ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

Mechanisms and Research Progress of Plant-Derived Active Compounds against Respiratory Syncytial Virus

Bingyao Wang[1,a,†], Daishun Liu[2,b,*,†]

[1]*Zhuhai Campus of Zunyi Medical University, Zhuhai, China*
[2]*The Fifth Affiliated Hospital (Zhuhai) of Zunyi Medical University, Zhuhai, China*
[a]*625006253@qq.com*, [b]*ldsdoc@126.com*
[*]*Corresponding author*
[†]*The Author Contributed Equally to This Study*

Abstract: *Respiratory syncytial virus (RSV) is a leading cause of lower respiratory tract infections in infants, young children, and the elderly, yet effective therapeutic options remain limited. Plant-derived active compounds, owing to their multi-target mechanisms and low toxicity, have emerged as a promising resource for anti-RSV drug development. This review systematically summarizes recent progress on plant phytochemicals such as quercetin and andrographolide against RSV. Mechanisms of action include blocking viral attachment (e.g., resveratrol competitively binding to heparan sulfate proteoglycan receptors), inhibiting viral genome replication (e.g., quercetin regulating purine metabolism), and enhancing host immune responses (e.g., polysaccharides modulating the TLR/NF-κB pathway), thereby achieving synergistic antiviral effects. Key compounds focus on polyphenols (flavonoids, phenolic acids), terpenoids (monoterpenes, diterpenes), and alkaloids, with emphasis on their structure–activity relationships. Translational challenges such as poor bioavailability and component complexity are discussed, with proposed strategies including nanocarrier delivery systems (e.g., matrine liposomes) and structural modification approaches. The multi-target characteristics of plant-derived compounds provide new directions for the development of novel anti-RSV therapies.*

Keywords: *Respiratory Syncytial Virus; Natural Products; Mechanisms; Antiviral; Immunomodulation*

1. Background

Respiratory syncytial virus (RSV), belonging to the genus Pneumovirus of the family Paramyxoviridae, is a single-stranded, negative-sense RNA virus. Its genome encodes multiple proteins and is enclosed within a lipid envelope derived from the host cell membrane. The envelope contains key structural proteins, including the fusion protein (F protein) and the attachment glycoprotein (G protein). RSV can be classified into two major genotypes: A and B[1].RSV infection is the leading etiological factor of severe lower respiratory tract infections (LRTIs) in infants and young children worldwide, accounting for approximately 22% to 40% of severe LRTI cases in children under two years of age. Moreover, the disease burden has significantly extended to elderly populations (≥65 years) and immunocompromised individuals, such as recipients of hematopoietic stem cell transplantation.[2,3], Epidemiological data indicate that in 2019, approximately 4.1 million children under the age of five were hospitalized worldwide due to RSV infection [4], Among them, approximately 100,000 deaths occurred in children, accounting for 2.0% of the total global mortality in this age group[5].Currently, preventive measures against RSV include palivizumab, which is used for prophylaxis in high-risk infants [6] and nirsevimab, which is used for the prevention of RSV-associated lower respiratory tract infections (RSV-LRTIs) in newborns[7].Both are monoclonal antibodies, however, there remains a significant lack of effective and specific therapeutic agents for RSV in clinical practice [8], The clinical use of ribavirin is also limited due to its toxicity and controversial efficacy. Therefore, the development of safe and effective novel anti-RSV therapeutics represents an urgent unmet need in the field of global public health.

Plant-derived bioactive compounds, as a vital category of natural products, have garnered significant attention in antiviral drug development due to their structural diversity, multi-target mechanisms of action, and relatively low cytotoxicity. Numerous studies have demonstrated that various plant extracts and their isolated monomeric compounds—such as flavonoids, terpenoids, alkaloids, and polysaccharides—exhibit potent inhibitory effects against RSV both in vitro and in vivo. Additionally, some of these

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

compounds have shown promising immunomodulatory activities.

However, the translation of plant-derived bioactive compounds from basic research to clinical applications faces multiple challenges. These include precise screening and identification of active constituents, in-depth elucidation of complex mechanisms of action, optimization of pharmacokinetic properties—especially bioavailability—and breakthroughs in formulation technologies.

