

## REVIEW ARTICLE

# Natural compounds as antivirals against influenza, SARS-CoV-2, and other respiratory viruses: A therapeutic perspective

**Shihuan Ding<sup>1,2†</sup>**, **Jiyan Cui<sup>1,3†</sup>**, **Xin Zhao<sup>1,3</sup>**, **Yiru Hou<sup>1,3</sup>**, **Xiaowei Tian<sup>3\*</sup>**, and **Xianfeng Hui<sup>1,2\*</sup>**

<sup>1</sup>Department of Immunology, School of Basic Medical Sciences, Henan Medical University, Xinxiang, Henan, China

<sup>2</sup>Unit of Metabolic Immunology Team, Xinxiang Engineering Technology Research Center of Immune Checkpoint Drug for Liver-Intestinal Tumors, Henan Medical University, Xinxiang, Henan, China

<sup>3</sup>Department of Pathogenic Biology, School of Basic Medical Sciences, Henan Medical University, Xinxiang, Henan, China

(This article belongs to the *Special Issue: Natural Products in the Prevention and Treatment of Microbiological, Immunological, and Infectious Diseases: Integrating Wild Edible Plants and Beyond*)

<sup>†</sup>These authors contributed equally to this work.

### \*Corresponding authors:

Xiaowei Tian  
(tianxw2020@163.com)  
Xianfeng Hui  
(xianfenghui@163.com)

**Citation:** Ding S, Cui J, Zhao X, Hou Y, Tian X, Hui X. Natural compounds as antivirals against influenza, SARS-CoV-2, and other respiratory viruses: A therapeutic perspective. *Microbes & Immunity*. 2026;3(2):025350092.  
doi: 10.36922/MI025350092

**Received:** August 29, 2025

**Revised:** November 14, 2025

**Accepted:** November 27, 2025

**Published online:** January 7, 2026

**Copyright:** © 2026 Author(s). This is an Open-Access article distributed under the terms of the Creative Commons Attribution License, permitting distribution, and reproduction in any medium, provided the original work is properly cited.

**Publisher's Note:** AccScience Publishing remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

## Abstract

Respiratory viruses—including influenza, severe acute respiratory syndrome coronavirus 2, and respiratory syncytial virus—remain major global health challenges, contributing to substantial morbidity, mortality, and socioeconomic burden. Although vaccines and antiviral agents, such as oseltamivir, ribavirin, and Paxlovid (nirmatrelvir/ritonavir), have advanced disease management, their effectiveness is often compromised by the rapid mutation of viruses, the emergence of drug-resistant strains, and adverse toxicities. These limitations underscore the urgent need for novel therapeutic strategies. Natural products have attracted growing attention as promising antiviral candidates due to their remarkable structural diversity, multi-target mechanisms, and generally favorable safety profiles. They can inhibit viral entry, replication, and assembly while simultaneously modulating host immune and inflammatory responses. In addition, natural compounds may act synergistically with existing antivirals, enhancing efficacy and reducing the risk of resistance. Despite ongoing challenges in pharmacokinetics, standardization, and clinical validation, natural products represent a compelling frontier for the development of broad-spectrum, safe, and effective antiviral therapeutics.

**Keywords:** Natural products; Respiratory viruses; Influenza; Severe acute respiratory syndrome coronavirus 2; Antiviral therapy

## 1. Introduction

Respiratory viral infections represent a major global cause of acute respiratory illness, hospitalizations, and mortality, posing a serious threat to human health and imposing a substantial burden on healthcare systems. According to data from the World Health Organization,<sup>1</sup> seasonal influenza alone accounts for an estimated 3–5 million severe

cases and 290,000–650,000 deaths annually.<sup>2</sup> The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) at the end of 2019 led to a rapid and widespread pandemic (coronavirus disease 2019 [COVID-19]), resulting in over 700 million confirmed cases and millions of deaths worldwide, with profound repercussions for public health and the global economy.<sup>3</sup> In addition to influenza and SARS-CoV-2, other respiratory viruses such as respiratory syncytial virus (RSV), human adenovirus (HAdV), parainfluenza virus, and human metapneumovirus are also prevalent, particularly among children, the elderly, and immunocompromised individuals. These pathogens are characterized by high transmissibility and the capacity to cause recurrent infections.

Despite notable progress in vaccine development and antiviral drug discovery in recent years, current antiviral therapies continue to face substantial challenges. Small-molecule agents targeting viral enzymes or structural proteins—such as amantadine, oseltamivir, ribavirin, and Paxlovid (nirmatrelvir/ritonavir)—are often undermined by the rapid emergence of resistance mutations.<sup>4</sup> This phenomenon is particularly evident in influenza and other RNA viruses, where high genetic variability facilitates the selection of escape variants; for example, according to the Centers for Disease Control and Prevention,<sup>5</sup> resistance to amantadine in circulating influenza A strains increased from 0.4% in 1994–1995 to over 12% in 2003–2004 and has since become nearly universal.

Likewise, oseltamivir resistance has been reported in up to 2% of treated patients and is associated with a higher risk of clinical complications such as pneumonia.<sup>6</sup> Moreover, several antivirals are associated with significant adverse effects, including neurotoxicity, hepatotoxicity, nephrotoxicity, and contraindications during pregnancy, limiting their clinical applicability.<sup>7</sup> For instance, oseltamivir therapy commonly causes nausea (approximately 10%) and vomiting (approximately 9%) in adults,<sup>8</sup> while high-dose ribavirin has been shown to induce anemia (odds ratio: 3.0; 99% confidence interval = 1.5–6.1) and hypomagnesemia (odds ratio: 21.0; 99% confidence interval = 5.8–73) in SARS-CoV-2 patients.<sup>9</sup> Most existing agents also exhibit narrow therapeutic windows and target a single viral or host factor, rendering them insufficient to address the multifaceted and dynamic pathogenesis of viral infections. This limitation is especially pronounced in severe cases involving concurrent viral replication, immune dysregulation, and tissue damage, where more comprehensive and stage-adaptive therapeutic strategies are urgently needed.

Against this backdrop, natural compounds—a term encompassing both isolated bioactive molecules and

complex extracts derived from plants, microorganisms, or marine organisms—have emerged as a promising frontier in the development of next-generation antiviral drugs. Positioned at the intersection of traditional medicine and modern pharmacology, these agents are characterized by remarkable structural diversity, broad-spectrum activity, low toxicity, and potent immunomodulatory properties. They can intervene at multiple stages of the viral life cycle—including attachment, membrane fusion, replication, assembly, and release—while also modulating host responses such as inflammation, antiviral immunity, and oxidative stress. Moreover, natural compounds may act synergistically with existing antiviral drugs to enhance efficacy and reduce the emergence of resistance, providing strategic advantages in the management of both established viral infections and emergent pandemics.

In this context, this review aims to explore the therapeutic potential of natural compounds against the influenza virus, SARS-CoV-2, and other major respiratory viruses. It provides a systematic overview of the biological characteristics and pathogenic mechanisms of these viruses, identifies key antiviral targets and molecular pathways modulated by natural products, and highlights representative compounds with experimentally validated antiviral activities. It also examines the principal challenges hindering the clinical translation of these natural agents and discusses how emerging technologies such as high-throughput screening, multi-omics approaches, and computational modeling are advancing compound discovery, mechanistic elucidation, and drug development. Through this comprehensive analysis, we aim to inform future strategies for the prevention and treatment of respiratory viral infections and support the development of natural products into broad-spectrum, efficacious, and low-toxicity antiviral therapeutics.

## 2. Overview and pathogenic mechanisms of major respiratory viruses

Respiratory viral infections are among the leading causes of acute respiratory illness worldwide, particularly affecting vulnerable populations such as infants, the elderly, and individuals with underlying chronic conditions. In these groups, infections often lead to severe pulmonary complications and increased mortality. Among the diverse array of respiratory viruses, influenza viruses, novel coronaviruses, RSV, HAdVs, and human parainfluenza viruses (HPIVs) represent the most prevalent and clinically significant pathogens. Despite their differences in genomic structure and replication strategies, these viruses share several common features: a high degree of host dependency for replication, robust mechanisms for evading or modulating host immune responses, and

efficient transmission dynamics. This section provides a comprehensive examination of the structural and biological properties of these major respiratory viruses, their mechanisms of pathogenesis, and the host immune responses they elicit, with the aim of elucidating the core determinants of viral virulence and disease progression.

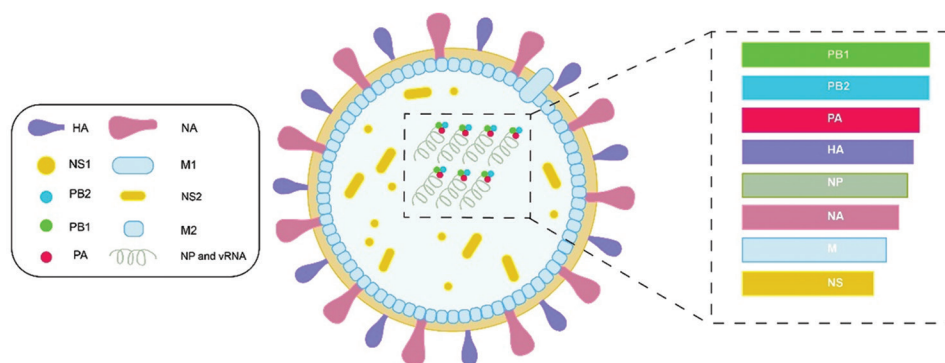
### 2.1. Influenza virus

Influenza viruses, members of the Orthomyxoviridae family, possess a segmented, single-stranded, negative-sense RNA genome comprising eight distinct segments.<sup>10,11</sup> These segments encode both structural and non-structural proteins critical for viral replication and pathogenesis, including hemagglutinin (HA), neuraminidase (NA), nucleoprotein (NP), and the RNA-dependent RNA polymerase (RdRp) complex—comprising polymerase basic (PB)-1, PB2, and polymerase acidic proteins<sup>10,11</sup> (Figure 1). The HA protein facilitates viral entry by specifically binding to sialic acid residues on the surface of host epithelial cells, initiating attachment and membrane fusion.<sup>12</sup> In contrast, NA plays a crucial role during viral egress, cleaving sialic acid residues from the host cell surface to enable efficient release and dissemination of progeny virions.<sup>13</sup> Due to their indispensable functions in viral attachment and release, HA and NA have long been established as major pharmacological targets. NA inhibitors such as oseltamivir and zanamivir, as well as emerging HA fusion-blocking agents derived from flavonoids and polyphenols, exemplify how interference with these surface glycoproteins can effectively suppress viral propagation.

