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MECHANISMS OF ANTIVIRAL ACTIVITY OF FLAVONOIDS

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The article examines the multifaceted mechanisms underlying the antiviral activity of flavonoids, compounds widely distributed in the plant kingdom.

The *aim* of the work was to review literature data on mechanisms of antiviral activity of flavonoids.

Methods. Publications were selected based on the PubMed (https://pubmed.ncbi.nlm.nih.gov/) databases published in 2015–2023. They include information on mechanisms of antiviral activity of flavonoids.

Results. Beginning with an overview of flavonoid structures, the document navigates through the intricate interactions between flavonoids and various stages of the viral life cycle. Drawing upon a comprehensive analysis of *in vitro* and *in vivo* studies, the review highlights the diverse ways in which flavonoids inhibit viral entry, replication, and release. Depending on their antiviral mechanisms, flavonoids can serve as preventive inhibitors, therapeutic inhibitors, or indirect inhibitors by influencing the immune system.

Conclusion. The synthesized information not only contributes to the advancement of antiviral research but also lays the foundation for the development of novel therapeutic interventions against a spectrum of viral infections.

Key words: flavonoids; antiviral activity; viral infection; bioactive compounds; host-pathogen interaction.

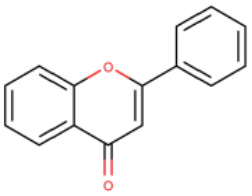
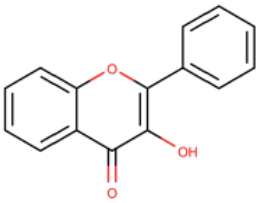
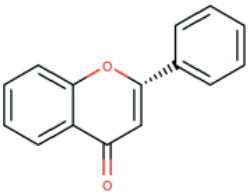
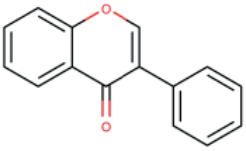
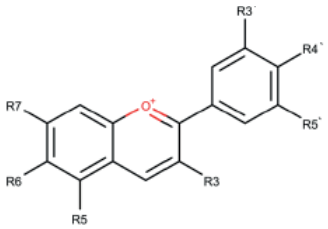
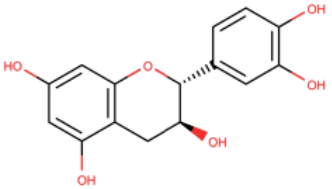
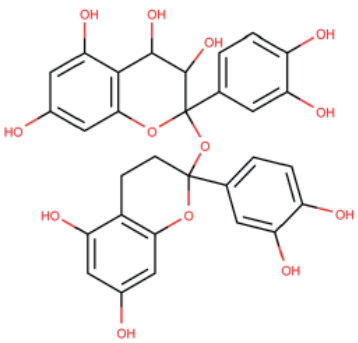
In the past few years, there has been an increased focus on exploring natural reservoirs of antioxidants. Flavonoids are a diverse group of polyphenolic compounds found in various plants and are known for their wide range of biological activities and health benefits [1, 2]. The flavonoids act at different stages of viral infection, such as viral entrance, replication and translation of proteins. They play important roles in plant biology, including pigmentation, UV protection, and defense against pathogens and herbivores [3].

Flavonoids are characterized by their chemical structure, which consists of two aromatic rings (A and B) connected by a three-carbon bridge forming a heterocyclic ring (C-ring). Depending on the substitution of this basic structure, flavonoids can be further categorized into different classes, including flavones, flavonols, flavanones, isoflavones, anthocyanins, and flavanols (catechins and proanthocyanidins) [4] (Table 1).

Flavonoids are crucial natural compounds with the capacity to demonstrate antiviral properties. Their importance in this context lies in their capability to engage with viruses at multiple stages of the viral life cycle, thereby making them promising candidates for the development of antiviral therapies [5].

Flavonoids have been demonstrated to disrupt viral replication by specifically targeting critical enzymes and essential proteins involved in the replication process [6]. One notable example is their ability to inhibit the function of viral polymerases, which play a vital role in synthesizing viral genetic material. This interference results in the disruption of

Table 1. **Common chemical structures of different flavonoid classes**

Class	Examples of compounds	The common structure of some classes of flavonoids
Flavones	Luteolin, tangeretin, apigenin	
Flavonols	Quercetin, kaempferol	
Flavanones	Eriodictyol, blumeatin, naringenin	
Isoflavones	Genistein, daidzein	
Anthocyanins	Cyanidin, delphinidin, malvidin, peonidin	
Flavanols (catechins and proanthocyanidins)	Catechin, epicatechin, epigallocatechin	 Structural formula of Catechin  Structural formula of Proanthocyanidins

new virus particle production, consequently restricting the infection's spread.

Numerous flavonoids are renowned for their potent antioxidant and anti-inflammatory characteristics [7]. Viral infections frequently induce oxidative stress and inflammation within the host, which can worsen the disease's impact. Flavonoids have the capacity to alleviate these effects, thereby diminishing tissue damage and alleviating the severity of symptoms linked to viral infections.

Flavonoids possess the ability to regulate the immune response, bolstering the body's capacity to protect against viral infections [5]. They have the potential to trigger the generation of immune cells and cytokines, crucial components of the antiviral immune response. This immunomodulatory impact can empower the host to mount a more efficient defense against the virus.

Certain flavonoids have been identified as effective blockers of viral attachment and entry into host cells [8]. They can disrupt viral attachment proteins or receptors on the surface of host cells, thus impeding the virus from entering and commencing the infection.

Flavonoids derived from food sources also display significant anti-viral effects by inhibiting the reverse transcriptase of various retroviruses, including HIV. Research has confirmed that extracts derived from hyssop leaves, which include tannic acids and flavonoids, effectively blocked the activity of reverse transcriptase, prevented syncytium formation, and reduced the expression of P17 and p24 HIV antigens in HIV-infected cells. Furthermore, recent preliminary studies have suggested that flavonoids and polyphenolic compounds like ferulic, gallic, and caffeic acids, ethyl gallate, curcumin, and a-tocopheryl-succinyl-O-ethyl ferulate can inhibit HIV replication by as much as 80% and also safeguard against the depletion of cellular glutathione [9].

- Flavonoids can interfere with viral entry by disrupting the integrity of the viral envelope.
- They can inhibit viral membrane fusion by affecting the conformational changes required for fusion.
- Flavonoids can disrupt the stability of the viral capsid, rendering the virus non-infectious.
- They can inhibit the activity of viral proteases, which are essential for viral replication and entry.
- Flavonoids can inhibit endocytosis, a process by which viruses enter host cells through vesicular uptake.

This mechanism plays a pivotal role in thwarting the initial phases of viral infection.

Flavonoids have the capacity to diminish the viral load in individuals who are infected, a critical factor in managing the virus's transmission and enhancing clinical outcomes. Reduced viral loads can result in milder symptoms and a shorter duration of illness.

Many flavonoids demonstrate a broad-spectrum antiviral capability, implying that they may have the potential to be effective against a diverse array of viruses, encompassing both RNA and DNA viruses [10]. This adaptability renders them valuable in the pursuit of antiviral treatment development.

Flavonoids are typically regarded as safe for consumption and exhibit low toxicity, particularly when contrasted with certain synthetic antiviral medications. This characteristic renders them appealing candidates for incorporation into antiviral therapies, as they are less prone to induce adverse side effects.

Owing to their various modes of action, flavonoids have the potential to reduce the emergence of antiviral resistance. When treatments target multiple phases of a virus's life cycle simultaneously, viruses are less inclined to develop resistance against them.

To highlight and understand all possible mechanisms of flavonoid's antiviral activity this systematic review was made.

Materials and Methods

The systematic review methodology for this article involves a structured approach to identifying, selecting, and analyzing relevant studies.