This review aims to systematically summarize the recent advances in the anti-RSV effects of plant-derived bioactive compounds, with a focus on their major chemical classes, representative active molecules, and detailed mechanisms of action, including viral life cycle interference and host immune regulation. Furthermore, the current challenges and potential strategies for overcoming these obstacles are discussed in depth. By integrating existing knowledge, this review intends to provide a theoretical foundation and new perspectives for the development of novel anti-RSV therapeutics based on plant-derived bioactive compounds.

2. Mechanisms of Action of Plant-Derived Bioactive Compounds Against RSV and Representative Compounds

2.1 Flavonoids

Flavonoids are widely distributed in the plant kingdom and have become a major focus in anti-RSV research due to their notable antiviral, anti-inflammatory, and antioxidant activities. Their effects are not limited to the direct inhibition of viral replication but also involve the regulation of host metabolism and immune responses to alleviate virus-induced pathological damage.

Representative compounds include quercetin, hesperetin, catechin, and resveratrol[9].Quercetin: Studies have found that uric acid levels are significantly elevated in the lung aspirates of infants with severe RSV infection[10], Purine metabolism disorder plays a significant role in the pathogenesis of RSV. Quercetin exerts its therapeutic effects by regulating key purine metabolism targets, including hypoxanthine-guanine phosphoribosyltransferase 1 (HPRT1), thymidine phosphorylase (TYMP), lipoxygenase (LPO), and myeloperoxidase (MPO). Through modulating these enzymes, quercetin influences the levels of metabolites such as adenosine monophosphate (AMP), hypoxanthine, and uric acid, thereby restoring metabolic balance disrupted by RSV infection and alleviating pulmonary inflammation and tissue damage[11].Resveratrol: Heparan sulfate proteoglycan (HSPG) serves as the primary receptor for RSV attachment to host cells in immortalized cell lines in vitro[12].Studies have shown that resveratrol can bind to the negatively charged sites on HSPG, effectively competing with RSV for early attachment to host receptors, thereby blocking the viral infection process[13].Catechin and Citrus Flavanone Derivatives: Catechin exhibits stage-specific antiviral effects against RSV, primarily by interfering with the membrane fusion process mediated by viral glycoproteins, while having limited impact on the activity of viral RNA-dependent RNA polymerase. In contrast, certain citrus flavanone derivatives mainly target the viral genome replication stage, significantly reducing viral load and demonstrating broad-spectrum inhibitory activity against enveloped viruses [14].

Flavonoids demonstrate the ability to intervene in RSV infection through multiple pathways, including blocking viral attachment and entry, inhibiting replication, and modulating host metabolism and immune responses. In-depth investigation of their specific molecular targets and signaling pathways is crucial for understanding the pathogenesis of RSV and for the development of novel antiviral strategies.

2.2 Phenolic acids

Phenolic acids are common phenylpropanoid derivatives in plants, exhibiting antioxidant, anti-inflammatory, and antiviral activities.

Caffeic Acid (CA): Studies have shown that CA exhibits inhibitory effects on RSV-induced cytopathic effects (CPE). Its antiviral mechanism does not involve blocking viral attachment or entry into host cells but rather significantly suppresses RSV genomic replication and the proliferation of progeny viruses [15]. Ferulic Acid and Isoferulic Acid: Both compounds have been shown to effectively inhibit the production of macrophage inflammatory protein-2 (MIP-2) in RSV-infected RAW264.7 macrophages, thereby attenuating the inflammation caused by viral infection [16]. In addition, Protocatechuic Acid: As a potent antioxidant, protocatechuic acid protects cells by scavenging free radicals and alleviating oxidative stress. It has also been demonstrated to possess strong in vitro anti-RSV activity [17].

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

Phenolic acid compounds, especially their antioxidant and anti-inflammatory properties, provide a solid scientific foundation for their potential as candidate drugs against RSV. However, their precise antiviral mechanisms remain to be fully elucidated.