Upon entry into the host cell, the viral ribonucleoprotein complexes (vRNPs) engage with host nuclear factors and

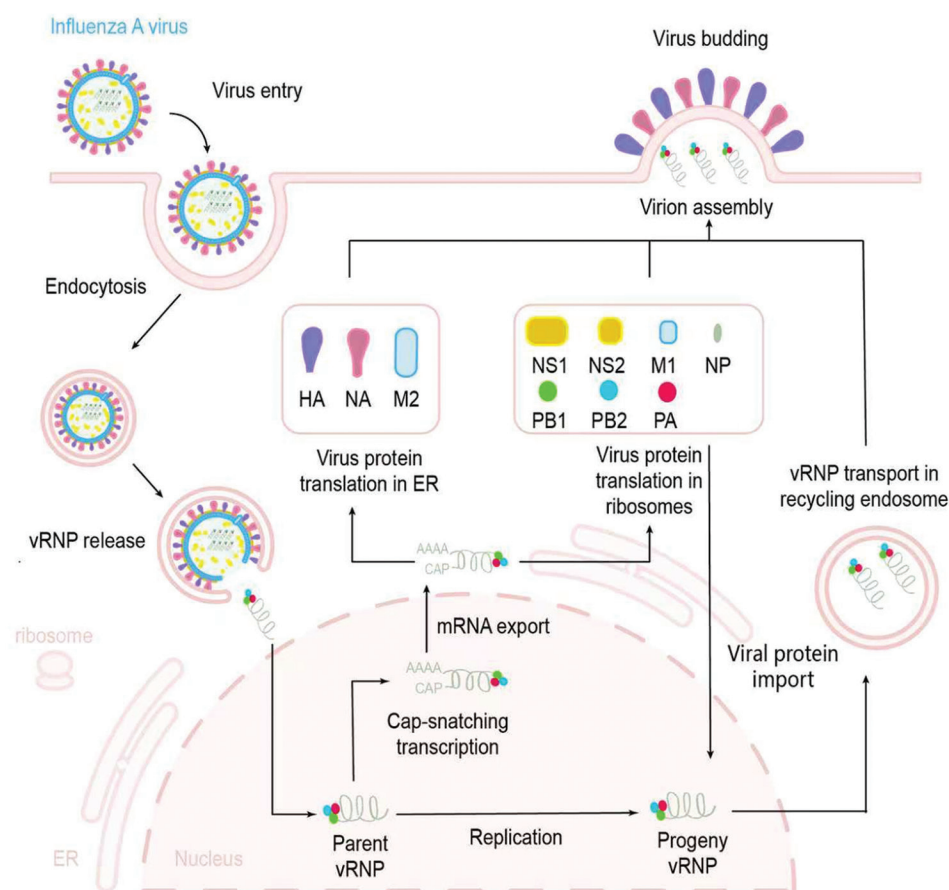
are subsequently transported into the nucleus. Within the nuclear compartment, the virus initiates mRNA transcription by hijacking the host's transcriptional machinery through a mechanism known as cap-snatching. The viral RdRp complex plays a central role in this process<sup>14</sup> (Figure 2). However, due to intrinsic functional limitations, the virus relies heavily on various host nuclear proteins, including splicing factors and nuclear export machinery, to complete its replication cycle. These host-dependent pathways represent promising targets for antiviral drug development, particularly for strategies aimed at disrupting viral transcription, translation, and intranuclear replication. Recent studies have revealed that several natural products—such as alkaloids, terpenoids, and phenolic acids—can inhibit RdRp activity or interfere with the interaction between vRNPs and host cofactors, thereby impeding viral genome replication and mRNA synthesis. These findings highlight the potential of multi-target natural agents to complement or overcome the limitations of single-enzyme inhibitors.

Concurrently, host cells initiate antiviral defenses upon recognizing viral RNA through pattern recognition receptors such as retinoic acid-inducible gene I (RIG-I) and toll-like receptor 7 (TLR7).<sup>15</sup> Activation of these sensors leads to the induction of type I interferon (IFN) signaling and the expression of a broad array of antiviral effectors. Nevertheless, influenza viruses have evolved sophisticated immune evasion strategies, primarily mediated by the influenza-specific non-structural protein 1 (NS1). NS1 interacts with the E3 ubiquitin ligase, tripartite motif-containing 25 (TRIM25), preventing the ubiquitination and activation of RIG-I, thereby suppressing IFN- $\beta$  production.<sup>16</sup> In addition, NS1 binds to



**Figure 1.** Structural diagram of the influenza virus. The figure illustrates the structural organization of the influenza virus. The viral envelope contains two major surface glycoproteins—HA and NA—responsible for mediating host cell binding and viral release. Embedded within the membrane is the ion channel protein M2, which regulates proton transport during viral uncoating and maturation. Beneath the lipid bilayer lies the M1, which provides structural support and maintains virion integrity. Inside the virion, the segmented vRNA is coated with NPs, forming the genetic core essential for replication and transcription. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc., United States of America.

Abbreviations: HA: Hemagglutinin; NA: Neuraminidase; NP: Nucleoprotein; NS: Non-structural protein; M: Matrix protein; PA: Polymerase acidic; PB: Polymerase basic; vRNA: Viral RNA.



**Figure 2.** The lifecycle and main structural components of the influenza A virus. The virus binds to host receptors via HA and enters cells via endocytosis. Acidification of the endosome activates the M2 ion channel, allowing proton influx and vRNP release into the cytoplasm. vRNPs are transported into the nucleus for RNA transcription and replication through a cap-snatching mechanism. Viral mRNAs are exported for translation: HA, NA, and M2 are synthesized in the endoplasmic reticulum, whereas internal proteins (e.g., NS1, NS2, M1, NP, PB1, PB2, and PA) are produced in ribosomes. Newly formed vRNPs and viral proteins assemble at the plasma membrane, and mature virions bud from the cell to complete the replication cycle. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc., United States of America.

Abbreviations: HA: Hemagglutinin; NA: Neuraminidase; NP: Nucleoprotein; NS: Non-structural protein; M: Matrix protein; PA: Polymerase acidic; PB: Polymerase basic; vRNP: Viral ribonucleoprotein.

the host cleavage and polyadenylation specificity factor 30 (CPSF30), inhibiting host mRNA processing and reducing the expression of antiviral genes.<sup>17</sup>

Another key immune antagonist is the PB1-F2 protein, which targets host mitochondria to disrupt mitochondrial antiviral signaling (MAVS)-mediated pathways, further dampening innate antiviral responses.<sup>18</sup> PB1-F2 also contributes to the activation of the NLR family pyrin domain-containing 3 (NLRP3) inflammasome, enhancing local inflammatory responses that, paradoxically, may facilitate viral replication by promoting tissue damage and cellular turnover.<sup>19</sup> Targeting these viral proteins, which modulate host immunity, has thus become an emerging therapeutic strategy. Compounds capable of restoring IFN signaling or inhibiting the NS1–TRIM25 interactions, such as polysaccharides, lignans, and plant-

derived flavones, have shown immunomodulatory and antiviral activities, suggesting a dual mechanism of viral suppression and host defense reinforcement. Through this multifaceted interplay between immune suppression and inflammatory modulation, influenza viruses achieve a finely tuned balance between immune evasion and replication efficiency, thereby enhancing their pathogenic potential and transmission fitness.

The adaptive capacity of influenza viruses is exemplified by the high variability of their surface antigens, particularly HA and NA.<sup>20</sup> Through antigenic drift and antigenic shift, influenza viruses undergo rapid genetic changes that enable them to evade host immune surveillance.<sup>20</sup> Antigenic drift arises from point mutations within the viral genome, whereas antigenic shift results from reassortment events between distinct influenza strains.<sup>20</sup> These antigenic



alterations not only facilitate interspecies transmission but also pose significant challenges to the annual design of influenza vaccines.<sup>21</sup> Moreover, they provide the molecular basis for both seasonal epidemics and the emergence of global pandemics.<sup>20</sup> The continuous antigenic evolution of HA and NA underscores the importance of developing broad-spectrum antivirals that act on conserved viral enzymes or host-dependent pathways. Natural products, characterized by their structural diversity and multi-target interactions, are particularly well-suited for this purpose, offering a complementary pharmacological approach to conventional single-target therapies.

## 2.2. SARS-CoV-2

SARS-CoV-2, a member of the *Betacoronavirus* genus within the Coronaviridae family, is an enveloped, positive-sense single-stranded RNA virus with a genome of approximately 29.9 kb.<sup>22</sup> It encodes multiple structural proteins—including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins—as well as 16 non-structural proteins (NSP1–NSP16, specific to SARS-CoV-2) and a series of accessory proteins such as open reading frame (ORF)-3A, ORF6, ORF7A, and ORF9B.<sup>22</sup> These viral components collectively orchestrate the replication cycle and modulate host–virus interactions at various stages of infection<sup>22</sup> (Figure 3).

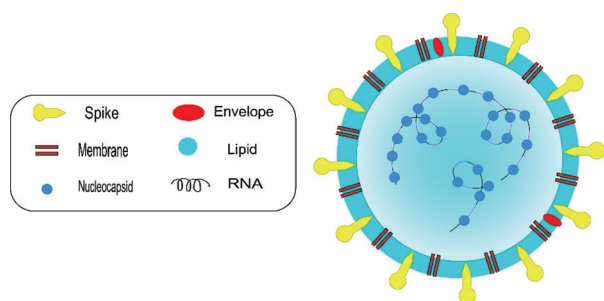
The S protein of SARS-CoV-2 is the critical mediator of viral entry into host cells and consists of two functional subunits: S1 and S2.<sup>23</sup> The S1 subunit is responsible for recognizing and binding to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell surface, whereas the S2 subunit contains the fusion peptide and transmembrane domain, facilitating the fusion of viral and cellular membranes.<sup>23</sup> Viral entry depends on the

proteolytic activation of the S protein by host cell surface serine proteases such as transmembrane serine protease 2 (TMPRSS2), or by endosomal cathepsin L.<sup>23</sup> Upon cleavage, the S2 fusion peptide is exposed and inserts into the host membrane, initiating membrane fusion and enabling the release of viral RNA into the cytoplasm.<sup>23</sup> Since the S protein and its associated host proteases are indispensable for viral entry, they constitute central pharmacological targets in anti-SARS-CoV-2 therapy. Studies have shown that certain polyphenols and flavonoids can effectively interfere with the S–ACE2 interaction or suppress TMPRSS2 activity, thereby inhibiting viral attachment and membrane fusion. These multi-target interactions provide a mechanistic foundation for the broad-spectrum antiviral potential of phytochemicals.

Following RNA release, the virus induces extensive remodeling of the host endoplasmic reticulum to generate double-membrane vesicles, which serve as specialized compartments for viral replication.<sup>24</sup> The viral NSP12 protein functions as the core RdRp and assembles with cofactors NSP7 and NSP8 to form the replication–transcription complex.<sup>22</sup> This complex synthesizes negative-sense RNA intermediates and generates a nested set of subgenomic mRNAs, supporting both genomic replication and structural protein translation, and ultimately driving the assembly of progeny virions.<sup>22</sup>

Moreover, SARS-CoV-2 employs multiple immune evasion strategies that effectively suppress the host's innate immune response and interfere with IFN signaling pathways, thereby gaining a replicative advantage during the early stages of infection. The viral NSP1 protein binds to the 40S ribosomal subunit, inhibiting host mRNA translation and effectively suppressing host protein synthesis.<sup>25</sup> ORF6 disrupts the nuclear pore complex, preventing the nuclear translocation of signal transducer and activator of transcription (STAT)-1 and STAT2, and thereby inhibiting IFN-stimulated gene (ISG) transcription.<sup>26</sup> Meanwhile, ORF9B localizes to the mitochondrial outer membrane and destabilizes the MAVS–translocase of outer mitochondrial membrane 70 complex, suppressing RIG-I-like receptor signaling.<sup>27</sup> These coordinated actions collectively impair the induction of type I IFNs and reduce downstream ISG expression, attenuating the host's early antiviral defenses.<sup>27</sup>

In severe cases of COVID-19, a dual pattern of immune dysregulation and hyperinflammation is frequently observed. On one hand, patients exhibit profound immunosuppression, characterized by lymphopenia, along with elevated expression of exhaustion markers such as programmed cell death protein 1 (PD-1) and lymphocyte-activation gene 3 (LAG-3).<sup>28</sup> On the other hand, persistent elevation of pro-inflammatory cytokines—including



**Figure 3.** Structural diagram of severe acute respiratory syndrome coronavirus 2 particle, illustrating its key structural components. The virion is enveloped by a lipid bilayer embedded with spike S glycoproteins, membrane proteins, and envelope proteins. Inside the envelope lies the nucleocapsid, which encapsulates the single-stranded positive-sense RNA genome. These structural elements collectively support viral entry, assembly, and release, forming the molecular basis for host recognition and infection. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc., United States of America.

interleukin (IL)-6, tumor necrosis factor (TNF)- $\alpha$ , and C-X-C motif chemokine ligand 10—drives the onset of a cytokine storm.<sup>29</sup> This exaggerated inflammatory response contributes to widespread tissue injury, promoting alveolar epithelial apoptosis, vascular endothelial barrier disruption, capillary leakage, and ultimately, multi-organ failure.

The imbalance between impaired antiviral immunity and uncontrolled inflammation exacerbates tissue pathology, facilitating secondary bacterial infections and the development of long-term sequelae. This complex immunopathology underscores the need for therapeutic agents that can modulate both antiviral and anti-inflammatory effects. Natural products such as curcuminoids, stilbenes, and flavonoids have demonstrated the ability to suppress key inflammatory mediators, including nuclear factor  $\kappa$ -light-chain-enhancer of activated B cells (NF- $\kappa$ B), IL-6, and TNF- $\alpha$ , while simultaneously promoting antiviral defenses. Such dual-action mechanisms position these compounds as valuable candidates for mitigating cytokine storms and improving clinical outcomes in severe COVID-19.