Search criteria was a research question and relevant keywords and phrases related to flavonoids, antiviral activity, synergies, and combinations such as "flavonoids," "antiviral," "mechanism," and specific flavonoid names (e.g., "quercetin," "rutin," "epigallocatechin gallate") etc.

Results and Discussion

Flavonoids have been extensively researched for their effectiveness against a diverse array of DNA and RNA viruses. Broadly, flavonoids employ multiple mechanisms of action. Mechanisms by which flavonoids can interfere with virus attachment and entry into host cell are direct interaction with viral receptors, inhibition of viral fusion, disruption of viral envelope integrity,

modulation of host cell signaling, stimulation of innate immune response, through anti-inflammatory, immunomodulatory effects and antioxidant activity, interference with viral replication (Fig. 1).

Therefore, flavonoids can impede the viruses by preventing their attachment and entry into host cells, disrupt various stages of viral replication processes, hinder translation and polyprotein processing, thereby curtailing the release of viruses for infecting other cells. Various flavonoids have been discovered to inhibit viruses through diverse mechanisms. Depending on their antiviral mechanisms, flavonoids can serve as preventive inhibitors, therapeutic inhibitors, or indirect inhibitors by influencing the immune system [11].

I. Direct Interaction with Viral Receptors

Flavonoids can bind directly to viral receptors, blocking the attachment of the virus to host cells. They have the capacity to bind specifically to viral receptors on the surface of viruses. These receptors are often proteins or glycoproteins that viruses use to recognize and attach to host cells. Flavonoids can form non-covalent interactions, such as hydrogen bonds or van der Waals forces, with these receptors, effectively blocking their active sites.

1. *Direct Binding to Viral Envelope Proteins and Altering Envelope Protein Conformation*: Flavonoids can directly bind to viral envelope proteins, such as glycoproteins, spike proteins, or hemagglutinins, which are responsible for recognizing and attaching to host cell receptors. Epigallocatechin-3-gallate inhibit hepatitis C virus E2 envelope glycoprotein *in silico* [12–14]. This interaction can interfere with the ability of the viral protein to bind to its cellular receptor, effectively blocking the initial attachment step.

Flavonoids can induce structural changes in viral envelope proteins.

Such compounds as flavonols (quercetin, kaempferol), flavones (apigenin, nobiletin), isoflavones (genistein), flavanones (naringenin), gingerols (6-gingerol, 8-gingerol), polyphenols (resveratrol), and catechins (epigallocatechin gallate, EGCG) were studied against E protein of the SARS CoV-1 with patch-clamp electrophysiology and a cell viability assay [15]. EGCG showing the highest inhibitory activity.

In another study [16] among different studied flavonoids (baicalein, fisetin, hesperetin, naringenin/ naringin, quercetin and rutin) that possess anti dengue activity only quercetin can interrupt the fusion process of virus by inhibiting the hinge region movement and by blocking the conformational rearrangement in envelope protein *in silico*.

This structural disruption can hinder the proper conformation of viral proteins required for attachment to host cells. As a result, the

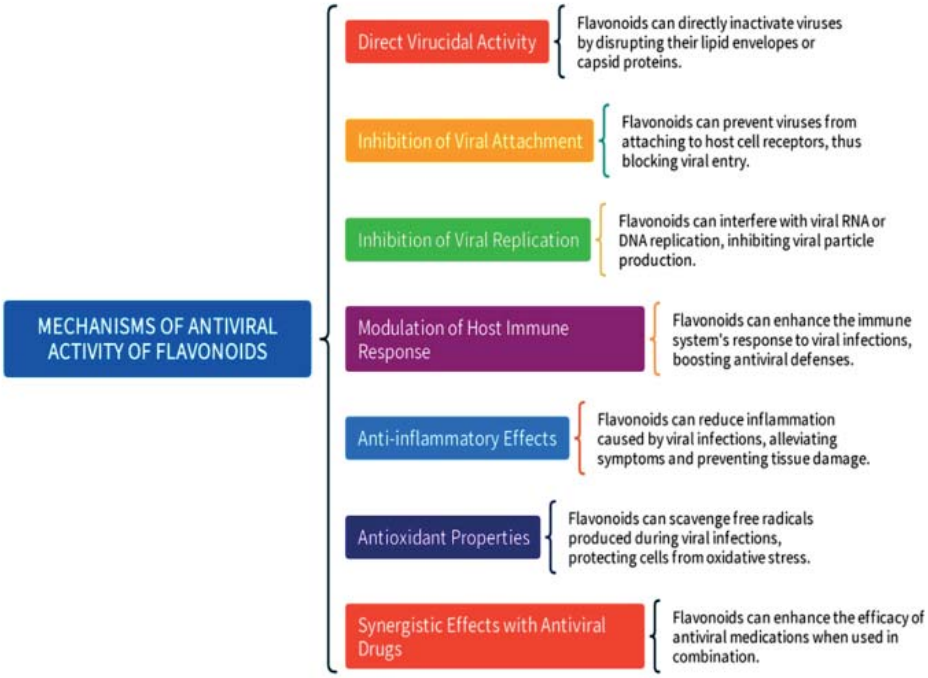


Fig. 1. **Common schema for mechanisms of antiviral activity of flavonoids**

virus may lose its ability to recognize and bind to cellular receptors effectively.

2. *Inhibition of Fusion Peptides*: Some flavonoids can interact with fusion peptides present in viral envelope proteins [17]. These peptides play a crucial role in facilitating the fusion of the viral envelope with the host cell membrane [18]. Flavonoids can interfere with this fusion process by binding to or blocking the fusion peptides. This physical interaction hinders the initial step of viral entry, preventing infection.

Summarized aspects of mechanisms of interaction between flavonoids and virus are described in [13] and represented in Fig. 2.

II. Inhibition of Viral Fusion

Several flavonoids have shown promising effects in inhibiting viral entry by interfering with the attachment and fusion processes [10, 19]. While the effectiveness of specific flavonoids may vary depending on the virus and host cell type, here are some examples of flavonoids that have demonstrated antiviral properties in inhibiting viral entry:

Quercetin inhibits the attachment of influenza A virus to host cells by interfering with the interaction between viral envelope proteins and host cell receptors [20, 21]. It can also inhibit viral entry by preventing the fusion of the viral envelope with the host cell membrane [22].

Epigallocatechin-3-*O*-gallate has been shown to block the binding of various types of enveloped DNA, (+)-RNA, and (–)-RNA viral attachment proteins to host cell receptors [14, 23–25]. It can also inhibit viral entry by interfering with the fusion process between the viral envelope and the host cell membrane.

