Flavonoid

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A particular group of phytochemicals, called flavonoids, have shown a wide range of biological effects, including antiviral activities. The molecular mechanisms of their antiviral effects mainly consist in the inhibition of viral neuraminidase, proteases and DNA/RNA polymerases, as well as in the modification of various viral proteins. Mixtures of different flavonoids or combination of flavonoids with antiviral synthetic drugs provide an enhancement of their antiviral effects. Frequent viral infections worldwide have led to the need for new effective antiviral agents, which can be identified among the various flavonoids.

flavonoids antiviral properties viral enzymes

1. Introduction

Flavonoids possess important health protective effects, including anti-inflammatory, anticancer and antiviral properties[1][2][3][4][5][6][7]. There are in nature more than 6000 flavonoids, which have been structurally identified and divided in classes: flavones (e.g., apigenin), flavanols (e.g., quercetin), flavins (e.g., epigallocatechin-3-gallate), isoflavones (e.g., genistein) and anthocyanidins (e.g., cyanidin). Flavonoids occur in their free or conjugated form or are often esterified with one or two sugars with *O*-glycosidic or C-glycosidic bonds[8].

2. Antiviral Effects of Flavonoids

The most common flow chart for studies regarding the antiviral activity of phytochemicals is focused on the immediate testing of the whole natural extract, by dividing the polar from the non-polar constituents. After that, fractions with remarkable activity in in vitro antiviral assays, such as cytophatic effect, neutralization assay, hemagglutination, viral enzyme inhibition, or virion number reduction assay, are further fractionated through chromatographic techniques in order to purify the active phytochemicals. Effective compounds are then used on virus-infected animals or in human clinical trials in order to assess their effective antiviral properties[9]. The complete procedure, when interfaced with chemical libraries, represents the basis for high throughput screening assays[9]. The parameter used for assessing antiviral efficiency of drugs and phytochemicals is represented by 50% Inhibitory Concentrations (IC_{50}) or by 50% Effective Concentration (EC_{50}). Table 1 shows the main flavonoids studied for antiviral activity along with their investigated mechanisms of action. In the first section, we point out the studies focused on apigenin, vitexin and their derivatives, which were found active against many viruses like human Hepatitis C Virus (HCV), Herpes Simplex Virus-1 (HSV-1), human Hepatitis A and B Viruses (HAV; HBV), rhesus rotavirus (RRV) and influenza virus.

2.1. Flavonoids Targeting HCV, HBV and HAV Viruses

The natural extract of *Eclipta alba* (Asteraceae) was shown to be able to inhibit the HCV replicase in a cell culture system, which resulted in reduced HCV RNA titer and translation level of viral proteins[10]. Through bioassay-based fractionations of the natural extract, the authors identified two flavonoid compounds: apigenin and luteolin, which, tested individually, exhibited a dose-dependent inhibition of HCV replicase in vitro[10]. Quercetin, extracted from *Embelia ribes* (Mirsinaceae), exhibited antiviral effects against HCV, exerted through activity inhibition of the viral protease Non-Structural protein 3 (NS3), leading to a decrease in HCV replication[11]. Furthermore, the flavanol quercetagetin was found to inhibit HCV RNA-dependent RNA polymerase (RdRp) through inhibition of RNA binding to the viral polymerase, a mechanism associated with broad genotypic activity against several HCV strains and a high barrier to resistance mechanisms[12]. Luteolin and quercetin showed anti-HCV effects in hepatoma Huh-7 cells transfected with Non-Structural protein 5B (*NS5B*) cloned gene vector, that codifies for the NS5B polymerase of HCV virus[13]. Naringenin and quercetin possess antiviral activity against HCV, but naringenin showed stronger inhibition of virion assembly, whereas quercetin inhibited viral translation by blocking Non-Structural protein 5A (NS5A) and Internal Ribosome Entry Site (IRES)-mediated translation, as well as heat shock protein 70 (HSP70) induction[14]. Bioinformatics tools were also used to study the interaction of various phytochemicals with viral proteins that possess pivotal roles in the production of new virions and in the infection of the host cells. This approach may be a useful premise for deeper investigation regarding flavonoids which have provided interesting evidence of interactions with viral proteins. For instance, naringenin, diosmetin, apigenin and luteolin were all able to bind to the NS5B protein of HCV with higher affinity when compared with the antiviral drug sofosbuvir, inhibiting the activity of this viral enzyme[15].

Epigallocatechin-3-gallate (EGCG), the principal tea derived catechin, efficiently inhibited cell culture-derived HBV entry into hepatocellular cell lines, independent of the HBV genotypes, through a mechanism that involves the clathrin-dependent endocytosis of the HBV receptor sodium taurocholate co-transporting polypeptide (NTCP) from the plasma membrane, followed by its protein degradation[16].