Collectively, the mechanistic insights into SARS-CoV-2 pathogenesis provide a framework for identifying pharmacological targets across multiple viral and host pathways. Natural compounds, with their capacity to inhibit viral entry, replication, and immune evasion while modulating inflammatory cascades, offer a holistic therapeutic paradigm that aligns with the multifactorial nature of COVID-19 pathology.

## 2.3. Other respiratory viruses

### 2.3.1. RSV

RSV is a member of the Paramyxoviridae family and is the most common cause of severe lower respiratory tract infections in infants and young children.<sup>30</sup> The infection process begins with RSV binding to host cell surface receptors, such as C-X3-C motif receptor 1, through its surface glycoprotein G.<sup>31</sup> Subsequently, the viral fusion (F) protein mediates the fusion of the viral envelope with the host cell membrane, allowing the viral genome to enter the cytoplasm and initiate replication.<sup>32</sup> A key feature of RSV infection is the induction of cell-to-cell fusion, forming multinucleated syncytia.<sup>30</sup> This phenomenon not only facilitates viral spread within local tissue but also enhances the production and release of viral particles, contributing to its virulence. Since both the G and F glycoproteins are indispensable for viral attachment and membrane fusion, they represent central pharmacological targets for antiviral intervention. Several plant-derived compounds—particularly certain flavonoids, curcuminoids, and

stilbenes—have demonstrated inhibitory effects on RSV F protein-mediated membrane fusion, effectively inhibiting viral entry and syncytium formation. These findings highlight the potential of such natural products to disrupt early stages of RSV infection through multi-targeted interference.

Similar to influenza and SARS-CoV-2, RSV possesses potent immune evasion mechanisms.<sup>33</sup> It can delay the host's immune response, allowing sustained viral replication before the immune system mounts a full antiviral defense.<sup>33</sup> Specifically, RSV uses its non-structural proteins, NS1 and NS2, to inhibit the activation of IFN regulatory factor (IRF)-3 and IRF7, thereby suppressing IFN-I production.<sup>34</sup> This suppression prolongs the replication cycle, allowing the virus to persist and spread within the respiratory epithelium. Therapeutic agents capable of restoring IFN signaling or enhancing IRF activation may therefore offer a dual benefit, providing both antiviral and immunomodulatory effects. Specific flavonoids and triterpenoids have been reported to upregulate IFN-stimulated gene expression or stabilize RIG-I signaling pathways, thereby limiting RSV replication and improving host antiviral defenses. This dual antiviral and anti-inflammatory potential provides a promising pharmacological basis for managing RSV-induced respiratory pathology.

RSV infection is typically characterized by a Th2-skewed immune response, marked by an overproduction of cytokines such as IL-4 and IL-13.<sup>35,36</sup> While these cytokines play essential roles in immune defense, their excessive secretion in RSV infections exacerbates airway hyperreactivity, mucus secretion, and smooth muscle contraction.<sup>35,36</sup> These effects worsen symptoms such as wheezing and airway obstruction, contributing to the pathogenesis of bronchiolitis and pneumonia.<sup>35,36</sup> Hence, therapeutic strategies targeting RSV should not only focus on suppressing viral replication but also on rebalancing the dysregulated immune response.

Taken together, RSV pathogenesis involves a delicate interplay between viral replication, immune evasion, and host inflammatory responses. Understanding these processes has significant pharmacological implications: Natural compounds capable of concurrently targeting viral entry, replication, and immune modulation may serve as valuable leads for developing next-generation therapeutics against RSV.

### 2.3.2. HAdV

HAdV is a non-enveloped, double-stranded DNA virus with a broad host range and a complex pathogenic mechanism. The virus enters host cells through interactions

between its fiber protein and cell surface receptors, such as the coxsackievirus and adenovirus receptor or class of differentiation (CD) 46.<sup>37</sup> Upon receptor binding, the virus is internalized by receptor-mediated endocytosis and processed within the acidic environment of endosomes.<sup>38</sup> The viral genome is then transported through the nuclear pore complex, where it is released into the host cell nucleus, initiating transcription and replication.<sup>39</sup>

The early genes of HAdV, such as *E1A* and *E1B*, play crucial regulatory roles within the host cell.<sup>40</sup> *E1A* interacts with host cell cycle regulatory factors to promote cell cycle progression, particularly driving the host cell into the S phase, thus providing a favorable environment for viral genome replication.<sup>40</sup> Meanwhile, the *E1B* protein inhibits apoptotic pathways, extending the survival time of infected cells and allowing for prolonged viral replication.<sup>41</sup> This ability to delay cell apoptosis enables the virus to continue replicating and spreading efficiently, thereby preventing premature host cell death.

Moreover, HAdV employs multiple strategies to evade host immune surveillance, thereby enhancing its ability to persist and replicate within the host. The virus downregulates the expression of major histocompatibility complex class I molecules on the surface of infected cells, thereby reducing the likelihood of recognition and destruction by cytotoxic T cells.<sup>42,43</sup> In addition, HAdV interferes with the maturation process of dendritic cells, impairing their ability to activate T cells and weakening the adaptive immune response.<sup>43</sup> These immune evasion mechanisms enable HAdV to effectively spread in immunocompromised hosts, making it a common opportunistic pathogen in patients undergoing organ transplantation, chemotherapy, or other immunosuppressive treatments. In these individuals, HAdV infection can lead to severe clinical consequences, including life-threatening respiratory and systemic diseases.

Recent studies have also shown that several natural products, including flavonoids, terpenoids, and alkaloids, can modulate these molecular pathways, offering a foundation for future antiviral exploration. Integrating such pharmacological insights into the understanding of HAdV biology may thus facilitate the development of more targeted and less toxic therapeutic strategies.

### 2.3.3. HPIV

HPIVs, members of the Paramyxoviridae family, are significant respiratory pathogens, with HPIV-1 and HPIV-3 being the most prevalent and clinically relevant types. These viruses primarily cause upper and lower respiratory tract infections in children.<sup>44</sup> HPIV pathogenesis is largely driven by its surface glycoproteins. The G protein mediates viral attachment by binding to receptors on the host

cell surface, facilitating initial viral entry.<sup>44</sup> The HA–NA protein contributes to this process by promoting viral attachment and exhibiting NA activity, which removes sialylated glycoconjugates from the host cell surface, thereby enhancing viral release and dissemination.<sup>45</sup> The F protein plays a pivotal role in membrane fusion between the viral envelope and host cell membrane, a critical step that enables the delivery of viral genetic material into the host cell to initiate replication.<sup>46</sup>

During HPIV infection, the virus interacts with host cell signaling pathways, particularly the NF- $\kappa$ B and mitogen-activated protein kinase (MAPK) pathways.<sup>47</sup> Activation of these pathways results in the production of pro-inflammatory cytokines and chemokines, with notable upregulation of IL-8 and C-C motif chemokine ligand 2, which attract neutrophils to the site of infection and increase airway mucus secretion.<sup>47</sup> This inflammatory response in airway epithelial cells is responsible for the hallmark clinical symptoms of HPIV infection, including wheezing and laryngitis.<sup>47</sup> These symptoms not only reflect the host's immune response but also exacerbate respiratory pathology.<sup>47</sup>

Excessive inflammation may lead to airway hyperreactivity, mucus plugging, and further structural damage to the airways, creating a vicious cycle that prolongs the disease course.<sup>47</sup> Moreover, HPIV replication requires a coordinated interaction between viral polymerase complex components and host chaperone proteins such as HSP70 and HSP90, which assist in the proper folding of viral proteins.<sup>48</sup> These host factors have emerged as promising antiviral targets, as their inhibition can suppress viral replication without directly targeting viral enzymes, thereby reducing the likelihood of resistance. Natural compounds and small-molecule inhibitors that disrupt these virus–host interactions are under increasing investigation. Certain stilbenes and curcuminoids have been demonstrated to block such virus–host interactions by suppressing NF- $\kappa$ B activation and alleviating oxidative stress, with related mechanistic investigations currently undergoing in-depth exploration.

Although respiratory viruses differ in their structural and biological characteristics, as well as their pathogenic mechanisms, they all share the ability to rely on host cell factors, modulate innate immune responses, and evade adaptive immune surveillance. These mechanisms enable efficient viral replication and contribute to the inflammatory and pathological responses that characterize viral infections. Understanding these key molecular mechanisms is essential not only for the development of antiviral natural products but also for optimizing vaccines and developing novel immune intervention strategies.

Despite differences in genome composition and replication strategies, respiratory viruses such as influenza virus, parainfluenza virus, and coronaviruses share several conserved steps during infection, including viral attachment to host receptors, endocytic uptake, genome replication, and virion assembly. These common processes provide potential intervention points for broad-spectrum antiviral strategies. Increasing evidence suggests that various natural compounds interfere with these conserved viral and host functions. Flavonoids such as quercetin and epigallocatechin gallate (EGCG) have been shown to disrupt viral binding and membrane fusion, thereby preventing entry into host cells.<sup>49,50</sup> Similarly, compounds such as baicalin and hesperidin modulate host immune pathways, including NF- $\kappa$ B and IRF3 signaling, attenuating excessive inflammation and inhibiting viral replication.<sup>51</sup> By targeting multiple conserved mechanisms, natural products offer promising potential as adjunct or broad-spectrum antiviral agents.

### 3. Antiviral activity and mechanisms of natural products

Over the past decade, natural products have demonstrated significant potential in the prevention and treatment of respiratory viral infections, gradually emerging as a crucial research and therapeutic avenue following vaccines and small-molecule targeted drugs. Natural compounds are characterized by high structural diversity and often exert their effects through a multi-target, multi-pathway synergistic approach.<sup>52</sup> They can directly inhibit viral replication while also modulating the host immune response, enabling a dual regulation of the virus–host interaction.<sup>52</sup> This complex mechanism provides both a theoretical foundation and practical potential for their application against a range of respiratory viruses. The majority of reported bioactive natural products are derived from traditional herbal medicines, plant extracts, or microbial metabolites, encompassing various structural categories such as flavonoids, polyphenols, alkaloids, terpenes, and polysaccharides.<sup>53</sup> Their intervention primarily focuses on key stages of the viral life cycle and the regulation of the host immune system's inflammatory pathways.<sup>52</sup>

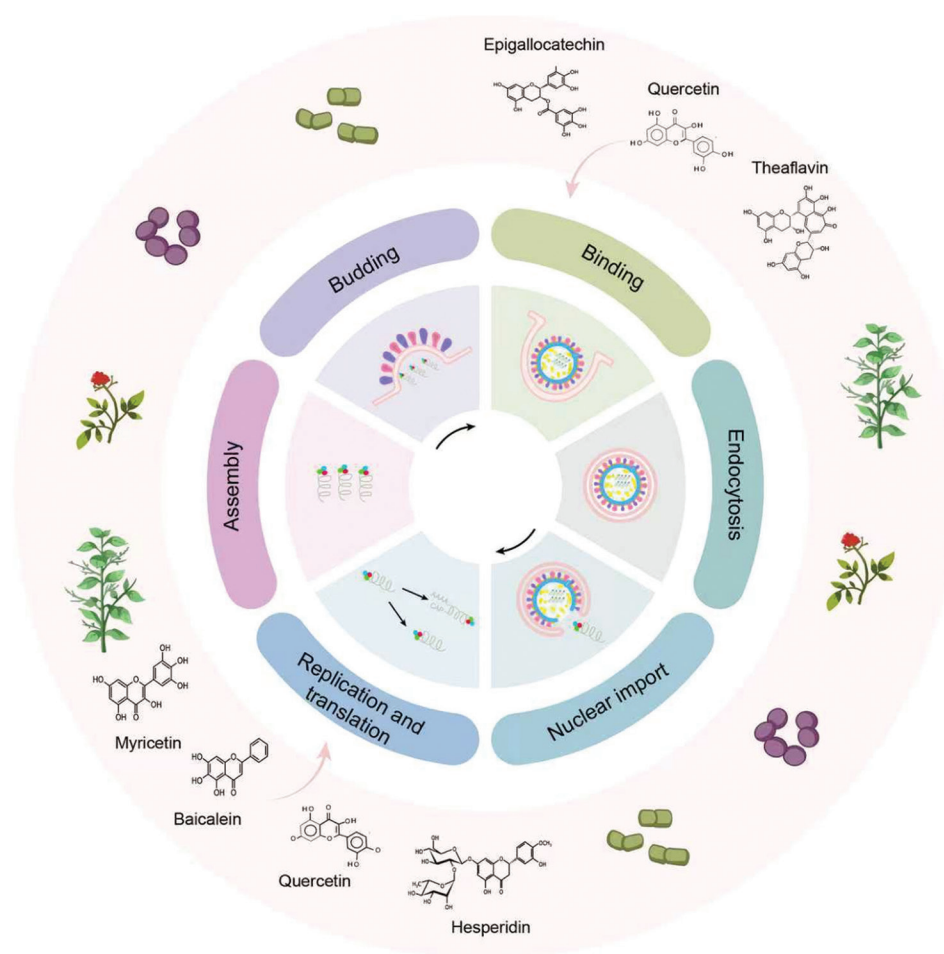
Natural products exert inhibitory effects at multiple stages of the viral life cycle. Viral entry into host cells typically relies on the specific interaction between viral surface glycoproteins and host cell receptors.<sup>54</sup> For example, the influenza virus uses HA to bind sialic acid, whereas SARS-CoV-2 utilizes the S protein to bind ACE2, facilitated by TMPRSS2-mediated cleavage for membrane fusion.<sup>55</sup> Some natural compounds can form non-covalent, stable complexes with the receptor-binding regions of