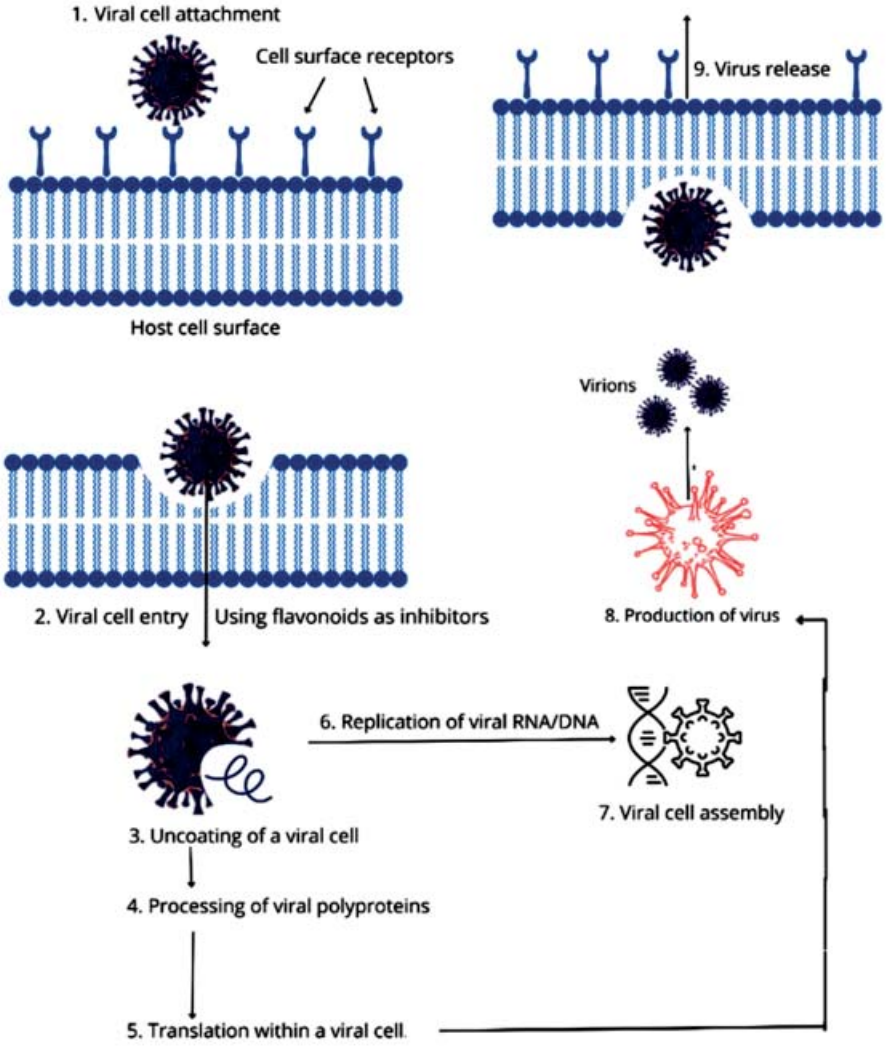


Fig. 2. **The mechanism of interaction between flavonoids and virus**

Baicalin interferes with dengue virus attachment by inhibiting the binding of viral glycoproteins to host cell receptors [24, 26].

Rutin, apigenin and luteolin can block viral attachment by interfering with the interaction between HIV-1 viral glycoproteins and host cell receptors [27–31]. It can also inhibit viral entry by disrupting the fusion process between the viral envelope and the host cell membrane.

It's important to note that while these flavonoids have shown promise in laboratory studies for their antiviral effects, their effectiveness can vary depending on the specific virus, the concentration of flavonoids used, and the experimental conditions.

III. Disruption of Viral Envelope Integrity

Disruption of viral envelope integrity is yet another mechanism through which flavonoids can exert their antiviral effects as it was described for rotavirus for catechin isomers and proanthocyanidins in [32]. Many viruses rely on their outer lipid envelope for protection. This interference can lead to changes in the fluidity, organization, or structural integrity of the lipid membrane, making it more vulnerable to damage.

IV. Modulation of Host Cell Signaling

1. *Competitive Binding*: Flavonoids can compete with viral particles for binding to host cell receptors. By occupying these receptors, flavonoids effectively block the attachment of the virus to host cells. This competitive binding is particularly relevant for viruses that require specific receptors to enter host cells.

2. *Modulation of Receptor Expression*: Some flavonoids can modulate the expression of host cell receptors involved in viral attachment and entry. For example, they may downregulate the expression of these receptors, making it more challenging for viruses to find and attach to host cells.

3. *Alteration of Receptor Properties*: Flavonoids may affect the physical properties of host cell receptors, such as changes in receptor conformation or charge. These alterations can make it more difficult for viral attachment proteins to bind to the receptors effectively.

4. *Inhibition of Signaling Pathways*: Flavonoids can interfere with host cell signaling pathways involved in the regulation of receptor expression and viral entry. By modulating these pathways, flavonoids can reduce the susceptibility of host cells to viral attachment and entry. through the activation of specific kinases or transcription factors that are required for viral replication. By disrupting these signaling pathways, flavonoids can impede viral multiplication. For example, luteolin can interfere with various cell signaling pathways – it may inhibit the PI3K/Akt/mTOR pathway, which is involved in cell survival and proliferation [21].

Flavonoids can modulate signaling pathways that control the balance between pro-apoptotic and anti-apoptotic factors. For instance, they may activate stress-activated protein kinases, such as JNK (c-Jun N-terminal kinase) or p38 MAPK (mitogen-activated protein kinase), which can promote pro-apoptotic signals.

5. *Strengthening the Host Immune Response*: Flavonoids with immunomodulatory properties can enhance the host immune response. A robust immune response can reduce the viral load and the likelihood of successful viral attachment and entry into host cells [33].

It's important to note that the specific interactions between flavonoids, viral envelope proteins, and host cell receptors can vary depending on the flavonoid compound and the virus in question. Additionally, the efficacy of flavonoids as antiviral agents may be influenced by factors such as the concentration of flavonoids, the timing of treatment, and the viral strain's characteristics.

V. Stimulation of Innate Immune Response

Flavonoids can influence the host's immune system to combat viral infections through various mechanisms [34]. Their immunomodulatory properties make them valuable in enhancing the body's ability to defend against viruses.

This mechanism is carried out through the stimulation of cytokine production (flavonoids can promote the release of interferons (IFNs), which have antiviral properties and help the immune system combat viral infections); enhancement of antigen presentation (flavonoids can improve antigen presentation by antigen-presenting cells (APCs) such as dendritic cells. This facilitates the recognition of viral antigens by immune cells like T cells, leading to a more robust immune response).

Other aspects of this action are activation of natural killer (NK) cells; modulation of T cell responses (flavonoids can influence T cell responses, including the activation and proliferation of cytotoxic T cells (CTLs) that directly target infected cells [35]. This

helps eliminate virus-infected cells from the body); regulation of inflammatory responses; protection of immune cells from damage caused by oxidative stress, which is often elevated during viral infections; enhancement of humoral immunity; modulation of inflammatory signaling pathways (flavonoids can interfere with pro-inflammatory signaling pathways, such as nuclear factor-kappa B (NF-κB), which are often activated during viral infections), that contribute to a balanced immune response; reduction of immunosuppression and enhancement of mucosal immunity.

Found in green tea, EGCG exhibits immunomodulatory properties by enhancing the activity of NK cells and promoting the production of interferons [36]. It can also suppress the production of pro-inflammatory cytokines, helping to control excessive inflammation during viral infections.

Baicalin, derived from *Scutellaria baicalensis* (Chinese skullcap), has demonstrated immunomodulatory effects by enhancing the phagocytic activity of macrophages and increasing the production of pro-inflammatory cytokines, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), which are important for antiviral responses [37, 38, 39].

VI. Anti-Inflammatory Effects

Flavonoids possess anti-inflammatory properties that can help regulate excessive inflammation during viral infections. By reducing inflammation, flavonoids can alleviate symptoms and limit tissue damage [40].

Flavonoids can inhibit the production and release of pro-inflammatory mediators, such as cytokines (e.g., interleukin-1 beta, interleukin-6, tumor necrosis factor-alpha), chemokines, and prostaglandins. By reducing the levels of these inflammatory molecules, flavonoids dampen the overall inflammatory response triggered by viral infections [41, 42].

Flavonoids can interfere with signaling pathways involved in inflammation. For example, they may inhibit the activation of nuclear factor-kappa B (NF-κB), a key transcription factor that promotes the expression of pro-inflammatory genes. By blocking NF-κB activation, flavonoids reduce the production of inflammatory cytokines [34].

Quercetin is a widely studied flavonoid found in various foods such as apples, onions, and citrus fruits. It possesses strong antioxidant properties and has been shown to inhibit the production of pro-inflammatory cytokines, making it a potent anti-inflammatory agent in [43–45].