2.3 Tannins

Tannins are a class of plant secondary metabolites characterized by multiple phenolic hydroxyl groups and the ability to precipitate proteins. Tannic Acid: Insulin-like growth factor 1 receptor (IGF1R) has been identified as a key receptor facilitating RSV entry into host cells. Molecular dynamics simulations have demonstrated that tannic acid can bind to the IGF1R protein. Both in vitro and in vivo experiments have confirmed that tannic acid effectively reduces viral load, alleviates pulmonary inflammation and airway hyperresponsiveness, and preserves the structural integrity of alveolar tissues [18]. Grape Seed Proanthocyanidins (GSPs): GSPs are typical condensed tannins. Studies have shown that pretreatment with GSPs (5–10 mg/L) can significantly inhibit the mRNA and protein expression of multiple mucins (MUC1, MUC2, MUC5AC, MUC5B, MUC8) in RSV-infected human airway epithelial A549 cells, thereby alleviating virus-induced mucus hypersecretion. In addition, GSPs suppress multiple signaling pathways activated by RSV, including extracellular signal-regulated kinase (ERK), c-Jun N-terminal kinase (JNK), p38 mitogen-activated protein kinase (MAPK), NF-κB, and activator protein-1 (AP-1, including c-Jun and c-Fos), ultimately leading to a reduction in viral replication within host cells[19].

Tannin compounds, with their polyphenolic nature and multi-target activities, exhibit distinct advantages in interfering with the RSV life cycle (e.g., viral entry) and modulating host responses (e.g., inhibition of mucus secretion and inflammatory signaling). These characteristics make tannins promising natural candidates for anti-RSV drug development.

2.4 Polysaccharides

Plant-derived polysaccharides possess various biological activities, including immunomodulatory and antiviral effects, making them important candidates for the development of anti-RSV therapeutics [20].

Salvia plebeia R. Br. Polysaccharides (SPP): SPP fractions with molecular weights greater than 10,000 have demonstrated significant anti-RSV activity both in vitro and in vivo. Their mechanism involves the inhibition of Toll-like receptor 3 (TLR3) and Toll-like receptor 4 (TLR4) expression, upregulation of interferon-gamma (IFN-γ) and interleukin-2 (IL-2), and suppression of tumor necrosis factor-alpha (TNF-α) release, thereby exerting immunomodulatory and antiviral effects[21].Platycodon grandiflorus Polysaccharides: This polysaccharide significantly reduces levels of inflammatory cytokines in the lungs of RSV-infected mice, decreases inflammatory cell infiltration, and alleviates apoptosis in RSV-infected human laryngeal epithelial carcinoma (HEp-2) cells. Its effects may be related to the inhibition of microRNA-181a-5p (miR-181a-5p) expression, which subsequently activates the Hippo and sirtuin 1 (SIRT1) signaling pathways[22].Astragalus Polysaccharides (APS): APS alleviates inflammatory responses and oxidative stress by inhibiting the activation of the TLR4/MAPK/NF-κB signaling pathway. Additionally, it modulates the peripheral blood $CD4^+/CD8^+$ T cell ratio, improving lung pathology, weight loss, and increased lung index in RSV-infected mice[23].Garlic Polysaccharides: These polysaccharides effectively inhibit RSV biosynthesis by downregulating the expression of the viral L and P genes. They also significantly reduce the levels of inflammatory cytokines such as IL-6 and IL-8, exhibiting an inhibitory effect comparable to that of ribavirin[24].Pectin and Its Derivatives: Sulfated pectin extracted from mango peels exhibited no cytotoxicity at a concentration of 2000 mg/L and significantly inhibited RSV infection, with a half-maximal inhibitory concentration (IC_{50}) of 0.77 ± 0.11 mg/L, demonstrating strong antiviral potential[25].Hot water extract of Arthrospira maxima (SHD1) effectively inhibits RSV attachment and internalization. Its mechanism primarily involves interfering with the binding of the RSV G protein to the host cell surface HSPG receptor, thereby reducing viral attachment. The half-maximal effective concentration (EC_{50}) is 91.5 mg/L, with a selectivity index (SI) greater than 261.5[26].

Polysaccharides exert anti-RSV effects through multiple mechanisms, including inhibition of viral replication, modulation of host innate and adaptive immunity (such as activation of immune cells and regulation of cytokine secretion), and alleviation of inflammation and oxidative stress, demonstrating promising potential for further development.

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

2.5 Terpenoids

Terpenoids (also known as isoprenoids) exhibit diverse structures and a wide range of biological activities, making them an important source for the development of anti-RSV drugs [27].