viral glycoproteins, blocking their interaction with host receptors and preventing viral entry.<sup>56</sup> *In vitro* studies have demonstrated that specific polyphenols and flavonoids derived from tea leaves can effectively inhibit the entry or infectivity of SARS-CoV-2. For example, EGCG inhibits S–ACE2 interaction and suppresses both pseudovirus and live virus infection in cell culture;<sup>57</sup> theaflavin derivatives significantly inactivate SARS-CoV-2 and reduce receptor-binding domain–ACE2 binding *in vitro*;<sup>58</sup> and quercetin has been shown to inhibit SARS-CoV-2 replication and syncytium formation in cellular models.<sup>59</sup> In addition, certain compounds may interfere with viral invasion by inhibiting the expression of host surface receptors or by upregulating their soluble forms, which competitively bind viral particles.

Once the virus has entered the host cell and begins replication, natural products can intervene in viral RNA or DNA synthesis, protein translation, and virion assembly. For negative-sense RNA viruses such as influenza and RSV, replication depends on the viral RdRp, a complex enzyme comprising multiple subunits such as PB1, PB2, and PA, all of which are potential targets for inhibition.<sup>60</sup> Studies have shown that quercetin can directly bind to the cap-binding site of the PB2 subunit, inhibiting the “cap-snatching” process and suppressing the initiation of viral mRNA transcription.<sup>61</sup> In SARS-CoV-2, NSP12 serves as the core RdRp enzyme, and its active site is highly conserved, making it a major binding target for several clinical drugs (e.g., remdesivir) and candidate natural products (e.g., hesperidin).<sup>62</sup>

Recent biochemical and cell-based studies have provided more direct evidence supporting the inhibitory potential of natural polyphenols and gallic acid derivatives against key non-structural proteins of SARS-CoV-2. Enzymatic assays have demonstrated that EGCG, theaflavin, and related compounds inhibit the activity of the main protease (3C-like protease) and papain-like protease *in vitro*, with measurable half-maximal inhibitory concentration (IC<sub>50</sub>) values in the low micromolar range.<sup>63,64</sup> Moreover, cell-based infection assays have shown that EGCG and theaflavin-3-gallate can suppress SARS-CoV-2 replication and pseudovirus entry into lung epithelial cells, further confirming their antiviral effects beyond molecular docking predictions.<sup>65,66</sup> Other studies have further confirmed that flavonoids such as myricetin can inhibit the ATPase and helicase activities of NSP13, thereby interfering with viral replication.<sup>61</sup> Baicalein has also been reported to inhibit SARS-CoV-2 replication by targeting viral enzymes, including NSP13.<sup>67</sup> Although computational predictions indicate potential inhibitory effects of some polyphenolic and alkaloid compounds on NSP12 (RdRp) and NSP14 (exonuclease), these findings still require further experimental validation (Figure 4).



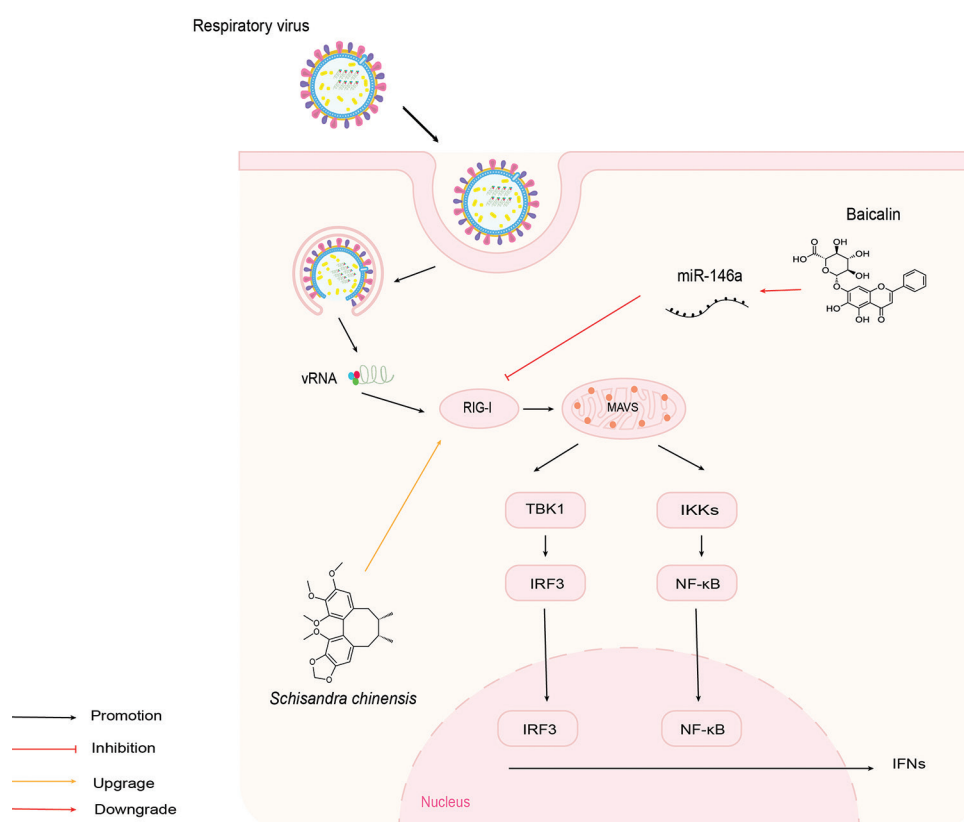


**Figure 4.** The role of several natural products in the lifecycle of respiratory viruses. Schematic representation of natural compounds targeting different stages of the viral life cycle, including viral binding, endocytosis, nuclear import, replication and translation, assembly, and budding. Representative natural compounds—such as epigallocatechin, quercetin, theaflavin, myricetin, baicalein, and hesperidin—are shown to interfere with these key steps by inhibiting viral entry, replication, and release. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc. United States of America.

In addition to directly targeting the virus, an increasing body of research focuses on the indirect antiviral effects of natural products through the modulation of the host's immune response. Following respiratory viral infections, host cells produce type I IFN via the RIG-I/melanoma differentiation-associated protein 5–TANK-binding kinase–IRF3 pathway, inducing the expression of ISGs and establishing an antiviral state.<sup>68</sup> However, most viruses have evolved mechanisms to evade this immune response by encoding inhibitory factors, such as influenza-specific NS1, ORF6, and SARS-CoV-2–specific NSP1, that interfere with this pathway.<sup>69</sup> As a result, enhancing host IFN signaling has become another key focus of natural product action. For example, in the influenza A virus mouse model, baicalin has been confirmed *in vivo* to enhance RIG-I-mediated signaling by downregulating microRNA-146a, thereby promoting type I IFN production and significantly

suppressing viral replication.<sup>70</sup> Lignans from *Schisandra chinensis* have been shown primarily *in vitro* to activate RIG-I and upregulate ISG15 expression in RSV-infected epithelial cells, suggesting a potential yet unvalidated mechanism in animal systems.<sup>71</sup> Moreover, several flavonoid and coumarin derivatives have been reported to restore Janus kinase (JAK)–STAT signaling by enhancing STAT1/2 phosphorylation, though these findings are mostly derived from cell-based mechanistic studies rather than pre-clinical models<sup>72</sup> (Figure 5).

Viral infections are often accompanied by extensive inflammatory responses, especially in cases such as SARS-CoV-2, where immune imbalance is characterized by elevated levels of pro-inflammatory cytokines (e.g., IL-6, TNF- $\alpha$ , and monocyte chemoattractant protein-1), leading to tissue damage and immune exhaustion.<sup>73</sup> Several natural compounds exhibit significant anti-inflammatory



**Figure 5.** Natural products inhibit virus replication by promoting the innate immunity of the RIG-I pathway. Schematic illustration of natural compounds modulating the RIG-I–MAVS antiviral signaling pathway. Baicalin enhances antiviral responses by suppressing miR-146a-mediated inhibition of RIG-I, thereby promoting downstream activation of TBK1–IRF3 and IKK–NF-κB signaling cascades. *Schisandra chinensis* extract upregulates RIG-I/MAVS signaling, augmenting IRF3 and NF-κB activation and promoting IFN production. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc., United States of America.

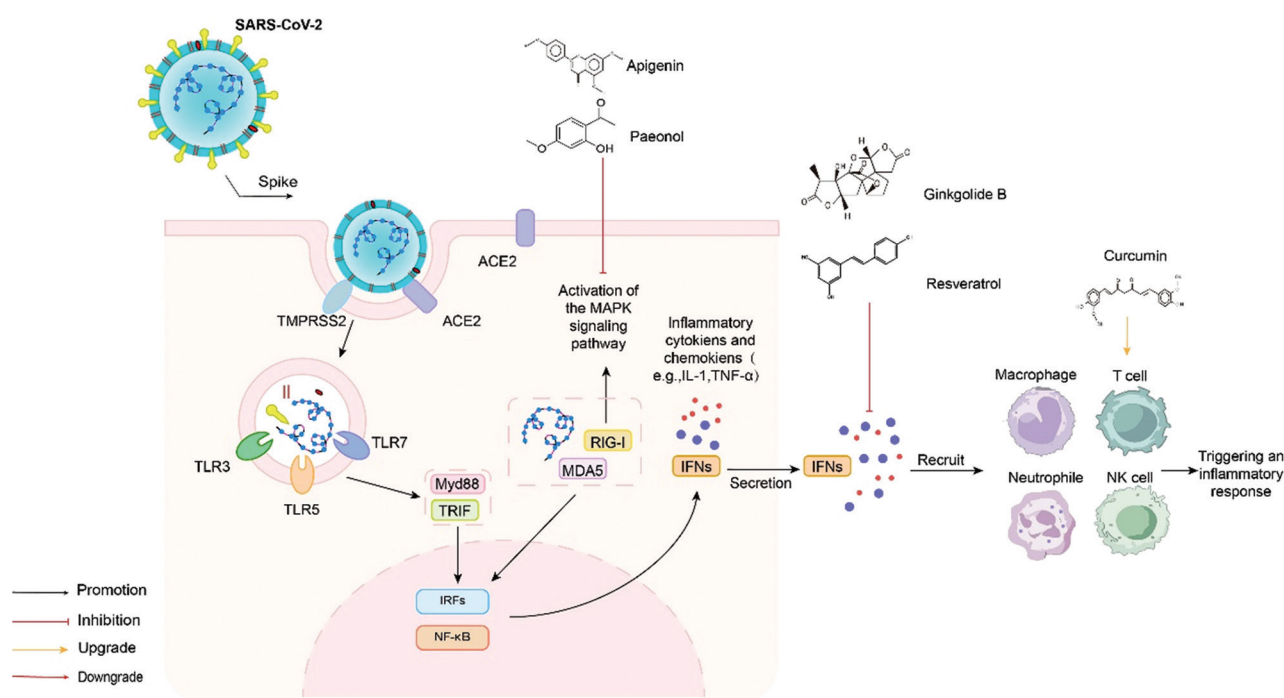
Abbreviations: IFN: Interferon; IKK: IκB kinase; IRF3: Interferon regulatory factor 3; MAVS: Mitochondrial antiviral signaling; miR-146a: MicroRNA-146a; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; RIG-I: Retinoic acid-inducible gene I; TBK1: TANK-binding kinase 1; vRNA: Viral RNA.

properties by inhibiting NF-κB and NLRP3 inflammasome signaling pathways, downregulating the expression of pro-inflammatory cytokines, and alleviating virus-induced pathological inflammation. For instance, ginkgolide B and resveratrol can significantly reduce IL-1β and TNF-α levels in the airways following viral infection, thereby improving lung tissue damage.<sup>74</sup>

In addition, compounds such as paeonol and apigenin can inhibit MAPK activation induced by oxidative stress, thereby mitigating the oxidative-damage environment created during viral infection and providing favorable conditions for cellular repair.<sup>75</sup> It is noteworthy that certain natural products possess both antiviral and immune-regulatory properties, making them particularly suitable for respiratory viruses that have evolved immune evasion mechanisms. In the context of T-cell dysfunction and exhaustion, natural compounds that can restore T-cell proliferation or inhibit the expression of immune checkpoint proteins, such as PD-1 or LAG-3, offer potential

therapeutic strategies for clearing viral reservoirs and enhancing vaccine responses.<sup>76</sup> Preliminary studies have shown that curcumin can enhance CD8<sup>+</sup> T-cell activity in influenza models, and the combination of quercetin and EGCG can boost local immunoglobulin A antibody levels in mucosal tissues, suggesting that natural products also exert a positive regulatory effect on acquired immunity<sup>77</sup> (Figure 6).