VII. Interference with Viral Replication

Flavonoids can impact viral replication and multiplication within host cells through various mechanisms. Their ability to interfere with different stages of the viral life cycle makes them valuable candidates for controlling viral infections. Here's an exploration of how flavonoids can affect viral replication and multiplication:

1. *Inhibition of Viral Enzymes*: Many flavonoids have been shown to inhibit key viral enzymes involved in replication. For example, flavonoids can inhibit viral RNA polymerases or reverse transcriptases, essential for the replication of RNA and retroviruses, respectively. By blocking these enzymes, flavonoids can significantly reduce viral genome replication, hindering the production of new virus particles. In [46, 47] quercetin potently inhibits Enterovirus 71 and porcine epidemic diarrhea virus activity 3C protease activity, thereby blocking its replication. Proanthocyanidins from blueberry has strong antiviral activity against hepatitis C virus (HCV) and human T-lymphocytic leukemia virus type 1 (HTLV-1) via inhibition of ACE2 and viral 3CLpro (3-chymotrypsin-like) enzymes [48]. Herbacetin, rhoifolin and pectolinarin in the study [49] demonstrated inhibitory activity against SARS-CoV 3C-like protease.

2. *Interference with Viral Protein Synthesis*: Flavonoids may also interfere with the synthesis of viral proteins, which are crucial for the assembly of new virus particles. By inhibiting viral protein synthesis, flavonoids can disrupt the virus's ability to replicate and multiply within host cells. Myricetin demonstrated both in vitro and in vivo blocking HSV infection through direct interaction with virus gD protein [50, 51].

Disruption of RNA/DNA replication - flavonoid-mediated inhibition of viral enzymes and RNA/DNA replication represents a multifaceted approach to disrupting the viral life cycle.

• Interference with Nucleotide Incorporation: Flavonoids can interfere with the incorporation of nucleotides into the growing viral RNA or DNA strand [52]. By competing with nucleotides for binding to the viral polymerase or by modifying the structure of nucleotides, flavonoids can disrupt the elongation of the viral genome, preventing the

formation of complete viral genetic material.

• Template Strand Destabilization: Flavonoids can destabilize the template RNA or DNA strand that serves as a blueprint for viral genome replication, for example against SARS-CoV-2 targets [53, 54]. This destabilization can make it more challenging for viral polymerases to use the template for accurate replication, leading to errors in the newly synthesized genetic material.

• RNA/DNA Cleavage: Some flavonoids possess the ability to cleave RNA or DNA molecules [55, 56]. By inducing breaks in the viral genome, flavonoids can introduce mutations and inhibit proper replication. This can lead to the production of nonfunctional viral genetic material.

• Inhibition of Helicases: Helicase enzymes are essential for unwinding the viral genome during replication. Flavonoids can inhibit helicase activity, preventing the separation of the DNA or RNA strands required for replication. Authors [57] report for the first time myricetin, quercetin, kaempferol and licoflavone C as selective inhibitors of SARS-CoV-2 nps13 helicase with low micromolar activity in both *in silico* and *in vitro*.

• Impairment of Nucleotide Synthesis: Flavonoids can affect the host cell's ability to synthesize nucleotides, which are essential building blocks for viral RNA and DNA replication as it is described for human T cell leukemia virus by the plant flavonoid baicalin [58]. By disrupting nucleotide biosynthesis, flavonoids limit the availability of raw materials required for viral genome replication.

These mechanisms not only hinder the synthesis of viral genetic material but can also introduce errors and mutations into the viral genome, further compromising the virus's ability to replicate effectively.

4. *Induction of Host Antiviral Responses and Reduction of Oxidative Stress*: Some flavonoids can stimulate the host's innate antiviral responses. They can promote the production of antiviral cytokines, such as interferons, and activate immune cells like natural killer (NK) cells. These responses can limit viral replication and the spread of infection.

Viral replication often generates oxidative stress in host cells. Flavonoids, known for their antioxidant properties, can help mitigate this stress by scavenging reactive oxygen species (ROS). Lowering oxidative stress can indirectly hinder viral replication, as viruses may exploit ROS for their own replication.

5. *Preventing Viral Assembly and Budding*: Some flavonoids can interfere with the assembly and budding of new virus particles from host cells. By inhibiting the interaction between viral structural proteins and host cell membranes, flavonoids can block the release of virions, reducing viral replication and spread.

6. *Modulation of Cellular Microenvironment*: Flavonoids can modify the cellular microenvironment, making it less conducive to viral replication. For example, they may alter the pH within endosomes or lysosomes, which can hinder the release and processing of viral components.

7. *Impairment of Viral Protein Transport and Decreased Viral Entry and Attachment*: Flavonoids can interfere with the transport of viral proteins within host cells. This disruption can prevent the proper assembly of new virus particles and reduce viral multiplication.

Flavonoids can also impact viral replication by reducing viral entry and attachment, as discussed in previous responses. By blocking these early stages of infection, they limit the number of cells that become infected and reduce the potential for viral multiplication.

VIII. Antioxidant Activity

Almost all polyphenolic compounds and flavonoids among them posseses antioxidant activity because of the presence of phenolic hydroxyl radicals.

Flavonoids can act as scavengers of reactive oxygen species, such as superoxide radicals ($O_2 \cdot -$), hydroxyl radicals ($\cdot OH$), and hydrogen peroxide (H_2O_2). They neutralize these harmful molecules, preventing oxidative damage to cellular components. Flavonoids can chelate metal ions like iron and copper, which can participate in the generation of ROS through Fenton reactions. By binding to these ions, flavonoids reduce their ability to catalyze oxidative reactions [59]. Flavonoids can upregulate the activity of endogenous antioxidant enzymes, such as superoxide dismutase (SOD), catalase, and glutathione peroxidase. These enzymes help detoxify ROS and maintain cellular redox balance. Some flavonoids have the capacity to regenerate other antioxidants like vitamin C and vitamin E, which further enhances the cellular defense against oxidative stress [60].

But it is not only antioxidant properties of flavonoids are responsible for this mechanism. Rutin is known for its antioxidant properties, which help reduce oxidative stress and inflammation [61]. During viral infections, the virus can induce oxidative stress within

host cells. Viral replication processes and host immune responses can generate ROS, leading to oxidative damage to cellular structures. And rutin's antioxidant activity may protect cells from damage caused by free radicals.

Viral-induced oxidative stress can result in DNA damage, protein oxidation, and lipid peroxidation. These effects can impair cell function and promote viral replication. Flavonoids, by acting as antioxidants, can protect cellular components from oxidative damage. They scavenge ROS and reduce the oxidative burden on DNA, proteins, and lipids. Flavonoids' anti-inflammatory properties can help mitigate the oxidative stress associated with viral infections. By suppressing inflammation, they indirectly reduce ROS production. This group of biologically active substances can boost the activity of endogenous antioxidant enzymes, reinforcing the cell's ability to neutralize ROS generated during viral infections.

Some studies [55, 62] suggest that flavonoids may directly inhibit viral replication by disrupting the redox balance required for efficient

IX. Induction of Cell Death

Flavonoid-induced apoptosis is a mechanism by which certain flavonoid compounds can trigger programmed cell death in virus-infected cells. Apoptosis is a tightly regulated and controlled process that plays a critical role in the body's defense against viral infections [63].

Flavonoid-induced apoptosis works to eliminate virus-infected cells through recognition of virus-infected cells, activation of apoptotic pathways, inhibition of anti-apoptotic proteins such as Bcl-2 and Bcl-xL, release of pro-apoptotic factors, such as cytochrome c, from the mitochondria into the cytoplasm, activation of caspases (they cleave and activate downstream effector proteins), DNA fragmentation and cell shrinkage, formation of apoptotic bodies with its further phagocytosis and as a result limiting viral spread (Fig. 3).