The extract obtained from *Erythrina speciosa* (Fabaceae) exerted antiviral effects against HAV-H10 viruses mainly due to vitexin which, isolated from the extract, exhibited an antiviral activity against this virus with EC_{50} = 41.6 ± 7.6 μM[17]. The authors showed that the flavone vitexin can interact with the binding pocket of HAV 3C proteinase, inhibiting this enzyme[17].

Table 1. Molecular mechanisms and targets of antiviral activities of flavonoids reported in this entry.

Flavonoids	Inhibited Virus	Targets	Molecular Mechanisms	Ref.
Apigenin, Luteolin	HCV	HCV replicase	Inhibition of HCV replication	[10]

Vitexin, Apigenin-7-*O*-glucoside,	Rhesus Rotavirus	Rotavirus virions	Inhibition of viral replication	[18]
Vitexin	H1N1 influenza	TLR3, TLR4,	Decrease of inflammatory injury,	[19]
		TLR7 pathways	Increase of IFN-β levels	
Vitexin	HSV-1 and HAV	HSV-1 virions,	Inhibition of viral replication	[17]
		HAV virions		
Apigenin, Isoquercetin, Quercetin	HCV	NS3 protease	Inhibition of HCV replication	[20]
Quercetin-3-rhamnoside	Influenza A/WS/33	Influenza virions	Inhibition of virus infection	[21]
EGCG	HIV	Reverse transcriptase	Inhibition of HIV replication	[22]
Myricetin-3-rhamnoside	HIV	Reverse transcriptase	Inhibition of HIV replication	[23]

Quercetin, Catechin, Naringenin	HCV	NS5A, HSP70,	Inhibition of viral translation,	[14]
		HCV virions	Inhibition of virion assembly	
Delphinidin-3-rutinoside	HSV-1	NOX4	Inhibition of HSV-1 replication	[24]
EGCG	HBV	NTCP receptor	Inhibition of HBV entry into cells	[16]
Quercetin	HCV	NS3 protease	Inhibition of HCV replication,	[11]
			Inhibition of virion production	
Luteolin, Quercetin	HCV	NS5B polymerase	Inhibition of HCV replication	[25]
EGCG,	Dengue	NS1	Inhibition of NS1 glycosylation	[26]

Sanggenon O, Chamaejasmin				
Baicalin	Dengue Virus-2 (DENV-2)	DENV-2 virions	Inhibition of viral replication,	[13]
			Viricidal activity	
Baicalin, Baicalein	H1N1 influenza	Nrf2	Inhibition of viral replication	[27]
Luteolin	HCV	NS5B polymerase	Inhibition of HCV replication	[13]
Naringenin, Quercetin	HCV	Envelope 2 protein,	Inhibition of virion assembly,	[14]
		NS5A, NS3	Inhibition of HCV entry into cells	
Tangeretin, Nobiletin	RSV	Phosphoprotein P	Inhibition of viral replication,	[28]
			Inhibition of RSV entry into cells	

Kaempferol-7-*O*-glucoside, EGCG	HIV	HIV protease	Inhibition of virion production	[29]
Quercetagetin	HCV	NS5B polymerase	Inhibition of RNA binding to NS5B	[12]
Pinocembrin	Zika	Viral RNAs	Envelope protein synthesis inhibition	[25]