Overall, natural products demonstrate a rich array of intervention targets, complex mechanisms, and multi-layered synergistic effects in antiviral therapy. These compounds can directly suppress critical nodes in the viral life cycle while also exerting indirect control through the modulation of host signaling pathways, the alleviation of inflammatory environments, and the remodeling of the immune microenvironment (Table 1). As molecular pharmacology and systems biology continue to advance, the antiviral mechanisms of an increasing number of natural compounds are being elucidated, providing a solid



**Figure 6.** Schematic illustration of SARS-CoV-2-induced immune signaling and the modulatory roles of natural compounds. Upon SARS-CoV-2 entry via ACE2 and TMPRSS2, viral components are recognized by pattern recognition receptors (e.g., TLR3, TLR7, TLR5, MDA5, and RIG-I). Signaling through adaptor proteins MyD88 and TRIF leads to activation of the MAPK pathway and transcription factors NF-κB and IRFs. This promotes the secretion of type I/III IFNs and pro-inflammatory cytokines/chemokines (e.g., IL-1 and TNF-α), and recruits immune cells, including macrophages, neutrophils, T cells, and NK cells, thereby triggering inflammatory responses. Several natural compounds (e.g., paeonol, apigenin, ginkgolide B, resveratrol, curcumin) are indicated at specific nodes, suggesting their potential to modulate these signaling pathways. Image created by the authors using Adobe Illustrator version 29.3, Adobe Inc., United States of America.

Abbreviations: ACE2: Angiotensin-converting enzyme 2; IFN: Interferon; IL: Interleukin; IRF: Interferon regulatory factor; MAPK: Mitogen-activated protein kinase; MDA5: Melanoma differentiation-associated protein 5; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; NK: Natural killer; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; RIG-I: Retinoic acid-inducible gene I; TLR: Toll-like receptor; TMPRSS2: Transmembrane serine protease 2; TNF: Tumor necrosis factor; TRIF: TIR-domain-containing adapter-inducing interferon-β.

foundation for the development of novel broad-spectrum antiviral drugs. Future research should focus on structural optimization, improvements in pharmacokinetics, and the potential for combination therapies with vaccines or existing antiviral agents, thereby offering new solutions to combat the ongoing threat posed by various respiratory viruses.

#### 4. Challenges and prospects of antiviral research on natural products

Natural products hold considerable promise in antiviral drug development; however, their translation from basic research to clinical application remains hindered by multiple challenges. These include unclear mechanisms of action, suboptimal pharmacokinetic profiles, low bioavailability, difficulties in standardizing active constituents, and a lack of large-scale clinical validation. Addressing how to advance the therapeutic development of natural products for respiratory virus prevention and

treatment in a scientific, efficient, and systematic manner has become a central focus in the field.

##### 4.1. Complex targeting and limitations in mechanistic research

Natural products exhibit broad antiviral potential owing to their intrinsic multi-target and multi-pathway characteristics. However, this same complexity often obscures their precise mechanisms of action and limits the reproducibility of experimental results. As mentioned above, although many studies have demonstrated the antiviral activity of plant-derived compounds through molecular docking or *in vitro* assays, the direct molecular targets and downstream signaling cascades responsible for these effects remain underexplored.

Recent advances in experimental and computational tools now offer new opportunities to address these gaps. Integrating chemical proteomics, cellular thermal shift assays, clustered regularly interspaced short palindromic

**Table 1. Experimental evidence levels of antiviral natural compounds**

Natural compound	Virus target/model	Level of evidence
Baicalin/baicalin	SARS-CoV-2: NSP12; influenza: IFN pathway	I
Curcumin	Influenza: T-cell activation	I
Ginkgolide B	NF-κB/IL-1β/TNF-α	I
Quercetin	Influenza: PB2; SARS-CoV-2 replication	I–II
Resveratrol	RSV/SARS-CoV-2 anti-inflammatory	I–II
Epigallocatechin gallate	SARS-CoV-2: Spike protein–ACE2, 3CLpro, PLpro	II
Theaflavin/theaflavin-3-gallate	SARS-CoV-2 RBD–ACE2 binding, 3CLpro	II
Myricetin	SARS-CoV-2 NSP13 helicase	II
Lignans ( <i>Schisandra chinensis</i> )	RSV/RIG-I activation	II
Paenonol	MAPK pathway	III
Apigenin	MAPK pathway	III
Hesperidin	SARS-CoV-2 RdRp (NSP12)	IV
Polyphenolic and alkaloid compounds (general)	SARS-CoV-2 NSP12/NSP14	IV

Notes: Evidence grading criteria: Level I (high evidence): confirmed *in vivo* efficacy in validated animal models and/or supported by early clinical data with mechanistic insights; level II (moderate evidence): Demonstrated antiviral or immunomodulatory effects in cell-based assays or enzyme inhibition experiments, with quantitative data (e.g., IC<sub>50</sub>, EC<sub>50</sub>); level III (preliminary evidence): Mechanistic indication from biochemical or target-based assays without cellular confirmation; and level IV (computational evidence): Predicted interactions or binding activity derived solely from *in silico* modeling, molecular docking, or virtual screening, lacking experimental validation. Abbreviations: 3CLpro: 3C-like protease; ACE2: Angiotensin-converting enzyme 2; IFN: Interferon; IL: Interleukin; MAPK: Mitogen-activated protein kinase; NF-κB: Nuclear factor κ-light-chain-enhancer of activated B cells; NSP: Non-structural protein; PB2: Polymerase basic 2; PLpro: Papain-like protease; RBD: Receptor-binding domain; RdRp: RNA-dependent RNA polymerase; RIG-I: Retinoic acid-inducible gene I; RSV: Respiratory syncytial virus; SARS-CoV-2: Severe acute respiratory syndrome corona virus 2; TNF: Tumor necrosis factor.

repeats-based target screening, and multi-omics approaches can help systematically identify direct binding partners and clarify the “compound–target–pathway–phenotype” network of antiviral natural products.<sup>78</sup> Likewise, the combination of structural biology and biochemical validation can provide high-resolution evidence of specific target engagement, thereby strengthening the mechanistic credibility beyond preliminary docking or expression analyses. Future research should therefore emphasize mechanistic depth over breadth, focusing on a few

representative compounds with proven antiviral efficacy in cell and animal models. Such work will refine the mechanistic framework of natural product pharmacology and accelerate translation from molecular discovery to clinically actionable antivirals.

#### 4.2. Low bioavailability and poor pharmacokinetic properties

Many natural compounds are characterized by structural complexity and an inherent polarity—either hydrophilic or lipophilic—resulting in poor absorption, short plasma half-life, and low bioavailability *in vivo*. For instance, EGCG is prone to oxidative degradation and methylation in the gastrointestinal tract, making it difficult to maintain therapeutically relevant plasma concentrations.<sup>79</sup> Similarly, flavonoids are often rapidly eliminated by hepatic metabolic enzymes, leading to diminished pharmacological effects.<sup>80</sup>

To overcome these limitations, various strategies have been employed to optimize the pharmacokinetic properties of natural compounds. These include the development of nanoparticle-based delivery systems (e.g., solid lipid nanoparticles and poly[lactic-co-glycolic acid] microspheres), salt modification, prodrug approaches, liposomal encapsulation, and structural derivatization.<sup>81</sup> In addition, comprehensive studies on tissue distribution and quantification of compound levels in viral target sites are essential to evaluate their biodistribution in the lungs, airways, and immune-related organs—critical for enhancing therapeutic outcomes.

#### 4.3. Complex composition and inconsistent quality standards

Traditional Chinese medicine (TCM) and plant extracts, as major sources of natural products, often face challenges such as complex compositions, significant source variability, and batch-to-batch inconsistency. These issues severely hinder the clinical application of these products. The lack of well-defined active monomeric components, coupled with the considerable fluctuations in the content of active compounds and unstable extraction processes, presents critical bottlenecks in the development of natural product-based formulations.<sup>82</sup>

To address these challenges, the extraction phase must focus on purifying effective compounds and establishing comprehensive active tracking and evaluation systems to ensure the stability of therapeutic substances.<sup>83</sup> In addition, multi-omics technologies, such as metabolomics and proteomics, should be employed to accurately identify and verify key active pharmaceutical ingredients.<sup>84</sup> Moreover, to meet international regulatory requirements and facilitate the global clinical transformation of natural products,



establishing unified international quality standards and strictly adhering to Good Manufacturing Practices production guidelines are critical steps. These measures will ensure that TCM and plant extracts are developed with higher quality assurance, enabling their successful global application in antiviral drug development and clinical treatments.

#### 4.4. Lack of systematic *in vivo* validation and clinical evidence

Currently, most progress in antiviral research involving natural products remains at the cellular level or in small animal models, with clinical evidence still relatively scarce. For instance, compounds such as baicalin, quercetin, and EGCG have demonstrated promising antiviral activity against influenza and SARS-CoV-2 *in vitro* and in mouse models, yet no phase II or III clinical trials have confirmed their efficacy or safety in human subjects.<sup>57,85,86</sup> In infection models for respiratory viruses such as influenza and SARS-CoV-2, researchers often face challenges such as short time windows, difficulty in controlling viral loads, and unstable symptom phenotypes. These issues complicate the evaluation systems for natural products in *in vivo* studies.

In addition, current clinical observations, such as small-scale studies on Lianhua Qingwen and Shuanghuanglian formulations, remain limited by single-center designs and lack randomized, double-blind validation, making it difficult to draw generalizable conclusions.<sup>87,88</sup> Particularly during the acute phase of viral infections, fluctuations in symptom severity and viral loads can impact the reproducibility and reliability of study results. Moreover, natural products are generally not single-target drugs and may exert bidirectional regulatory effects at different pathological stages, such as during the viral replication phase and the immune storm phase. This complexity adds an additional layer of challenge to animal experimental design. In the viral replication phase, natural products may primarily act by inhibiting viral activity, while during the immune storm phase, they may regulate immune responses to exert anti-inflammatory or immunomodulatory effects. Thus, experimental designs need to carefully distinguish the roles of natural products across various pathological states.

Future research should not only develop animal and *in vitro* models that better replicate human pathological processes, such as human ACE2 transgenic mouse models, humanized peripheral blood mononuclear cell models, and organoid systems, but also prioritize bridging pre-clinical findings with well-structured clinical evaluations. These models would provide more accurate simulations of human immune responses and viral infection dynamics.

In addition, the establishment of multicenter, randomized controlled clinical trials is urgently needed to provide robust evidence for the therapeutic efficacy and safety of natural products in respiratory viral infections. Such efforts will provide the scientific basis needed for their clinical application, address the current lack of clinical evidence, and facilitate their broader use in antiviral therapies.