Andrographolide: Derived from Andrographis paniculata, a traditional medicinal herb known for its heat-clearing and detoxifying properties[28], In A549 and human bronchial epithelial (16HBE) cell models, andrographolide significantly inhibits RSV replication and reduces levels of pro-inflammatory cytokines. Network pharmacology and transcriptomic analyses have revealed that the heme oxygenase-1 (HO-1) gene plays a central role in its anti-RSV effects. Knockdown experiments of the HO-1 gene confirmed that andrographolide exerts its antiviral activity primarily by inducing HO-1 expression, rather than relying on the traditional interferon pathway [29]. Further studies have shown that andrographolide can also inhibit apoptosis induced by RSV infection and promote pyroptosis by upregulating key proteins such as caspase-1, cleaved caspase-1, interleukin-1β (IL-1β), and the N-terminal domain of gasdermin D (GSDMD). This regulation of cell death modes—suppressing apoptosis while promoting pyroptosis—may aid in the clearance of infected cells and the modulation of inflammation [30].Forsyshiyanins, a group of novel diterpenoid compounds including forsyshiyanins A and B, were isolated from the fruits of Forsythia suspensa. Structural characterization through spectroscopic analysis and X-ray diffraction confirmed their identities, and some of these compounds have demonstrated significant anti-RSV activity [31]. Coumarin-monoterpene conjugates: These compounds exhibit potent inhibitory effects against both RSV subtypes A and B, primarily targeting the early stages of the viral life cycle. Molecular docking studies suggest that the RSV fusion (F) protein may serve as their main target[32].Cassaine diterpenoids: Seven novel cassaine diterpenoids isolated from the seeds of Erythrophleum fordii Oliv. have been identified, with several compounds demonstrating significant in vitro antiviral activity against RSV (IC_{50} values of 0.0063, 0.0078, and 0.0094 mol/L, respectively), alongside notable anti-inflammatory effects [33]. Thapsigargin (TG): TG has been identified as a broad-spectrum antiviral agent, exhibiting significant inhibitory effects against RSV, influenza virus, and coronaviruses. It suppresses viral replication by activating the host innate immune response, and its anti-RSV efficacy surpasses that of remdesivir and ribavirin [34].

Terpenoids, especially diterpenoid and monoterpenoid derivatives, exhibit potent anti-RSV effects through multiple mechanisms, including targeting viral entry and replication (e.g., acting on the F protein) and modulating host responses (such as inducing HO-1 expression, regulating cell death pathways, and activating innate immunity). They represent a valuable resource for novel drug discovery.

2.6 Alkaloids

Alkaloids are nitrogen-containing organic compounds renowned for their complex structures, diverse bioactivities, and wide-ranging applications. In plants, alkaloids typically function as secondary metabolites involved in defense mechanisms and signal transduction [35]. Sesquiterpene pyridine alkaloids: A sesquiterpene pyridine alkaloid was isolated from the stems and leaves of Euonymus fortunei (Fufang Teng). Its structure was elucidated using comprehensive spectroscopic techniques, including IR, UV, NMR, HRESIMS, and ECD. This compound exhibited significant in vitro anti-RSV activity, with an IC_{50} value lower than that of the positive control drug ribavirin [36]. Matrine: Matrine exhibits antiviral activity against RSV. To enhance its pulmonary targeting and retention time, researchers have developed chitosan-coated matrine liposomes. This inhalable formulation leverages the bioadhesive properties of chitosan to effectively overcome the mucus barrier of the upper respiratory tract, significantly improving matrine's anti-RSV efficacy in the lungs. This approach offers a novel strategy for the localized treatment of respiratory infections [37]. Papaverine: Studies have shown that papaverine exhibits inhibitory effects against various influenza viruses and paramyxoviruses, including RSV, human parainfluenza virus type 3 (HPIV3), and parainfluenza virus type 5 (PIV5). Its mechanism involves interfering with late stages of the viral life cycle, such as the nuclear export of viral ribonucleoproteins (vRNP), as well as modulating host cell cyclic adenosine monophosphate (cAMP) levels and the MAPK/ERK signaling pathway. Additionally, papaverine can alter the morphology of influenza viruses [38].