Further research is needed to understand the precise mechanisms of flavonoid-induced apoptosis and its potential applications in antiviral therapies.

X. Synergistic Effects with Antiviral Drugs

The combination of flavonoids with conventional antiviral agents can offer several potential benefits in the management of viral infections [64]. While flavonoids alone may not replace conventional antiviral drugs, they can complement these agents in several ways:

– *Enhanced Antiviral Activity*: Combining flavonoids with conventional antiviral agents may enhance their overall antiviral activity. Flavonoids can target different stages of the viral life cycle, potentially inhibiting viral replication through mechanisms that differ from those of conventional antivirals.

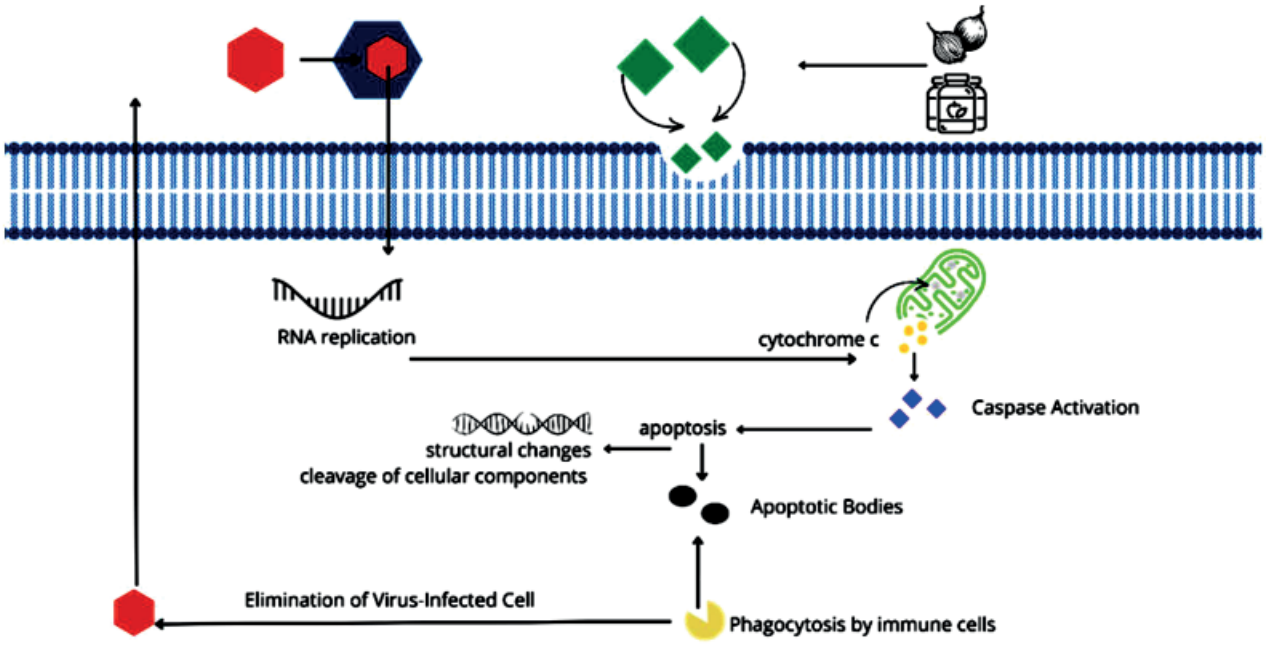


Fig. 3. **Flavonoids' potential in reducing viral spread through programmed cell death**

– *Reduced Antiviral Resistance*: The use of combination therapy with flavonoids and conventional antiviral drugs can reduce the likelihood of antiviral resistance. Viruses that develop resistance to one type of drug may still be vulnerable to inhibition by flavonoids, providing an alternative means of control.

– *Broad-Spectrum Antiviral Activity*: Flavonoids often exhibit broad-spectrum antiviral activity, meaning they can be effective against multiple types of viruses. This versatility is valuable when dealing with viral infections for which specific antiviral drugs may not be available.

– *Immunomodulation*: Flavonoids can modulate the immune response, helping to strike a balance between viral suppression and preventing excessive inflammation [65]. This can be especially important in cases where the immune response itself contributes to tissue damage and disease severity.

– *Reduction of Drug Toxicity*: Some conventional antiviral drugs can have side effects or toxicity concerns. Flavonoids, being natural compounds found in many foods, are generally considered safe and may help reduce the overall toxicity of antiviral treatments when used in combination.

– *Antioxidant and Anti-Inflammatory Effects*: Viral infections often induce oxidative stress and inflammation. Flavonoids' antioxidant and anti-inflammatory properties can help mitigate these effects, improving the overall health of the host and potentially reducing disease severity [66].

– *Support for the Immune System*: Flavonoids can support the immune system, enhancing its ability to combat viral infections. This can include the activation of immune cells, the regulation of cytokine production, and the reduction of immunosuppression induced by some viruses.

– *Potential Synergistic Effects*: In some cases, flavonoids and conventional antiviral agents may have synergistic effects, meaning their combined action is more effective than the sum of their individual effects. This synergy can lead to improved viral control.

– *Reduced Reliance on High Drug Doses*: Using flavonoids in combination with antiviral agents may allow for the use of lower doses of the conventional drugs. This can help reduce the risk of side effects associated with high drug doses.

The effectiveness of combination therapy with flavonoids and conventional antiviral agents may vary depending on the specific flavonoid compounds, the viral strain, and the stage of infection. Clinical studies and trials are necessary to determine the optimal combinations and dosages for specific viral infections. Additionally, healthcare professionals should be consulted when considering the use of such combinations to ensure safety and efficacy.

Conclusions

The antiviral activity of flavonoids involves multiple mechanisms:

Inhibition of Viral Entry: Flavonoids may interfere with viral attachment to host cells, preventing successful entry.

Disruption of Viral Envelope: Some flavonoids can destabilize viral envelopes, compromising the integrity of the viral structure.

Interference with Viral Replication: Flavonoids might target various stages of the viral replication cycle, inhibiting synthesis of viral components.

Modulation of Host Immune Response: Flavonoids may enhance the host immune system, aiding in the recognition and elimination of infected cells.

Antioxidant Effects: The antioxidant properties of flavonoids could contribute to their antiviral activity by reducing oxidative stress associated with viral infections.

Flavonoids such as quercetin, kaemferol, myricetin, catechin, and epigallocatechin gallate have been found to block the attachment of viruses [14, 45, 67, 68]. On the other hand, flavonoids including luteolin, apigenin, naringenin [69], hesperidin [70], and chrysoriol have been identified as inhibitors of viral replication. Certain combinations of these flavonoids, such as quercetin with luteolin or kaemferol with apigenin, have shown potential synergistic effects. However, the most effective combination of flavonoids will vary depending on the type of virus, the host cell, and other factors. Flavonoids also offer additional health benefits, including antioxidant, anti-inflammatory, and anti-cancer properties. Due to these properties, flavonoids hold promise as natural antiviral agents and may be considered for the development of antiviral drugs.

In conclusion, the diverse mechanisms by which flavonoids act against viruses make them a promising class of antiviral agents. Their ability to target different stages of the viral life cycle, coupled with potential immunomodulatory effects, highlights the potential of flavonoids in the development of novel antiviral therapies.

However, it's essential to note that further research and clinical studies are needed to fully understand their efficacy and safety in specific viral infections.