### 5. Emerging technological platforms and future prospects for natural antiviral drug research

Natural products remain an invaluable reservoir for antiviral drug discovery, characterized by their structural diversity and multi-target activity. However, their clinical translation has long been hampered by limited resources, complex compositions, and insufficient mechanistic understanding. In recent years, the integration of artificial intelligence (AI), multi-omics analysis, synthetic biology, and advanced delivery systems has driven a paradigm shift from traditional empirical screening to mechanism-guided and technology-empowered drug discovery, significantly enhancing the efficiency, accuracy, and translational potential of natural antiviral agents.

#### 5.1. AI-driven drug discovery and structural optimization

AI has revolutionized the exploration of natural products by enabling large-scale virtual screening, target prediction, and the optimization of lead compounds. Through deep learning-based molecular docking and multi-task learning frameworks, AI can identify compounds with strong binding affinity to critical viral targets—such as RdRp, S protein, and PB2 subunits—across multiple viral strains.<sup>89</sup> These approaches facilitate the rapid discovery of broad-spectrum antiviral leads.

In addition, AI-assisted structure–activity relationship modeling and generative algorithms enable the automated design of derivatives based on active cores, optimizing pharmacokinetic and toxicity profiles while retaining antiviral potency.<sup>90</sup> Combined with advanced structure-prediction tools such as AlphaFold2, AI provides a precise understanding of molecular recognition and supports the rational optimization of natural scaffolds into clinically viable drugs.<sup>91,92</sup>

#### 5.2. Multi-omics integration and mechanistic elucidation

Modern multi-omics technologies—including transcriptomics, proteomics, and metabolomics—offer system-level insights into the antiviral mechanisms of

natural products.<sup>93</sup> Techniques such as drug affinity responsive target stability, cellular thermal shift assays, and tandem mass tag labeling help identify direct molecular targets, whereas transcriptomic and pathway enrichment analyses reveal how these compounds regulate key antiviral signaling cascades (e.g., RIG-I, NF- $\kappa$ B, JAK-STAT).<sup>94,95</sup>

Furthermore, metabolomic profiling has revealed the capacity of natural products to reprogram host metabolic pathways—such as glycolysis, lipid metabolism, and glutamine metabolism—thereby restraining viral replication and modulating immune responses. Integrating multi-omics datasets with AI-based network analysis enables the construction of compound–target–pathway–phenotype networks, providing mechanistic clarity and a theoretical foundation for precision interventions.<sup>96</sup>

However, multi-omics approaches also face notable limitations. Technical variations, such as batch effects, platform bias, and inconsistent normalization, can distort biological interpretation and lead to false-positive associations.<sup>97</sup> Integrating multi-layer omics data poses additional computational challenges, where noise accumulation may mask true antiviral mechanisms. Importantly, reproducibility remains a concern due to the limited use of standardized pipelines and the lack of independent validation cohorts. Future studies should adopt unified preprocessing standards, robust statistical frameworks, and external validation to ensure reliable and reproducible mechanistic conclusions.

### 5.3. Synthetic biology, metabolic engineering, and scalable production

The low yield and complex extraction of natural products have long constrained their translational use. Synthetic biology now provides sustainable solutions through microbial chassis engineering (e.g., *Escherichia coli*, *Saccharomyces cerevisiae*, and *Streptomyces*), enabling heterologous biosynthesis of active molecules such as quercetin, curcumin, and ursolic acid.<sup>98,99</sup>

By reprogramming metabolic flux and modular enzyme pathways, microbial “cell factories” can dramatically increase yields and purity.<sup>100</sup> Moreover, semi-synthetic modification and enzyme-catalyzed derivatization based on natural scaffolds offer avenues for structural innovation, enhancing pharmacological stability, targeting, and clinical applicability.<sup>101,102</sup> Together, these technologies build the molecular and industrial foundation for scalable natural antiviral production.

### 5.4. Advanced drug delivery systems and translational models

Innovations in drug delivery are equally critical for clinical success. Localized delivery routes—such as pulmonary

inhalation or intranasal administration—enhance drug concentration at infection sites, improve bioavailability, and reduce systemic toxicity.<sup>103</sup> Emerging nanocarriers and targeted delivery systems further enable precise distribution to infected tissues.<sup>104</sup>

Parallel advances in organoid and lung-on-a-chip technologies now simulate physiological infection microenvironments, allowing for accurate evaluation of antiviral efficacy, immune modulation, and toxicity.<sup>105,106</sup> These next-generation models offer a realistic and ethical alternative to animal testing, serving as essential platforms that bridge basic research and clinical translation.

### 5.5. Integration, regulation, and future directions

The convergence of these emerging technologies marks a new era for natural antiviral drug development—one driven by data integration, mechanistic precision, and translational feasibility. Future progress will rely on multidisciplinary collaboration among pharmacology, structural biology, immunology, and computational science.

Equally important is the establishment of standardized and ethically grounded regulatory frameworks to facilitate the transition of natural products from traditional “functional foods” to modern therapeutic drugs. From an ethical and regulatory perspective, the development of natural products requires adherence to rigorous research standards comparable to those of registered pharmaceuticals. TCM and other ethnobotanical systems often rely on historical evidence and empirical efficacy, which differ from the standardized evaluation pathways of modern drug registration. Therefore, integrating traditional knowledge with evidence-based pharmacology should be guided by transparent ethical principles, scientific validation, and international harmonization of regulatory criteria. Establishing clear frameworks for safety testing, quality control, pharmacopeia standards, approval pathways, and intellectual property protection will not only ensure research integrity but also promote the responsible and sustainable use of natural resources.

Combination therapies that integrate natural compounds with antiviral agents or vaccines, based on multi-target synergistic mechanisms, also hold promise for enhancing efficacy, mitigating resistance, and improving host immune responses.

## 6. Key future research directions

Key areas for future investigation include:

- (i) Mechanistic elucidation: Utilize multi-omics and systems biology approaches to identify precise molecular targets and pathways

- (ii) Pharmacokinetic optimization: Improve bioavailability and tissue targeting through innovative formulation and delivery strategies
- (iii) Standardization and quality control: Develop global standards for the identification, quantification, and efficacy assessment of active compounds
- (iv) Clinical translation: Conduct multicenter, randomized controlled trials and employ advanced disease models to validate safety and therapeutic efficacy
- (v) Technological integration: Leverage AI and synthetic biology to accelerate compound discovery and enable rational structural optimization.

## 7. Conclusion

Respiratory viral infections, particularly recurrent outbreaks of influenza and novel coronavirus, remain significant global public health challenges. Current antiviral strategies face limitations in efficacy, resistance, and safety. In this context, natural products—with their structural diversity, multiple targets, and low toxicity—have gained increasing attention in antiviral drug discovery.

This review summarizes the antiviral potential of natural products against influenza viruses, SARS-CoV-2, and other respiratory pathogens, emphasizing their regulatory roles in viral replication, immune modulation, and inflammation. However, their clinical translation is still hindered by unclear mechanisms, low bioavailability, and insufficient large-scale clinical validation.

To advance translation, it is crucial to establish clear mechanistic links and validated pharmacological pathways that connect pre-clinical findings to clinical outcomes. First, integrating multi-omics technologies and molecular modeling can systematically clarify the interactions between natural compounds, targets, and signaling pathways, providing a mechanistic basis for precision antiviral interventions.

Second, integrating nanoparticle-based delivery, structural optimization, and synthetic biology can improve stability, bioavailability, and target specificity, creating a bridge between discovery and clinical application. Third, standardized criteria for compound identification, quality control, and bioactivity assessment are needed to support pharmaceutical development and regulatory approval. Fourth, advanced *in vitro* models—such as organoids and lung-on-a-chip systems—alongside multicenter clinical studies, will enhance translational reliability and evidence-based validation. In addition, ensuring a rational balance between efficacy and safety through systematic toxicological validation will be critical for the successful clinical development of natural product-based antivirals.

Looking ahead, interdisciplinary integration among AI, systems biology, and immunoregulation will accelerate the discovery and evaluation of antiviral natural products. In conclusion, natural products may represent a valuable source for the development of broad-spectrum and low-toxicity antiviral agents. However, their successful translation into clinical use requires continued efforts to integrate mechanistic understanding, technological innovation, systematic toxicological evaluation, and rigorous clinical validation. Strengthening these aspects will help clarify their therapeutic value and practical feasibility in combating respiratory viral diseases.

## Acknowledgments

The authors would like to express their sincere appreciation to colleagues and collaborators for their thoughtful discussions and helpful suggestions throughout the preparation of this manuscript. The authors are also grateful to the laboratory members and institutional facilities for their technical and administrative assistance. Although these contributions do not meet the criteria for authorship, they were greatly valued and contributed meaningfully to the completion of this work.

## Funding

This review was supported by the National Natural Science Foundation of China (32300120), the Key Scientific Research Project of Higher Education of Henan Province (25A310013), and Xinxiang Medical University.

## Conflict of interest

The authors declare that they have no competing interests.

## Author contributions

*Conceptualization:* Xiaowei Tian

*Visualization:* Shihuan Ding, Jiyan Cui

*Writing—original draft:* Xiaowei Tian

*Writing—review & editing:* All authors

## Ethics approval and consent to participate

Not applicable.

## Consent for publication

Not applicable.

## Availability of data

Not applicable.

## References

1. Collaborators GBDI. Mortality, morbidity, and hospitalisations due to influenza lower respiratory tract infections, 2017: An analysis for the global burden of disease

- study 2017. *Lancet Respir Med*. 2019;7(1):69-89.  
doi: 10.1016/S2213-2600(18)30496-X
2. Soudani S, Mafi A, Al Mayahi Z, *et al*. A systematic review of influenza epidemiology and surveillance in the Eastern Mediterranean and North African region. *Infect Dis Ther*. 2022;11(1):15-52.  
doi: 10.1007/s40121-021-00534-3
  3. Qiao H, Deng X, Qiu L, *et al*. SARS-CoV-2 induces blood-brain barrier and choroid plexus barrier impairments and vascular inflammation in mice. *J Med Virol*. 2024;96(5):e29671.  
doi: 10.1002/jmv.29671
  4. Zaraket H, Saito R, Suzuki Y, *et al*. Genetic makeup of amantadine-resistant and oseltamivir-resistant human influenza A/H1N1 viruses. *J Clin Microbiol*. 2010;48(4):1085-1092.  
doi: 10.1128/JCM.01532-09
  5. Whitley RJ, Monto AS. Resistance of influenza virus to antiviral medications. *Clin Infect Dis*. 2020;71(4):1092-1094.  
doi: 10.1093/cid/ciz911
  6. Thorlund K, Awad T, Boivin G, Thabane L. Systematic review of influenza resistance to the neuraminidase inhibitors. *BMC Infect Dis*. 2011;11:134.  
doi: 10.1186/1471-2334-11-134
  7. Khan MT, Ather A, Thompson KD, Gambari R. Extracts and molecules from medicinal plants against herpes simplex viruses. *Antiviral Res*. 2005;67(2):107-119.  
doi: 10.1016/j.antiviral.2005.05.002
  8. Centers for Disease Control and Prevention. *Antiviral Agents for the Treatment and Chemoprophylaxis of Influenza*; 2011. Available from: <https://www.cdc.gov/flu/hcp/antivirals/antiviral-adverse-events.html> [Last accessed on 2025 Dec 25].
  9. Muller MP, Dresser L, Raboud J, *et al*. Adverse events associated with high-dose ribavirin: Evidence from the Toronto outbreak of severe acute respiratory syndrome. *Pharmacotherapy*. 2007;27(4):494-503.  
doi: 10.1592/phco.27.4.494
  10. Krammer F, Smith GJD, Fouchier RAM, *et al*. Influenza. *Nat Rev Dis Primers*. 2018;4(1):3.  
doi: 10.1038/s41572-018-0002-y
  11. Bouvier NM, Palese P. The biology of influenza viruses. *Vaccine*. 2008;26(Suppl 4):D49-D53.  
doi: 10.1016/j.vaccine.2008.07.039
  12. Skehel JJ, Wiley DC. Receptor binding and membrane fusion in virus entry: the influenza hemagglutinin. *Annu Rev Biochem*. 2000;69:531-569.  
doi: 10.1146/annurev.biochem.69.1.531
  13. Moscona A. Neuraminidase inhibitors for influenza. *N Engl J Med*. 2005;353(13):1363-1373.  
doi: 10.1056/nejmra050740
  14. Fodor E, Te Velthuis AJ. Structure and function of the influenza virus transcription and replication machinery. *Cold Spring Harb Perspect Med*. 2020;10(9):a038398.  
doi: 10.1101/cshperspect.a038398
  15. Pang IK, Pillai PS, Iwasaki A. Efficient influenza A virus replication in the respiratory tract requires signals from TLR7 and RIG-I. *Proc Natl Acad Sci U S A*. 2013;110(34):13910-13915.  
doi: 10.1073/pnas.1303275110
  16. Gack MU, Albrecht RA, Urano T, *et al*. Influenza A virus NS1 targets the ubiquitin ligase TRIM25 to evade recognition by the host viral RNA sensor RIG-I. *Cell Host Microbe*. 2009;5(5):439-449.  
doi: 10.1016/j.chom.2009.04.006
  17. Nemeroff ME, Barabino SM, Li Y, Keller W, Krug RM. Influenza virus NS1 protein interacts with the cellular 30 kDa subunit of CPSF and inhibits 3'end formation of cellular pre-mRNAs. *Mol Cell*. 1998;1(7):991-1000.  
doi: 10.1016/s1097-2765(00)80099-4
  18. Varga ZT, Ramos I, Hai R, *et al*. The influenza virus protein PB1-F2 inhibits the induction of type I interferon at the level of the MAVS adaptor protein. *PLoS Pathog*. 2011;7(6):e1002067.  
doi: 10.1371/journal.ppat.1002067
  19. Hsu AC. Influenza virus: A master tactician in innate immune evasion and novel therapeutic interventions. *Front Immunol*. 2018;9:743.  
doi: 10.3389/fimmu.2018.00743
  20. Kim H, Webster RG, Webby RJ. Influenza virus: Dealing with a drifting and shifting pathogen. *Viral Immunol*. 2018;31(2):174-183.  
doi: 10.1089/vim.2017.0141
  21. Treanor J. Influenza vaccine--outmaneuvering antigenic shift and drift. *N Engl J Med*. 2004;350(3):218-220.  
doi: 10.1056/nejmp038238
  22. Brant AC, Tian W, Majerciak V, Yang W, Zheng ZM. SARS-CoV-2: From its discovery to genome structure, transcription, and replication. *Cell Biosci*. 2021;11(1):136.  
doi: 10.1186/s13578-021-00643-z
  23. Jackson CB, Farzan M, Chen B, Choe H. Mechanisms of SARS-CoV-2 entry into cells. *Nat Rev Mol Cell Biol*. 2022;23(1):3-20.  
doi: 10.1038/s41580-021-00418-x
  24. Chen A, Lupan AM, Quek RT, *et al*. A coronaviral pore-



