents have shown inhibitory activity against HCMV [89]. Kaempferol derivatives isolated from *Ficus benjamina* leaves were more effective against HSV-1 and HSV-2 than their aglycon form [145]. Kaempferol derivatives with rhamnose residue turned out to be potent inhibitors of the 3a channel of coronavirus, which is involved in the mechanism of virus release [112]. One of the kaempferol derivative, kaempferol 3-O-α-L-rhamnopyranoside, obtained from *Zanthoxylum piperitum* was shown to significantly inhibit the replication of influenza A virus *in vitro* [45]. Behbahani et al. found that kaempferol and kaempferol-7-*O*-glucoside have strong HIV-1 reverse transcriptase inhibitory activity [5]. These compounds exerted their effects, at a concentration of 100 μg/ml, on the early stage of HIV replication in target cells. Recently, kaempferol-3,7-bisrhamnoside isolated from Chinese medicinal *Taxillus sutchuenensis* was shown to have potent *in vitro* activity on HCV NS3 protease function [144]. Antiviral activity of kaempferol on the influenza viruses H1N1 and H9N2 were mentioned in a study conducted by a group of researchers in South Korea. Mechanistic and structural studies suggested that the compound acts on the virus neuraminidase protein and specific functional groups are responsible for kaempferol's efficacy [57]. A study comparing the antiviral activities of kaempferol and an isoflavone, daidzein, showed that kaempferol exerted more potent inhibitory

activities on JEV replication and protein expression, than daidzein. JEV's frameshift site RNA (fsRNA) has been proposed as the target site for kaempferol's inhibitory activity against this flavivirus [152]. Seo et al. conducted a study comparing the potency of different classes of flavonoids against two RNA viruses, namely murine norovirus and feline calicivirus. Their findings demonstrated that, among the flavonoids tested, kaempferol exhibited the most potent inhibitory activity against these two viruses [113].

There are number of other flavonols and derivatives acting as antivirals. For example, sulfated rutin, which is modified from glycoside rutin, demonstrated significant activity against different HIV-1 isolates [123]. This compound inhibited HIV-1 infection by blocking viral entry and virus-cell fusion, likely by interacting with HIV-1 envelope glycoproteins. Rutin at 200 μM concentration was shown to inhibit EV71 infection by suppressing the activation of MEK1-ERK signal pathway, which is required for EV71 replication of [129]. Rutin and fisetin also inhibited the replication of EV-A71 by affecting the enzymatic activity of the 3C protease [76]. Fisetin treatment caused a dose-dependent decrease in the production of CHIKV nonstructural proteins and inhibition of viral infection [73]. Moreover, Zandi et al. showed that DENV-2 RNA copy number was significantly reduced following addition of fisetin to infected cells [149]. Yu et al. found that myricetin may serve as chemical inhibitor of SARS-coronavirus because it affects the ATPase activity of the viral helicase [147].

Antiviral activity of flavans

Flavans are characterized by a 2-phenyl-3,4-dihydro-2H-chromene skeleton. These compounds include flavan-3-ols, flavan-4-ols and flavan-3,4-diols. Among flavan-3-ols, the antiviral activity of catechin and its derivatives epicatechin, epicatechin gallate, epigallocatechin (EGC), and epigallocatechin gallate (EGCG), which are found in tea, has been largely investigated [122]. Among different viruses studied as potential targets, influenza virus has received the most attention after an initial report by Nakayama et al. showing that tea catechins, particularly EGCG, are able to bind to the haemagglutinin of influenza virus, preventing its adsorption to Madin-Darby canine kidney cells [98]. Furthermore, it has been suggested that EGCG may be able to damage the physical properties of the viral envelope, resulting in the inhibition of hemifusion events between influenza virus and the cellular membrane [66]. Recently, Colpitts and Schang reported that EGCG competes with sialic acid for binding to influenza A virus, thereby blocking the primary low-affinity attachment to cells [22]. Another tea catechin, EGC, exerted the inhibitory effect on the acidification of endosomes and lysosomes, thereby reducing viral entry via clathrin-mediated endocytosis [52]. A structure-function relationship analysis of tea catechins revealed the important role of the 3-gallolyl group of the catechin skeleton for its antiviral activity [120]. The results also showed that modification of the 3-hydroxyl position significantly affected the antiviral activity. Catechin derivatives containing carbon chains at 3-hydroxyl position demonstrated potent anti-influenza activity *in vitro* and *in ovo* [121].