2.2. Antiviral Effects of Flavonoids Against Influenza Viruses

Vitexin, extracted from the plant *Flos Trollii* (Caryophyllaceae), exerted its anti-H1N1 influenza virus effects through partially down-regulating Toll-Like Receptor 3 (TLR3) and Toll-Like Receptor 7 (TLR7) pathways and up-regulating Toll-Like Receptor 4 (TLR4) molecular pathway[19]. TLRs are transmembrane glycoproteins, which are privileged targets of several viruses and can be activated by endogenous molecules in the context of inflammation. TLR activation produces pro-inflammatory cytokines through Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) signaling pathway or through Interferon regulatory factor 3 (IRF3) and Interferon regulatory factor 7 (IRF7). Some viruses enter the host cells by binding TLR3, but after their entrance the viruses are able to inhibit cytokine production, thus impairing the immune response. Phytochemicals able to decrease the binding between TLRs and virus particles can slow the infective process. Interestingly, virus infection can lead to an induction of the inflammation process, characterized by excessive production of nitric oxide (NO), Interleukin-1 (IL-1), Interleukin-6 (IL-6) and Tumor Necrosis Factor-α (TNF-α). It was shown that various flavonoids enhance the production of Interferon-β (IFN-β) in order to counteract the viral infections[19]. Baicalin, baicalein, wogonin, chrysin and oroxylin A, isolated from *Scutellaria baicalensis*, showed anti-H1N1 activities, with IC_{50} values of 7.4, 7.5, 2.1, 7.7 and 12.8 μM, respectively, and were all more potent than the conventional antiviral drug oseltamivir phosphate, which had an IC_{50} of 45.6 μM[30]. These flavonoids increased the transcriptional activity of Nuclear factor erythroid 2-related factor 2 (Nrf2), the master regulator of the antioxidant responses, whose activation is related to the antiviral effects of *Scutellaria baicalensis*[30]. The natural extract of *Tetrastigma hemsleyanum* (Vitaceae) contains many flavonoids, including vitexin, vitexin-2-O-rhamnoside, isorhamnetin, rutin, kaempferol, astragalin, quercitrin, quercetin and iso-quercetin, which were shown to be able to exert anti-influenza virus activity, with different efficiency, through the reduction of the number of plaques induced by the influenza virus in infected Madin-Darby Canine Kidney (MDCK)

cells[31]. Similarly, the flavonoid quercetin-3-rhamnoside, extracted from *Houttuynia cordata* (Saururaceae), exerted anti-influenza A/WS/33 activity reducing virus-mediated cytopathic effects, directly interacting with virus particles[21]. Furthermore, the same authors showed that quercetin-3-rhamnoside exerted anti-influenza virus activity in mice, when used at 6.25 mg/Kg/day for six days after influenza virus infection[32].

2.3. Antiviral Properties of Flavonoids Against Dengue and Zika Viruses

Flavonoids Sanggenon O, EGCG and Chamaejasmin were all potentially able to inhibit Dengue virus replication by blocking the Asn-130 glycosylation site of the viral protein Non Structural protein 1 (NS1)[26]. Baicalin, a flavonoid derived from *Scutellaria baicalensis* (Lamiaceae), exhibited viricidal activity against Dengue Virus-2 (DENV-2) extracellular virions with IC_{50} = 19.6 ± 0.2 μM, exerted an anti-adsorption effect with IC_{50} = 40.5 ± 0.4 μM and also inhibited virus replication with IC_{50} = 30.2 ± 0.2 μM[27]. Studies of the antiviral effects of the flavonoids fisetin, quercetagetin, and pinocembrin showed that fisetin can inhibit the replication molecular machineries of Dengue virus and Enterovirus A71[33]. Furthermore, other antiviral mechanisms of the pinocembrin consist in targeting the molecular machinery used by the Zika virus to replicate its own genome inside the host cells[25]. This flavanone acts on the post-entry processes of Zika virus replication cycle through the inhibition of both viral RNA production and synthesis of envelope proteins[25].

2.4. HSV, Respiratory Syncytial Virus (RSV), RRV: Antiviral Activities of Flavonoids

Interestingly, the plant *Moringa oleifera Lam* (Moringaceae) provides a rich and rare combination of several phytochemicals, including the flavonoids quercetin and kaempferol, and its leaves extract can be applied as a prophylactic or therapeutic anti-HSV-1 medicine[34]. The extract obtained from *Moringa oleifera Lam* remarkably reduced the plaque formation induced by wt HSV, thymidine kinase-deficient HSV and phosphonoacetate-resistant HSV strains[34]. Furthermore, the extract obtained from Erythrina speciosa possessed antiviral properties against the HSV-1 virus, mainly due to vitexin which exhibited an antiviral activity with EC_{50} = 80.9 ± 6.2 μM, exerted through the interaction of this flavone with the binding pocket of HSV-1 thymidine kinase[17].

Vitexin and luteolin from *Aspalathus linearis* (Fabaceae) showed antiviral activity against RRV with IC_{50} of 129 μM and 116 μM, respectively; interestingly, apigenin-7-O-glucoside from *Melissa officinalis* (Labiateae) inhibited viral growth, with an IC_{50} of 150 μM, through the reduction of the number of RRV-induced plaques in infected MA104 cells[18].

Tangeretin and nobiletin, two polymethoxyflavones extracted from *Citrus reticulate* "Chachi", possess anti-RSV properties. Tangeretin exhibited a dose-dependent inhibition of RSV-induced plaque formation on HEp-2 cells, through inhibition of RSV entry into host cells and viral replication. Furthermore, tangeretin decreased the levels of RSV phosphoprotein (P protein), which is associated with the viral genome to form the holo-nucleocapsid. The extent of the antiviral effect of this phytochemical was comparable to the conventional antiviral drug ribavirin[28].

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