- replicase complex links RNA synthesis and export from double-membrane vesicles. *Sci Adv.* 2024;10(45):eadq9580.  
doi: 10.1126/sciadv.adq9580
25. Schubert K, Karousis ED, Jomaa A, *et al.* SARS-CoV-2 Nsp1 binds the ribosomal mRNA channel to inhibit translation. *Nat Struct Mol Biol.* 2020;27(10):959-966.  
doi: 10.1038/s41594-020-0511-8
  26. Miorin L, Kehrer T, Sanchez-Aparicio MT, *et al.* SARS-CoV-2 Orf6 hijacks Nup98 to block STAT nuclear import and antagonize interferon signaling. *Proc Natl Acad Sci U S A.* 2020;117(45):28344-28354.  
doi: 10.1073/pnas.2016650117
  27. Jiang HW, Zhang HN, Meng QF, *et al.* SARS-CoV-2 Orf9b suppresses type I interferon responses by targeting TOM70. *Cell Mol Immunol.* 2020;17(9):998-1000.  
doi: 10.1038/s41423-020-0514-8
  28. Chen Z, John Wherry E. T cell responses in patients with COVID-19. *Nat Rev Immunol.* 2020;20(9):529-536.  
doi: 10.1038/s41577-020-0402-6
  29. Tang Y, Liu J, Zhang D, Xu Z, Ji J, Wen C. Cytokine storm in COVID-19: The current evidence and treatment strategies. *Front Immunol.* 2020;11:1708.  
doi: 10.3389/fimmu.2020.01708
  30. Feng Z, Xu L, Xie Z. Receptors for respiratory syncytial virus infection and host factors regulating the life cycle of respiratory syncytial virus. *Front Cell Infect Microbiol.* 2022;12:858629.  
doi: 10.3389/fcimb.2022.858629
  31. Johnson SM, McNally BA, Ioannidis I, *et al.* Respiratory syncytial virus uses CX3CR1 as a receptor on primary human airway epithelial cultures. *PLoS Pathog.* 2015;11(12):e1005318.  
doi: 10.1371/journal.ppat.1005318
  32. Cadena-Cruz C, Villarreal Camacho JL, De Avila-Arias M, Hurtado-Gomez L, Rodriguez A, San-Juan-Vergara H. Respiratory syncytial virus entry mechanism in host cells: A general overview. *Mol Microbiol.* 2023;120(3):341-350.  
doi: 10.1111/mmi.15133
  33. Thornhill EM, Verhoeven D. Respiratory syncytial virus's non-structural proteins: Masters of interference. *Front Cell Infect Microbiol.* 2020;10:225.  
doi: 10.3389/fcimb.2020.00225
  34. Sedeyn K, Schepens B, Saelens X. Respiratory syncytial virus nonstructural proteins 1 and 2: Exceptional disrupters of innate immune responses. *PLoS Pathog.* 2019;15(10):e1007984.  
doi: 10.1371/journal.ppat.1007984
  35. Becker Y. Respiratory syncytial virus (RSV) evades the human adaptive immune system by skewing the Th1/Th2 cytokine balance toward increased levels of Th2 cytokines and IgE, markers of allergy--a review. *Virus Genes.* 2006;33(2):235-252.  
doi: 10.1007/s11262-006-0064-x
  36. Pelaia C, Heffler E, Crimi C, *et al.* Interleukins 4 and 13 in asthma: Key pathophysiologic cytokines and druggable molecular targets. *Front Pharmacol.* 2022;13:851940.  
doi: 10.3389/fphar.2022.851940
  37. Stasiak AC, Stehle T. Human adenovirus binding to host cell receptors: A structural view. *Med Microbiol Immunol.* 2020;209(3):325-333.  
doi: 10.1007/s00430-019-00645-2
  38. Nestic D, Bozinovic K, Pehar I, Wallace R, Parker AL, Majhen D. The revolving door of adenovirus cell entry: Not all pathways are equal. *Pharmaceutics.* 2021;13(10):1585.  
doi: 10.3390/pharmaceutics13101585
  39. Greber UF, Suomalainen M, Stidwill RP, Boucke K, Ebersold MW, Helenius A. The role of the nuclear pore complex in adenovirus DNA entry. *EMBO J.* 1997;16(19):5998-6007.  
doi: 10.1093/emboj/16.19.5998
  40. King CR, Zhang A, Tessier TM, Gameiro SF, Mymryk JS. Hacking the Cell: Network intrusion and exploitation by adenovirus E1A. *mBio.* 2018;9(3):e00390-18.  
doi: 10.1128/mBio.00390-18
  41. Radke JR, Grigera F, Ucker DS, Cook JL. Adenovirus E1B 19-kilodalton protein modulates innate immunity through apoptotic mimicry. *J Virol.* 2014;88(5):2658-2669.  
doi: 10.1128/jvi.02372-13
  42. Wu Y, Sun Z, Xia L, *et al.* MHC-I pathway disruption by viruses: insights into immune evasion and vaccine design for animals. *Front Immunol.* 2025;16:1540159.  
doi: 10.3389/fimmu.2025.1540159
  43. McSharry BP, Burgert HG, Owen DP, *et al.* Adenovirus E3/19K promotes evasion of NK cell recognition by intracellular sequestration of the NKG2D ligands major histocompatibility complex class I chain-related proteins A and B. *J Virol.* 2008;82(9):4585-4594.  
doi: 10.1128/JVI.02251-07
  44. Moscona A. Entry of parainfluenza virus into cells as a target for interrupting childhood respiratory disease. *J Clin Invest.* 2005;115(7):1688-1698.  
doi: 10.1172/jci25669
  45. Tappert MM, Porterfield JZ, Mehta-D'Souza P, Gulati S, Air GM. Quantitative comparison of human parainfluenza virus hemagglutinin-neuraminidase receptor binding and

- receptor cleavage. *J Virol*. 2013;87(16):8962-8670.  
doi: 10.1128/JVI.00739-13
46. Marcink TC, Wang T, Des Georges A, Porotto M, Moscona A. Human parainfluenza virus fusion complex glycoproteins imaged in action on authentic viral surfaces. *PLoS Pathog*. 2020;16(9):e1008883.  
doi: 10.1371/journal.ppat.1008883
47. Yoshizumi M, Kimura H, Okayama Y, *et al*. Relationships between cytokine profiles and signaling pathways (IkappaB kinase and p38 MAPK) in parainfluenza virus-infected lung fibroblasts. *Front Microbiol*. 2010;1:124.  
doi: 10.3389/fmicb.2010.00124
48. Aviner R, Frydman J. Proteostasis in viral infection: Unfolding the complex virus-chaperone interplay. *Cold Spring Harb Perspect Biol*. 2020;12(3):a034090  
doi: 10.1101/cshperspect.a034090
49. Wu W, Li R, Li X, *et al*. Quercetin as an antiviral agent inhibits influenza A virus (IAV) entry. *Viruses*. 2015;8(1):6.  
doi: 10.3390/v8010006
50. Henss L, Auste A, Schurmann C, *et al*. The green tea catechin epigallocatechin gallate inhibits SARS-CoV-2 infection. *J Gen Virol*. 2021;102(4):001574.  
doi: 10.1099/jgv.0.001574
51. Pang P, Zheng K, Wu S, *et al*. Baicalin downregulates RLRs signaling pathway to control influenza A virus infection and improve the prognosis. *Evid Based Complement Alternat Med*. 2018;2018:4923062.  
doi: 10.1155/2018/4923062
52. Yang JY, Ma YX, Liu Y, Peng XJ, Chen XZ. A comprehensive review of natural flavonoids with anti-SARS-CoV-2 activity. *Molecules*. 2023;28(6):2735.  
doi: 10.3390/molecules28062735
53. Guo Y, Ma A, Wang X, *et al*. Research progress on the antiviral activities of natural products and their derivatives: Structure-activity relationships. *Front Chem*. 2022;10:1005360.  
doi: 10.3389/fchem.2022.1005360
54. Owen L, Laird K, Shivkumar M. Antiviral plant-derived natural products to combat RNA viruses: Targets throughout the viral life cycle. *Lett Appl Microbiol*. 2022;75(3):476-499.  
doi: 10.1111/lam.13637
55. Li CW, Chao TL, Lai CL, *et al*. Systematic studies on the anti-SARS-CoV-2 mechanisms of tea polyphenol-related natural products. *ACS Omega*. 2024;9(22):23984-23997.  
doi: 10.1021/acsomega.4c02392
56. Yang J, Petitjean SJL, Koehler M, *et al*. Molecular interaction and inhibition of SARS-CoV-2 binding to the ACE2 receptor. *Nat Commun*. 2020;11(1):4541.  
doi: 10.1038/s41467-020-18319-6
57. Liu J, Bodnar BH, Meng F, *et al*. Epigallocatechin gallate from green tea effectively blocks infection of SARS-CoV-2 and new variants by inhibiting spike binding to ACE2 receptor. *Cell Biosci*. 2021;11(1):168.  
doi: 10.1186/s13578-021-00680-8
58. Ohgitani E, Shin-Ya M, Ichitani M, *et al*. Significant inactivation of SARS-CoV-2 *in vitro* by a green tea catechin, a catechin-derivative, and black tea galloylated theaflavins. *Molecules*. 2021;26(12):3572.  
doi: 10.3390/molecules26123572
59. Roy AV, Chan M, Banadyga L, *et al*. Quercetin inhibits SARS-CoV-2 infection and prevents syncytium formation by cells co-expressing the viral spike protein and human ACE2. *Virol J*. 2024;21(1):29.  
doi: 10.1186/s12985-024-02299-w
60. Severin C, Rocha de Moura T, Liu Y, Li K, Zheng X, Luo M. The cap-binding site of influenza virus protein PB2 as a drug target. *Acta Crystallogr D Struct Biol*. 2016;72(Pt 2):245-53.  
doi: 10.1107/S2059798316000085
61. Corona A, Wycisk K, Talarico C, *et al*. Natural compounds inhibit SARS-CoV-2 nsp13 unwinding and ATPase enzyme activities. *ACS Pharmacol Transl Sci*. 2022;5(4):226-239.  
doi: 10.1021/acspsci.1c00253
62. Cheng FJ, Huynh TK, Yang CS, *et al*. Hesperidin is a potential inhibitor against SARS-CoV-2 infection. *Nutrients*. 2021;13(8):2800.  
doi: 10.3390/nu13082800
63. Jang M, Park YI, Cha YE, *et al*. Tea polyphenols EGCG and theaflavin inhibit the activity of SARS-CoV-2 3CL-protease *in vitro*. *Evid Based Complement Altern Med*. 2020;2020(1):5630838.  
doi: 10.1155/2020/5630838
64. Kawall A, Lewis DSM, Sharma A, *et al*. Inhibitory effect of phytochemicals towards SARS-CoV-2 papain like protease (PLpro) proteolytic and deubiquitinase activity. *Front Chem*. 2022;10:1100460.  
doi: 10.3389/fchem.2022.1100460
65. Chauhan M, Bhardwaj VK, Kumar A, *et al*. Theaflavin 3-gallate inhibits the main protease (M(pro)) of SARS-CoV-2 and reduces its count *in vitro*. *Sci Rep*. 2022;12(1):13146.  
doi: 10.1038/s41598-022-17558-5
66. LeBlanc EV, Colpitts CC. The green tea catechin EGCG provides proof-of-concept for a pan-coronavirus attachment inhibitor. *Sci Rep*. 2022;12(1):12899.  
doi: 10.1038/s41598-022-17088-0
67. Semper C, Watanabe N, Savchenko A. Structural characterization of nonstructural protein 1 from