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REFERENCES

1. *Lee E., Kang G., Cho S.* Effect of flavonoids on human health: Old subjects but new challenges. *Recent Patents on Biotechnology*. 2007. 1(2), 139–150. https://doi.org/10.2174/187220807780809445
2. *Watson R. R., Preedy V. R., Zibad S.* (2018). Polyphenols: Mechanisms of action in human health and disease. In *Elsevier eBooks*. https://doi.org/10.1016/c2016-0-04277-8
3. *Kumar S., Pandey, A. K.* Chemistry and Biological Activities of Flavonoids: An Overview. *The Scientific World Journal*. 2013, 1–16. https://doi.org/10.1155/2013/162750
4. *Panche A., Diwan A. D. Chandra S.* Flavonoids: an overview. *Journal of Nutritional Science*, *5*. https://doi.org/10.1017/jns.2016.41
5. Dias M. C., Pinto D., Silva A. M. S. Plant flavonoids: chemical characteristics and biological activity. *Molecules* 2021, 26(17), 5377. https://doi.org/10.3390/molecules26175377
6. *Montenegro-Landívar M. F., Tapia-Quirós P., Vecino X., Reig M., Valderrama C., Granados M., Cortina J. L., Saurina, J.* Polyphenols and their potential role to fight viral diseases: An overview. *Science of the Total Environment*. 2021, 801, 149719. https://doi.org/10.3390/molecules26175377
7. *Mahmud A. R., Ema T. I., Siddiquee M. A., Shahriar A., Hossain A., Mosfeq-Ul-Hasan M., Rahman N., Islam R., Uddin M. R. Mizan, M. F. R.* Natural flavonols: actions, mechanisms, and potential therapeutic utility for various diseases. *Beni-Suef University Journal of Basic and Applied Science*. 2023, 12(1). https://doi.org/10.1186/s43088-023-00387-4
8. *Russo M., Moccia S., Spagnuolo C., Tedesco I., Russo G. L.* Roles of flavonoids against coronavirus infection. *Chemico-Biological Interactions*, 2020, 328, 109211. https://doi.org/10.1016/j.cbi.2020.109211
9. *Nair M., Kandaswami C., Mahajan S. D., Nair H. N., Chawda R., Shanahan T., Schwartz S.A.* Grape seed extract proanthocyanidins downregulate HIV- 1 entry coreceptors, CCR2b, CCR3 and CCR5 gene expression by normal peripheral blood mononuclear cells. *Biological Research*. 2002, 35(3–4). https://doi.org/10.4067/s0716-97602002000300016
10. *Zakaryan H., Arabyan E., Oo A. Zandi K.* Flavonoids: promising natural compounds against viral infections. *Archives of Virology*. 2017, 162(9), 2539–2551. https://doi.org/10.1007/s00705-017-3417-y
11. *Lalani S., & Poh, C. L.* Flavonoids as antiviral agents for enterovirus A71 (EV-A71). Viruses, 2020, 12(2), 184. https://doi.org/10.3390/v12020184
12. *Shahid, F., Noreen Ali R., Badshah S. L., Jamal S. B., Ullah R., Bari A., Mahmood H. M., Sohaib M. Ansari S. A.* Identification of Potential HCV Inhibitors Based on the Interaction of Epigallocatechin-3-Gallate with Viral Envelope Proteins. *Molecules*. 2021, *26*(5), 1257. https://doi.org/10.3390/molecules26051257
13. *Badshah S.L., Faisal S., Akhtar M., Jaremko M. Emwas A.* Antiviral activities of flavonoids. *Biomedicine & Pharmacotherapy*. 2021, 140, 111596. https://doi.org/10.1016/j.biopha.2021.111596
14. *Wang, Y. Li Q., Zheng X., Lu J., Liang Y.* Antiviral Effects of Green Tea EGCG and Its Potential Application against COVID-19. *Molecules*. 2021, 26(13), 3962. https://doi.org/10.3390/molecules26133962
15. *Breitinger H., Ali N. K. M., Sticht H., Breitinger H..* Inhibition of SARS COV envelope protein by flavonoids and classical viroporin inhibitors. *Frontiers in Microbiology*. 2021, 12. https://doi.org/10.3389/fmicb.2021.692423
16. *Mir A., Ismatullah H., Rauf S., Niazi U. H.* Identification of bioflavonoid as fusion inhibitor of dengue virus using molecular docking approach. *Informatics in Medicine Unlocked*, 2016, 3, 1–6. https://doi.org/10.1016/j.imu.2016.06.001
17. *Sharma M., Bansal A., Sethi S., Sharma N.* Potential alphavirus inhibitors from phytocompounds — molecular docking and dynamics based approach. *Innovative Biosystems and Bioengineering*. 2023, 7(3), 21–31. https://doi.org/10.20535/ibb.2023.7.3.285245
18. *Wu W., Dong L., Shen X., Li F., Fang Y., Li K., Xun T., Yang G., Yang J., Liu S., He J.* New influenza A Virus Entry Inhibitors Derived from the Viral Fusion Peptides. *PLOS ONE*. 2015, 10(9), e0138426. https://doi.org/10.1371/journal.pone.0138426
19. *Wang L., Song J., Liu A., Xiao B., Li S., Zhang W., Lü Y., Du G.* Research progress of the antiviral bioactivities of natural flavonoids. *Natural Products and Bioprospecting*. 2020, 10(5), 271–283. https://doi.org/10.1007/s13659-020-00257-x
20. *Wu W., L, R., Li X., He J., Jiang S., Liu S., Yang J.* Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry.