Pentoxifylline: It can significantly inhibit the expression of TNF-α in human alveolar macrophages infected with RSV, thereby helping to alleviate the excessive inflammatory response following RSV infection [39]. Glycyrrhizic Acid (GA) and Ephedrine (EPH) Nanogel: The EPH-GA nanogel, self-assembled through hydrogen bonding and hydrophobic interactions, demonstrated significant synergistic antiviral effects in an RSV-infected mouse model. Its efficacy surpassed that of either component alone, markedly reducing pulmonary viral load, ameliorating lung injury, and enhancing the bioavailability and

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

stability of ephedrine[40], In addition to the studies mentioned above, berberine and its derivatives have been shown to effectively inhibit a variety of viruses, including HIV, influenza virus, and RSV . Their antiviral mechanisms primarily involve modulation of host cell signaling pathways, thereby interfering with critical stages of the viral life cycle—such as viral entry, replication, and release—to suppress viral proliferation [41].

Alkaloid compounds exhibit structural diversity and distinct mechanisms of action. Through structural modification and the development of novel drug delivery systems—such as nanogels and liposomes—the limitations of alkaloids, including poor bioavailability, can be effectively addressed. These advancements enhance their anti-RSV efficacy and demonstrate promising translational potential for future therapeutic applications.

2.7 Other Types of Natural Products

In addition to the aforementioned categories, other natural product classes such as anthraquinones and phenylpropanoids have also achieved significant breakthroughs and advancements in anti-RSV research.

Gastrodin (a phenylpropanoid compound): In RSV-infected rat models, gastrodin alleviated pulmonary neutrophil infiltration, alveolar structural damage, and lung inflammation by inhibiting the Notch/NF-κB signaling pathway, reducing the expression of pro-inflammatory cytokines such as TNF-α, IL-1β, IL-6, and IL-17A. Moreover, gastrodin restored the balance between T helper 17 (Th17) cells and regulatory T (Treg) cells, contributing to its overall anti-inflammatory and immunomodulatory effects[42].Emodin (Anthraquinone derivative):In vitro studies have demonstrated that emodin exhibits concentration- and time-dependent antiviral activity against RSV, with particularly pronounced effects during the early stages of infection (0–4 hours post-infection). The underlying mechanism may involve the suppression of interferon-α (IFN-α) mRNA expression and the upregulation of tumor necrosis factor-γ (TNF-γ) mRNA levels, thereby modulating the host immune response to inhibit viral replication[43].Eugenia-Derived Terpenoids and Naphthoquinone-Monoterpene Adducts:Compounds of this class, isolated from Eugenia caryophyllata (clove), have been shown to significantly inhibit RSV-induced nitric oxide (NO) production in RAW264.7 macrophage cells, demonstrating both anti-inflammatory and antiviral activities[44].

These compounds exert anti-RSV effects through various mechanisms, including modulation of immune signaling pathways (such as Notch/NF-κB), regulation of cytokine expression, or direct inhibition of viral replication. These findings further expand the pool of plant-derived candidates for antiviral drug development (Table 1).

Table 1. Intervention Mechanisms Targeting RSV Life Cycle

Stage	Intervention Agents	Mechanism of Action	Target/Pathway
Attachment	Resveratrol Spirulina Polysaccharide (SHD1)	Competitively binds to host cell surface receptors, blocking viral attachment	HSPG receptor
Entry	Tannic Acid Catechin	Inhibits IGF1R-mediated endocytosis Interferes with F protein-mediated membrane fusion	IGF1R / F protein
Uncoating	Matrine Liposomes	Disrupts viral envelope integrity	Viral envelope
Replication	Quercetin Caffeic Acid Naringenin	Regulates purine metabolism (via HPRT1/TYMP) Inhibits RSV RNA polymerase activity	Purine metabolism pathway RNA polymerase
Assembly	Berberine Derivatives	Interferes with viral nucleocapsid assembly	Nucleocapsid protein
Release	Papaverine	Blocks nuclear export of viral ribonucleoprotein (vRNP)	vRNP transport mechanism

3. Traditional Chinese Medicine (TCM) Formulas

Traditional Chinese medicine (TCM), with its core principles of "holistic concept" and "treatment based on syndrome differentiation," emphasizes the synergistic effects of multiple components acting on multiple targets. This approach offers unique advantages in treating complex diseases, particularly respiratory viral infections. Chinese herbal medicines are rich in natural products with low toxicity and diverse mechanisms of action. These compounds not only exert direct antiviral effects but also provide comprehensive therapeutic benefits through immunomodulation, anti-inflammatory, and antioxidant activities. This multi-level treatment strategy effectively reduces the risk of drug resistance, offering new

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

perspectives for the management of viral infections and highlighting the significant value of TCM in modern medicine.