Several reports have demonstrated that tea catechins have an antiviral effect against HIV infection. Among tea catechins, EGCG is the most effective because it exerts its antiviral effect throughout several steps of the HIV-1 life cycle. It directly binds to CD4 molecules with consequent inhibition of gp120 binding, an envelope protein of HIV-1 [62, 134]. These studies identified Trp69, Arg59 and Phe43 of CD4 as potential sites for interaction with the galloyl moiety of EGCG. The same residues are involved in interaction with viral gp120 [135]. Furthermore, early studies from Nakane and Ono showed that EGCG and ECG were effective at inhibiting HIV-1 reverse transcriptase *in vitro* [96, 97]. Tillekeratne et al. modified the molecular structure of EGCG to determine the minimum structural characteristics necessary for HIV-1 reverse transcriptase inhibition [124]. In their study, the gallate ester moiety was found to be important for inhibition. Besides these effects, EGCG has the ability to reduce viral production in chronically infected monocytoid cells [143]. The inhibitory effect was increased by approximately 25%, when EGCG was modified with lyposomes.

Tea catechins are also effective against herpesviruses. EGCG has been shown to block EBV lytic cycle by inhibiting expression of viral genes including Rta, Zta and EA-D [13]. Further studies indicated that one of the mechanisms by which EGCG may inhibit EBV lytic cycle involves the suppression of

MEK/ERK1/2 and PI3-K/Akt signaling pathways, which are involved in the EBV lytic cycle cascade [78]. Isaacs et al. found that EGCG can inactivate HSV virions by binding to the envelope glycoproteins gB and gD, which are essential for HSV infectivity [54]. The EGCG digallate dimers theasinensin A, P2, and theaflavin-3,3'-digallate inactivated HSV-1 and HSV-2 more effectively than did monomeric EGCG [55]. These dimers are stable at vaginal pH, indicating their potential to be antiviral agents against HSV infections.

The inhibitory effect of green tea extracts against HBV has been reported [140]. In HepG2.117 cells, EGCG inhibited HBV replication through impairing HBV replicative intermediates of DNA synthesis, thereby reducing the production of HBV covalently closed circular DNA [48]. In contrast, Huang et al. found that EGCG decreased HBV entry into immortalized human primary hepatocytes by more than 80% but had no effect on HBV genome replication [50]. Furthermore, EGCG is able to enhance lysosomal acidification, which is an unfavorable condition for HBV replication [155].

Besides these viruses, EGCG has been found to exert antiviral activity against HCV by preventing the attachment of the virus to the cell surface and suppressing RNA replication steps [8, 15]. A recent study also showed inhibitory activity of EGCG against another flavivirus, Zika virus (ZIKV): in this study, foci forming unit reduction assays were performed to evaluate the antiviral activity of EGCG on ZIKV at different stages of virus replication. Foci observed showed more than 90% inhibition when the cells were treated with EGCG during virus entry [10]. Similarly, EGCG is able to block CHIKV attachment to target cells, but has no effect on other stages of infection [132].

Antiviral activity of other flavonoids

Naringenin, which belongs to the flavanones class, has been shown to reduce the replication of a neurovirulent strain of Sindbis virus *in vitro* [102]. It also reduced Sindbis virus- and Semliki Forest virus-induced cytopathic effect in virus yield experiments [105]. Interestingly, naringin, the glycoside form of naringenin did not have anti-Sindbis virus activity, indicating that the rutinose moiety of this flavanone blocks its antiviral effect. Naringenin is also able to block the assembly of intracellular HCV particles and long-term treatment leads to 1.4 log reduction in HCV [39, 64]. The alphavirus CHIKV was effectively inhibited when infected Vero cells were treated with naringenin at the post-entry stage. In the same study, hesperetin, another flavanone which is found richly in citrus fruits, was found to exert most potent anti-CHIKV effect during the virus intracellular replication, with an IC_{50} of 8.5 μM [1]. Molecular docking and molecular dynamics studies by Oo et al. also revealed strong and stable interactions between hesperetin and CHIKV non-structural protein 2 (nsP2) as well as non-structural protein 3 (nsP3), suggesting that these proteins may be the target of hesperetin's anti-CHIKV activity [101].