Viruses. 2015, 8(1), 6. https://doi.org/10.3390/v8010006
21. *Wang Q., Wang H., Jia Y., Ding H., Zhang L., Pā, H*. Luteolin reduces migration of human glioblastoma cell lines via inhibition of the p-IGF-1R/PI3K/AKT/mTOR signaling pathway. *Oncology Letter*. 2017, 14(3), 3545–3551. https://doi.org/10.3892/ol.2017.6643
22. *Mehrbod P., Hudy D., Shyntum D.Y., Markowski J., Łos M., Ghavami S.* Quercetin as a natural therapeutic candidate for the treatment of influenza virus. *Biomolecules*. 2020, 11(1), 10. https://doi.org/10.3390/biom11010010
23. *Kim M., Kim S., Lee H. W., Shin J. S., Kim P., Jung Y., Jeong H., Hyun J. Lee C*. Inhibition of influenza virus internalization by (–)-epigallocatechin-3-gallate. *Antiviral Research*. 2013, 100(2), 460–472. https://doi.org/10.1016/j.antiviral.2013.08.002
24. *Moghaddam E., Teoh B., Sam S., Lani R., Hassandarvish P., Chik Z., Yueh A., Abu Bakar S., Zandi K*. Baicalin, a metabolite of baicalein with antiviral activity against dengue virus. *Scientific Reports*. 2014, 4(1). https://doi.org/10.1038/srep05452
25. *Yoneyama S., Kawai K., Tsuno N. H., Okaji Y., Asakage M., Tsuchiya T., Yamada J., Sunami E., Osada T., Kitayama J., Takahashi K., Nagawa H*. Epigallocatechin gallate affects human dendritic cell differentiation and maturation. *The Journal of Allergy and Clinical Immunology*, 2008Б 121(1), 209–214. https://doi.org/10.1016/j.jaci.2007.08.026
26. *Li K., Liang Y., Cheng A. S., Wang Q., Liu Y., Wei H., Chang-Zheng, Z., Wan X*. Antiviral Properties of Baicalin: a Concise Review. *Revista Brasileira De Farmacognosia*. 2021, 31(4), 408–419. https://doi.org/10.1007/s43450-021-00182-1
27. *Tao J., Hu Q., Yang J., Li R., Li X., Lu C., Chen C., Wang L., Shattock R. J., Ben K.. In vitro* anti-HIV and -HSV activity and safety of sodium rutin sulfate as a microbicide candidate. *Antiviral Research*. 2007, 75(3), 227–233. https://doi.org/10.1016/j.antiviral.2007.03.008
28. *Lü, P. Zhang T., Ren Y., Rao H., Lei J., Zhao G., Wang M., Gong D., Cao Z*. A literature review on the antiviral mechanism of luteolin. *Natural Product Communications*, 2023, *18*(4), 1934578X2311715. https://doi.org/10.1177/1934578x231171521
29. *Joo Y., Lee Y., Lim Y., Jeon H., Lee I., Cho Y., Hong S. I., Kim E. H., Choi S. H., Kim J., Kang S. C., Seo Y*. Anti-influenza A virus activity by Agrimonia pilosa and Galla rhois extract mixture. *Biomedicine & Pharmacotherapy*. 2022, 155, 113773. https://doi.org/10.1016/j.biopha.2022.113773
30. *Xu X., Jin M., Shao Q., Gao Y., Hong L*. Apigenin suppresses influenza A virus-induced RIG-I activation and viral replication. *Journal of Medical Virology*. 2020, 92(12), 3057–3066. https://doi.org/10.1002/jmv.26403
31. *Taheri Y., Sharifi-Rad J., Antika G., Yılmaz Y. B., Tumer T. B., Abuhamdah S., Chandra S., Saklani S., Kılıç C. S., Sestito S., DaştanS. D., Kumar M., Alshehri M. M., Rapposelli S., Cruz-Martins N., Cho W. C.*. Paving Luteolin Therapeutic potentialities and Agro-Food-Pharma applications: Emphasis on *in vivo* pharmacological effects and bioavailability traits. *Oxidative Medicine and Cellular Longevity*. 2021, 1–20. https://doi.org/10.1155/2021/1987588
32. *Lipson P*. Flavonoid-associated direct loss of rotavirus antigen/antigen activity in cell-free suspension. *Vadose Zone Journal*. 2013, 2(1), 10–24. https://doi.org/10.7275/r52b8vzj
33. *Shakoor H., Feehan J., Apostolopoulos V., Platat C., Dhaheri A. S. A., Ali H. I., Ismail L. C., Bosevski M., Stojanovska L*. Immunomodulatory effects of dietary polyphenols. *NutrientsЮ*. 2021, S13(3), 728. https://doi.org/10.3390/nu13030728
34. *Pérez-Cano F. J., Castellote C*. Flavonoids, inflammation and immune system. *Nutrients*. 2016, 8(10), 659. https://doi.org/10.3390/nu8100659
35. *Venigalla M., Gyengési E., Münch G*. Curcumin and Apigenin — novel and promising therapeutics against chronic neuroinflammation in Alzheimer's disease. *Neural Regeneration Research* 2015, 10(8), 1181. https://doi.org/10.4103/1673-5374.162686
36. *Wang S., Li Z., Ma Y., Liu Y., Lin C., Li S., Zhan J., Ho C*. Immunomodulatory effects of green tea polyphenols. *Molecules*. 2021, 26(12), 3755. https://doi.org/10.3390/molecules26123755
37. *Li Y., Song K., Zhang H., Yuan M., An N., Wei Y., Wang L., Sun Y., Xing Y., Gao Y. Anti*-inflammatory and immunomodulatory effects of baicalin in cerebrovascular and neurological disorders. *Brain Research Bulletin*. 2020, V.164, 314–324. https://doi.org/10.1016/j.brainresbull.2020.08.016
38. *Liao H., YeJ. Gao L., Liu Y*. The main bioactive compounds of Scutellaria baicalensis Georgi. for alleviation of inflammatory cytokines: A comprehensive review. *Biomedicine & Pharmacotherapy*. 2021, 133, 110917. https://doi.org/10.1016/j.biopha.2020.110917
39. Poronnik O. O. (2021). Obtaining of plant tissue culture Scutellaria baicalensis Georgi. and its biochemical analysis. *Biotechnologia Acta*, *14*(6), 53–58. https://doi.org/10.15407/biotech14.06.0053
40. *Ginwala, R., Bhavsar R., Chigbu D. G. I., Jain P., Khan Z. K*. Potential Role of Flavonoids in Treating Chronic Inflammatory Diseases with a Special Focus on the Anti-Inflammatory Activity of Apigenin.

Antioxidants. 2019, 8(2), 35. https://doi.org/10.3390/antiox8020035
41. *García–Lafuente A., Guillamón E., Villares A., Rostagno M. A., Martínéz J. A.*. Flavonoids as anti-inflammatory agents: implications in cancer and cardiovascular disease. *Inflammation Research*. 2009, 58(9), 537–552. https://doi.org/10.1007/s00011-009-0037-3
42. *Rathee P., Chaudhary H., Rathee S., Rathee D., Kumar V., Kohli K.*. Mechanism of action of flavonoids as anti-inflammatory agents: a review. *Inflammation and Allergy — Drug Targets*. 2009, 8(3), 229–235. https://doi.org/10.2174/187152809788681029
43. *Ahn H. I., Jang H., Kwon O., Kim J., Oh J., Kim S., Oh S., Han S., Ahn K. H., Park J. W.* Quercetin Attenuates the Production of Pro-Inflammatory Cytokines in H292 Human Lung Epithelial Cells Infected with Pseudomonas aeruginosa by Modulating ExoS Production. *Journal of Microbiology and Biotechnology*. 2023, 33(4), 430–440. https://doi.org/10.4014/jmb.2208.08034
44. *Sun H., Li J., Qian W., Yin M., Yin H., Huang G.* Quercetin suppresses inflammatory cytokine production in rheumatoid arthritis fibroblastlike synoviocytes. *Experimental and Therapeutic Medicine*. 2021, 22(5). https://doi.org/10.3892/etm.2021.10695
45. *David A. V. A., Arulmoli R., Parasuraman S.* Overviews of biological importance of quercetin: A bioactive flavonoid. *Pharmacognosy Reviews*. 2016, 10(20), 84. https://doi.org/10.4103/0973-7847.194044
46. *Yao C., Xi C., Hu K., Gao W., Cai X., Qin J., Lv S., Du C., Wei Y.* Inhibition of enterovirus 71 replication and viral 3C protease by quercetin. *Virology Journal*. 2018, 15(1). https://doi.org/10.1186/s12985-018-1023-6
47. *Li Z., Cao H., Cheng Y., Zhang X., Zeng W., Sun Y., Chen S., He Q., Han H.* Inhibition of porcine epidemic diarrhea virus replication and viral 3C-Like protease by quercetin. *International Journal of Molecular Sciences*. 2020, 21(21), 8095. https://doi.org/10.3390/ijms21218095
48. *Sugamoto K., Tanaka Y., Saito A., Goto Y., Nakayama T., Okabayashi T., Kunitake H., Morishita K.* Highly polymerized proanthocyanidins (PAC) components from blueberry leaf and stem significantly inhibit SARS-CoV-2 infection via inhibition of ACE2 and viral 3CLpro enzymes. *Biochemical and Biophysical Research Communications*. 2022, 615, 56–62. https://doi.org/10.1016/j.bbrc.2022.04.072
49. *Jo S., Kim S., Shin D., Kim M. S.* Inhibition of SARS-CoV 3CL protease by flavonoids. *Journal of Enzyme Inhibition and Medicinal Chemistry*. 2019, 35(1), 145–151. https://doi.org/10.1080/14756366.2019.1690480
50. *Li W., Xu C., Hao C., Zhang Y., Wang Z., Wang S., Wang W.* Inhibition of herpes simplex virus by myricetin through targeting viral gD protein and cellular EGFR/PI3K/Akt pathway. *Antiviral Research*. 2020, 177, 104714. https://doi.org/10.1016/j.antiviral.2020.104714
51. *Agraharam G., Girigoswami A., Girigoswami K.* Myricetin: a Multifunctional Flavonol in Biomedicine. *Current Pharmacology Reports*. 2022, 8(1), 48–61. https://doi.org/10.1007/s40495-021-00269-2
52. Silva J. H. C. E., Souza J. T., Schitine C. *De Freitas Santos Júnior, A., Bastos, E. M. S., & Costa, S. L.*. *Pharmacological Potential of Flavonoids against* Neurotropic Viruses. *Pharmaceuticals*. 2022, 15(9), 1149. https://doi.org/10.3390/ph15091149
53. *Kaul R., Paul P., Kumar S., Büsselberg D., Dwivedi V. D., Châari A.* Promising Antiviral Activities of Natural Flavonoids against SARS-CoV-2 Targets: Systematic Review. *International Journal of Molecular Sciences*. 2021, 22(20), 11069. https://doi.org/10.3390/ijms222011069
54. *Rehman S. U., Shafqat F., Fatima B., Nawaz M., Niaz K.*. Flavonoids and other polyphenols against SARS-CoV-2. In *Elsevier eBooks*. 2023, (pp. 83–123). https://doi.org/10.1016/b978-0-323-95047-3.00014-9
55. *Ninfali P., Antonelli A., Magnani M., Scarpa E. S.* Antiviral properties of flavonoids and delivery strategies. *Nutrients*. 2020, 12(9), 2534. https://doi.org/10.3390/nu12092534
56. *Cataneo A. H. D., Ávila E. P., De Oliveira Mendes L. A., De Oliveira V. G., Ferraz C. R., De Almeida M. V., Frabasile S., Santos C. N. D. D., Verri W. A., Bordignon J., Wowk P. F.* Flavonoids as Molecules With Anti-Zika virus Activity. *Frontiers in Microbiology*. 2021, 12. https://doi.org/10.3389/fmicb.2021.710359
57. *Corona A., Wycisk K., Talarico C., Manelfi C., Milia J., Cannalire R., Esposito F., Gribbon P., Zaliani A., Iaconis D., Beccari A. R., Summa V., Nowotny M., Tramontano E.* Natural Compounds Inhibit SARS-CoV-2 nsp13 Unwinding and ATPase Enzyme Activities. *ACS Pharmacology & Translational Science*. 2022, 5(4), 226–239. https://doi.org/10.1021/acsptsci.1c00253
58. Inhibition of human T cell leukemia virus by the plant flavonoid baicalin (7-Glucuronic acid, 5, 6-Dihydroxyflavone) on JSTOR. (n.d.). *www.jstor.org*. http://www.jstor.org/stable/30112044
59. *Pietta P.* Flavonoids as antioxidants. *Journal of Natural Products*, *63*(7). 2000, 1035–1042. https://doi.org/10.1021/np9904509
60. *Crozier A., Burns J. M., Aziz A. A., Stewart A., Rabiasz H. S., Jenkins G. I., Edwards C., Lean M. E. J.* Antioxidant flavonols from fruits, vegetables and beverages:

measurements and bioavailability. *Biological Research*. 2000, 33(2). https://doi.org/10.4067/s0716-97602000000200007
61. *Ganeshpurkar A., Saluja A. K.* The pharmacological potential of Rutin. *Saudi Pharmaceutical Journal*. 2017, 25(2), 149–164. https://doi.org/10.1016/j.jsps.2016.04.025
62. *Ciumărnean L., Milaciu M. V., Runcan O., Vesa Ş. C., Răchişan A. L., Negrean V., Perné M., Donca V., Alexescu T., Para I., Dogaru G.* The effects of flavonoids in cardiovascular diseases. *Molecules*. 2020, 25(18), 4320. https://doi.org/10.3390/molecules25184320
63. *Vetrivel P., Kim S. W., Saralamma V. V. G., Ha S. E., Kim E. H., Min T. S., Kim G. S.* Function of flavonoids on different types of programmed cell death and its mechanism: a review. *Journal of Nanjing Medical University*. 2019, 33(6), 363. https://doi.org/10.7555/jbr.33.20180126
64. *Bryan-Marrugo O. L., Ramos-Jiménez J., Barrera-Saldaña H. A., Rojas-MartíNez A., Vidaltamayo R., Rivas-Estilla A. M.* History and progress of antiviral drugs: From acyclovir to direct-acting antiviral agents (DAAs) for Hepatitis C. *Medicina Universitaria*. 2015, 17(68), 165–174. https://doi.org/10.1016/j.rmu.2015.05.003
65. *Hosseinzade A., Sadeghi O., Biregani A. N., Soukhtehzari S., Brandt G., Esmaillzadeh A.* Immunomodulatory effects of flavonoids: possible induction of T CD4+ regulatory cells through suppression of MTOR pathway signaling activity. *Frontiers in Immunology*. 2019, 10. https://doi.org/10.3389/fimmu.2019.00051
66. *Inflammaging*. Cell Guidance Systems. 2023, May 8. https://www.cellgs.com/blog/inflammaging-how-our-cytokines-age-us.html
67. *Peng S., Fang C., He H., Song X., Zhao X., Zou Y., Li L., Jia R., Yin Z.* Myricetin exerts its antiviral activity against infectious bronchitis virus by inhibiting the deubiquitinating activity of papain-like protease. *Poultry Science*. 2022, 101(3), 101626. https://doi.org/10.1016/j.psj.2021.101626
68. *Wang G., Wang Y., Yao L., Gu W., Zhao S., Shen Z., Lin Z., Liu W., Yan T.* Pharmacological activity of Quercetin: an updated review. *Evidence-based Complementary and Alternative Medicine*, *2022*, 1–12. https://doi.org/10.1155/2022/3997190
69. *Tutunchi H., Naeini F., Ostadrahimi A., Hosseinzadeh-Attar M. J.* Naringenin, a flavanone with antiviral and anti-inflammatory effects: A promising treatment strategy against COVID-19. *Phytotherapy Research*. 2022, 34(12), 3137–3147. https://doi.org/10.1002/ptr.6781
70. *Zalpoor H., Bakhtiyari M., Shapourian H., Rostampour P., Tavakol C., Nabi-Afjadi M.* Hesperetin as an anti-SARS-CoV-2 agent can inhibit COVID-19-associated cancer progression by suppressing intracellular signaling pathways. *Inflammopharmacology*. 2022, 30(5), 1533–1539. https://doi.org/10.1007/s10787-022-01054-3

МЕХАНІЗМИ ПРОТИВІРУСНОЇ ДІЇ ФЛАВОНІДІВ

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У статті розглядаються багатогранні механізми, що лежать в основі противірусної активності флавоноїдів — сполук, широко поширених у царині рослин.

Мета. Огляд даних літератури щодо механізму противірусної дії флавоноїдів.

Методи. Публікації відбиралися на основі баз даних PubMed (https://pubmed.ncbi.nlm.nih.gov/), опублікованих у 2015–2023 роках. Вони містять інформацію про механізми противірусної дії флавоноїдів.

Результати. Починаючи з огляду структур флавоноїдів, у документі обговорюється складна взаємодія між флавоноїдами та різними стадіями життєвого циклу вірусу. Спираючись на комплексний аналіз досліджень *in vitro* та *in vivo*, висвітлюються різноманітні способи, якими флавоноїди пригнічують проникнення, розмноження та вивільнення вірусу. Залежно від їхніх антивірусних механізмів, флавоноїди можуть слугувати профілактичними інгібіторами, терапевтичними інгібіторами або непрямими інгібіторами, впливаючи на імунну систему.

Висновок. Синтезована інформація не тільки сприяє розвитку антивірусних досліджень, але й закладає основу для розроблення нових терапевтичних методів подолання вірусних інфекцій.

Ключові слова: флавоноїди; противірусна активність; вірусна інфекція; біоактивні сполуки; взаємодія хазяїн-збудник.