- SARS-CoV-2. *iScience*. 2021;24(1):101903.  
doi: 10.1016/j.isci.2020.101903
68. Ezeonwumelu IJ, Garcia-Vidal E, Ballana E. JAK-STAT pathway: A novel target to tackle viral infections. *Viruses*. 2021;13(12):2379.  
doi: 10.3390/v13122379
69. Donelan NR, Dauber B, Wang X, Basler CF, Wolff T, Garcia-Sastre A. The N- and C-terminal domains of the NS1 protein of influenza B virus can independently inhibit IRF-3 and beta interferon promoter activation. *J Virol*. 2004;78(21):11574-11582.  
doi: 10.1128/jvi.78.21.11574-11582.2004
70. Li R, Wang L. Baicalin inhibits influenza virus A replication via activation of type I IFN signaling by reducing miR146a. *Mol Med Rep*. 2019;20(6):5041-5049.  
doi: 10.3892/mmr.2019.10743
71. Ehambarampillai D, Wan MLY. A comprehensive review of Schisandra chinensis lignans: Pharmacokinetics, pharmacological mechanisms, and future prospects in disease prevention and treatment. *Chin Med*. 2025;20(1):47.  
doi: 10.1186/s13020-025-01096-z
72. Rostom B, Karaky R, Kassab I, Sylla-Iyarreta Veitia M. Coumarins derivatives and inflammation: Review of their effects on the inflammatory signaling pathways. *Eur J Pharmacol*. 2022;922:174867.  
doi: 10.1016/j.ejphar.2022.174867
73. Cwilichowska-Puslecka N, Makowiecka A, Kalinka M, et al. Understanding the long-term interplay of SARS-CoV-2 immune and inflammatory responses with proteases in COVID-19 recovery: A longitudinal study. *Front Immunol*. 2025;16:1517933.  
doi: 10.3389/fimmu.2025.1517933
74. Huo R, Huang X, Yang Y, Yang Y, Lin J. Potential of resveratrol in the treatment of interstitial lung disease. *Front Pharmacol*. 2023;14:1139460.  
doi: 10.3389/fphar.2023.1139460
75. Barnes P, Agbo E, Halm-Lai F, et al. Insight into the immunomodulatory and chemotherapeutic mechanisms of paeonol (review). *Med Int (Lond)*. 2025;5(3):24.  
doi: 10.3892/mi.2025.223
76. Ma J, Yan S, Zhao Y, Yan H, Zhang Q, Li X. Blockade of PD-1 and LAG-3 expression on CD8+ T cells promotes the tumoricidal effects of CD8+ T cells. *Front Immunol*. 2023;14:1265255.  
doi: 10.3389/fimmu.2023.1265255
77. Liu Z, Ying Y. The inhibitory effect of curcumin on virus-induced cytokine storm and its potential use in the associated severe pneumonia. *Front Cell Dev Biol*. 2020;8:479.  
doi: 10.3389/fcell.2020.00479
78. See WR, Yousefi M, Ooi YS, Prasad VR. A review of virus host factor discovery using CRISPR screening. *mBio*. 2024;15(11):e0320523.  
doi: 10.1128/mbio.03205-23
79. Zhang S, Mao B, Cui S, et al. Absorption, metabolism, bioactivity, and biotransformation of epigallocatechin gallate. *Crit Rev Food Sci Nutr*. 2024;64(19):6546-6566.  
doi: 10.1080/10408398.2023.2170972
80. Manach C, Williamson G, Morand C, Scalbert A, Remesy C. Bioavailability and bioefficacy of polyphenols in humans. I. Review of 97 bioavailability studies. *Am J Clin Nutr*. 2005;81(1 Suppl):230S-242S.  
doi: 10.1093/ajcn/81.1.230S
81. Gokul V, Kothapalli P, Vasanthan M. A comprehensive review on solid lipid nanoparticles as a carrier for oral absorption of phyto-bioactives. *Cureus*. 2024;16(8):e68339.  
doi: 10.7759/cureus.68339
82. Shaw LH, Lin LC, Tsai TH. HPLC-MS/MS analysis of a traditional Chinese medical formulation of Bu-Yang-Huan-Wu-Tang and its pharmacokinetics after oral administration to rats. *PLoS One*. 2012;7(8):e43848.  
doi: 10.1371/journal.pone.0043848
83. Xue H, Li P, Bian J, Gao Y, Sang Y, Tan J. Extraction, purification, structure, modification, and biological activity of traditional Chinese medicine polysaccharides: A review. *Front Nutr*. 2022;9:1005181.  
doi: 10.3389/fnut.2022.1005181
84. Singh R, Singh PK, Kumar R, et al. Multi-omics approach in the identification of potential therapeutic biomolecule for COVID-19. *Front Pharmacol*. 2021;12:652335.  
doi: 10.3389/fphar.2021.652335
85. Geng P, Zhu H, Zhou W, et al. Baicalin inhibits influenza A virus infection via promotion of M1 macrophage polarization. *Front Pharmacol*. 2020;11:01298.  
doi: 10.3389/fphar.2020.01298
86. Davis JM, Murphy EA, McClellan JL, Carmichael MD, Gangemi JD. Quercetin reduces susceptibility to influenza infection following stressful exercise. *Am J Physiol Regul Integr Comp Physiol*. 2008;295(2):R505-R509.  
doi: 10.1152/ajpregu.90319.2008
87. Hu K, Guan WJ, Bi Y, et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: A multicenter, prospective, randomized controlled trial. *Phytomedicine*. 2021;85:153242.  
doi: 10.1016/j.phymed.2020.153242
88. Sun XH, Zhang S, Yang Z, et al. Efficacy and safety of Lianhua

- Qingwen for patients with COVID-19: A systematic review and meta-analysis. *Chin J Integr Med*. 2022;28(7):650-660.  
doi: 10.1007/s11655-022-3578-8
89. Wang S, Sun Q, Xu Y, Pei J, Lai L. A transferable deep learning approach to fast screen potential antiviral drugs against SARS-CoV-2. *Brief Bioinform*. 2021;22(6):bbab211.  
doi: 10.1093/bib/bbab211
90. Ancajas CMF, Oyedele AS, Butt CM, Walker AS. Advances, opportunities, and challenges in methods for interrogating the structure activity relationships of natural products. *Nat Prod Rep*. 2024;41(10):1543-1578.  
doi: 10.1039/d4np00009a
91. Jumper J, Evans R, Pritzel A, *et al*. Highly accurate protein structure prediction with AlphaFold. *Nature*. 2021;596(7873):583-589.  
doi: 10.1038/s41586-021-03819-2
92. Chigozie VU, Ugochukwu CG, Igboji KO, Okoye FB. Application of artificial intelligence in bioprospecting for natural products for biopharmaceutical purposes. *BMC Artif Intell*. 2025;1(1):4.  
doi: 10.1186/s44398-025-00004-7
93. Zhang HW, Lv C, Zhang LJ, *et al*. Application of omics- and multi-omics-based techniques for natural product target discovery. *Biomed Pharmacother*. 2021;141:111833.  
doi: 10.1016/j.biopha.2021.111833
94. Martinez Molina D, Jafari R, Ignatushchenko M, *et al*. Monitoring drug target engagement in cells and tissues using the cellular thermal shift assay. *Science*. 2013;341(6141):84-87.  
doi: 10.1126/science.1233606
95. Sadegh S, Skelton J, Anastasi E, *et al*. Network medicine for disease module identification and drug repurposing with the NeDRex platform. *Nat Commun*. 2021;12(1):6848.  
doi: 10.1038/s41467-021-27138-2
96. Saldivar-Gonzalez FI, Aldas-Bulos VD, Medina-Franco JL, Plisson F. Natural product drug discovery in the artificial intelligence era. *Chem Sci*. 2022;13(6):1526-1546.  
doi: 10.1039/d1sc04471k
97. Du P, Fan R, Zhang N, Wu C, Zhang Y. Advances in integrated multi-omics analysis for drug-target identification. *Biomolecules*. 2024;14(6):69.  
doi: 10.3390/biom14060692
98. Jaffe SR, Strutton B, Levarski Z, Pandhal J, Wright PC. *Escherichia coli* as a glycoprotein production host: Recent developments and challenges. *Curr Opin Biotechnol*. 2014;30:205-210.  
doi: 10.1016/j.copbio.2014.07.006
99. Rainha J, Rodrigues JL, Rodrigues LR. *De novo* biosynthesis of Curcumin in *Saccharomyces cerevisiae*. *ACS Synth Biol*. 2024;13(6):1727-1736.  
doi: 10.1021/acssynbio.4c00059
100. Smanski MJ, Zhou H, Claesen J, Shen B, Fischbach MA, Voigt CA. Synthetic biology to access and expand nature's chemical diversity. *Nat Rev Microbiol*. 2016;14(3):135-149.  
doi: 10.1038/nrmicro.2015.24
101. Lin D, Jiang S, Zhang A, Wu T, Qian Y, Shao Q. Structural derivatization strategies of natural phenols by semi-synthesis and total-synthesis. *Nat Prod Bioprospect*. 2022;12(1):8.  
doi: 10.1007/s13659-022-00331-6
102. Tanifuji R, Oguri H. Chemo-enzymatic total synthesis: current approaches toward the integration of chemical and enzymatic transformations. *Beilstein J Org Chem*. 2024;20:1693-1712.  
doi: 10.3762/bjoc.20.151
103. Cojocar E, Petris OR, Cojocar C. Nanoparticle-based drug delivery systems in inhaled therapy: Improving respiratory medicine. *Pharmaceuticals (Basel)*. 2024;17(8):1059.  
doi: 10.3390/ph17081059
104. Clementino AR, Pellegrini G, Banella S, *et al*. Structure and fate of nanoparticles designed for the nasal delivery of poorly soluble drugs. *Mol Pharm*. 2021;18(8):3132-3146.  
doi: 10.1021/acs.molpharmaceut.1c00366
105. Huh D, Matthews BD, Mammoto A, Montoya-Zavala M, Hsin HY, Ingber DE. Reconstituting organ-level lung functions on a chip. *Science*. 2010;328(5986):1662-1668.  
doi: 10.1126/science.1188302
106. Zamprogno P, Wuthrich S, Achenbach S, *et al*. Second-generation lung-on-a-chip with an array of stretchable alveoli made with a biological membrane. *Commun Biol*. 2021;4(1):168.  
doi: 10.1038/s42003-021-01695-0