Genistein is an isoflavonoid found in a number of plants including soybeans and fava beans. As a tyrosine kinase inhibitor, genistein reduced bovine herpesvirus type 1 and New World arenavirus Pichinde replication, by preventing the phosphorylation of viral proteins [2, 126]. Kinase inhibitor cocktails containing genistein displayed a broad-spectrum antiviral activity against arenaviruses and filoviruses [68]. Genistein was shown to inhibit HIV infection of resting CD4 T cells and macrophages through interference with HIV-mediated actin dynamics [42]. Furthermore, it may act against HIV ion channel since it has the ability to block the viral Vpu protein, which is believed to form a cation-permeable ion channel in infected cells [110]. Genistein also exerted its antiviral effects on the replication of HSV-1, HSV-2, and avian leucosis virus subgroup J, by inhibiting virus transcription [3, 106]. The antiviral activity of other flavonoids is presented in Table 2.

Table 2

Antiviral activity of other flavonoids

Flavonoids	Class	Source(s)	Antiviral activity	Other biological activities
Myricetin	Flavonol	Red (grape) wine, leaves of sweet potato (*Ipomoea batatas*), parsley (*Petroselinum crispum*), tea plant (*Camellia sinensis*), and fruits of blueberries (*Vaccinium* genus)	Moloney murine leukemia virus [7], SARS-CoV [63], influenza viruses [77], HIV-1 [103], Rauscher murine leukemia virus [104]	Anticarcinogenic, antioxidant, antithrombotic and anti-inflammatory activity
Hesperetin	Flavanone	Fruits of orange (*Citrus aurantium*), lemon (*Citrus limon*), mandarin (*Citrus reticulata*) and peppermint (*Mentha piperita*)	CHIKV [1], yellow fever virus [12], HSV-1 [61], Sindbis virus [102]	Antioxidant, anti-inflammatory, anti-allergic, hypolipidemic, vasoprotective and anticarcinogenic activity
Chrysin	Flavone	Honeycomb, leaves of passion flowers *(Passiflora caerulea* and *Passiflora incarnata)* and chamomile (*Matricaria chamomilla*)	HSV-1 [111], coxsackie B virus type 3 [117], EV71 [131]	Antioxidant, anticarcenogenic, anti-hypertension, anti-diabetic and antibacterial activity
Galangin	Flavonol	Propolis, leaves of lesser galangal (*Alpinia officinarum*) and rhizome of *Alpina galanga*	Coxsackie B virus type 1 [18], HCV [74], HSV-1 [111]	Antibacterial and anticarcinogenic activity
Morin	Flavonol	Bark, leaves and stem of white mulberry (*Morus alba*), leaves and fruit of Osage orange (*Maclura pomifera),* guava (*Psidium guajava*), and leaves of old fustic (*Maclura tinctoria*)	Canine distemper virus [11], Moloney murine leukemia virus [20], potato virus X [36], equid herpesvirus 1 [41]	Antihypertensive, anti-angiogenic, hepatoprotective, neuroprotectant and anti-inflammatory activity
Tangeretin	Flavone	Peels of tangerine (*Citrus tangerina*), orange (*Citrus*	RSV [141]	Anticarcinogenic activity

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Future perspectives

In spite of the wide range of biological health benefits which flavonoids possess, in addition to their high availability in humans' daily diets, there are challenges ahead for researchers before these natural compounds can be applied as therapeutic options in the clinical setting. Bioavailability, defined by the US Food and Drug Administration as "the rate and extent to which the active ingredient or active moiety is absorbed from a drug product and becomes available at the site of action", has been the main stumbling block to further advances in the potential use of flavonoids in the medical community. Intake

of metabolic derivatives of flavonoids from various food sources leads to relatively large differences in the final amount being successfully absorbed and utilized by humans [71]. Factors such as molecular sizes, glycosylation, esterification, lipophilicity, interactions with the enteric microorganisms, pKa, and other metabolic conjugations along the alimentary tract, affect the absorption and bioavailability of flavonoids in humans [49, 56, 69, 90, 93, 111, 133]. Hence, efforts in enhancing the bioavailability of flavonoids upon intake by humans are vitally necessary in order to develop these natural compounds into potential antiviral drugs. The following are a few examples of efforts being carried out to tackle this issue which can be used as platforms for further successes in the future.

In the past, researchers have looked into alternative methods to improve the compounds' solubility or to switch the site of absorption in the gut, with the aim of enhancing their bioavailability. A structural modification to hesperetin-7-glucoside, which resulted in a change in site of absorption from the large to the small intestine, has successfully yielded a higher plasma level of hesperetin in healthy subjects [100]. Wang et al. [130] formulated a way to increase the oral bioavailability of flavonols extracted from sea buckthorn, by forming a phospholipid complex via solvent evaporation method. Relative to the parent compounds, oral bioavailability of the tested flavonols was 172% - 242% higher when the phospholipid complex was administered into rats [130]. Flavonoids loaded in engineered nanoparticles have also been tested for their bioavailability following oral consumption. Improved stability of catechin and EGCG in chitosan nanoparticles have been shown to result in a higher rate of intestinal absorption [29]. Poly (D, L-Lactide) (PLA) nanoparticles and polymeric micelles contributed to a more sustainable release of quercetin, which has poor bioavailability and undergoes substantial first-pass metabolism, as well as of the poorly absorbed apigenin [70, 124, 151]. Self-Microemulsifying Drug Delivery System (SMDDS) is another technology which has been used to overcome the problem of low bioavailability of hydrophobic molecules. Upon entering the lumen of the intestine, an oil-in-water microemulsion containing the drug will be formed. The microemulsion increases the intestinal absorption of the drug or compound by avoiding the dissolution process [60, 108]. Puerarin, an isoflavone isolated from the root of *Pueraria lobata*, exhibited 2.6-fold higher bioavailability when prepared using SMDDS [154].

However, it is worth noting that while the bioavailability of flavonoids can be increased via different methodologies, it is vital that their biological efficacies are not affected, but maintained or enhanced. For instance, phosphorylated icariin has been found to inhibit duck hepatitis virus A more effectively than the parent compound [138]. Isorhamnetin is a methylated flavonol derived from the structure of quercetin. Dayem et al. investigated the antiviral potency of isorhamnetin against influenza A H1N1 virus and discovered that the methyl group on the B ring enhances its antiviral activity compared with the other tested flavonoids [25]. The efficacy of isorhamnetin against influenza virus was also shown when *in vivo* and *in ovo* models were tested [25]. Improvement in bioavailability will definitely enhance the efficacy of different biological effects of all classes of flavonoids. Hence, in addition to discovering the hidden potentials of flavonoids, scientists should also aim to identify ways to increase the amount of flavonoids available for the health benefits of human beings.

Conclusion

Natural compounds have been the center of attention among researchers working in various fields, including those related with antiviral drug development, due to their high availability and low side effects. The phytochemicals flavonoids, which are abundantly found in our daily diets of fruits and vegetables, have been actively studied as potential therapeutic options against viruses of different taxa in the past decade. Numerous positive findings have been reported on the *in vitro* efficacy of flavonoids, but less promising results have been obtained for most compounds in *in vivo* studies. Multiple factors contributed to this scenario, and *in vivo* studies must be prioritized by researchers. It is well-known that flavonoids possess enormous potential to be included in the daily prescriptions by physicians treating illnesses ranging from infectious and oncogenic to inflammatory and chronic degenerative diseases. However, it is time for researchers worldwide to take the initiative in making these compounds a success not only in the *in vitro* stage of research, but also in animal models, as well as in subsequent clinical studies. Biochemistry and mechanistic studies on the flavonoids' inhibitory activities can

improve our understanding of how these natural compounds work and, on the other hand, identify the stumbling block that is hindering further improvements in flavonoids antiviral research.

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Compliance with ethical standards

Ethical standards

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