Ge-Gen-Tang (GGT), a traditional Chinese herbal formula, has demonstrated potential anti-RSV activity. Studies have shown that the hot water extract of GGT significantly inhibits RSV-induced plaque formation in a dose-dependent manner, with particularly pronounced effects observed in A549 cells. Notably, its antiviral efficacy is more prominent when administered prior to viral infection. The underlying mechanisms involve the inhibition of viral attachment and internalization, as well as the enhancement of antiviral immune responses by stimulating the secretion of interferon-β (IFN-β) [45].

Guben-fangxiao decoction (GBFXD) demonstrated significant therapeutic effects in an RSV-induced asthma mouse model. The study revealed that GBFXD effectively reduced levels of pro-inflammatory factors transforming growth factor-β (TGF-β) and interleukin-6 (IL-6) in bronchoalveolar lavage fluid, while significantly downregulating the expression of the asthma susceptibility gene ORMDL3 in lung tissues. These mechanisms are likely associated with GBFXD's ability to alleviate airway inflammation, reduce airway remodeling, and inhibit immune dysregulation. Furthermore, treatment groups receiving high, medium, and low doses of GBFXD showed efficacy comparable to montelukast, indicating its promising potential in combating airway inflammation and modulating gene expression [46].

Maxing Ganshi Decoction (MXGSD) demonstrated significant protective effects in an RSV-exacerbated asthma mouse model, indicating its potential therapeutic value. Studies showed that MXGSD effectively alleviated inflammatory cell infiltration and pathological damage in lung tissue while reducing airway hyperresponsiveness. Its mechanism of action is likely closely related to the downregulation of TRPV1 channel mRNA and protein expression in lung tissues. Additionally, MXGSD markedly inhibited the release of Th2-type cytokines (such as IL-4 and IL-13) and neurogenic inflammatory mediators (such as PGE2 and substance P), further mitigating inflammation and airway remodeling. In vitro experiments also confirmed that MXGSD-containing serum significantly reduced the intracellular Ca^{2+} concentration increase induced by capsaicin stimulation in 16HBE cells, demonstrating its clear role in regulating airway neurogenic inflammation [47].

Wuhu Decoction is a classic traditional Chinese medicine formula first recorded in the Treatise on Febrile Diseases (Shang Han Lun), primarily used to treat respiratory issues such as cough and asthma caused by wind-cold invasion. The formula contains Ephedra (Ma Huang), Apricot Kernel (Xing Ren), Licorice (Gan Cao), Gypsum (Shi Gao), and Fresh Ginger (Sheng Jiang), which work synergistically to release the exterior and dispel cold, clear heat and resolve phlegm, and relieve asthma by promoting lung function.

Through the combined actions of multiple components targeting multiple pathways, Wuhu Decoction significantly improves lung function in RSV-induced asthma model mice, reduces levels of pro-inflammatory cytokines such as IL-6, IL-17, and TNF-α, and inhibits the expression of key proteins including NLRP3, MAPK1, MAPK14, and NFKB1. Its main mechanisms involve regulation of the NOD-like receptor signaling pathway and other inflammation-related pathways, thereby alleviating airway inflammation and injury. This provides theoretical support and practical reference for the application of traditional Chinese medicine in the treatment of pediatric asthma[48].

Studies have found that Qingfei Oral Liquid significantly alleviates RSV-induced lung inflammation in mice by regulating the Akt signaling pathway and promoting fatty acid metabolism. In mouse experiments, it effectively suppressed the expression of pro-inflammatory cytokines such as IL-1β, TNF-α, and IL-6, while markedly increasing levels of the anti-inflammatory cytokine IL-10. Additionally, Qingfei Oral Liquid modulates fatty acid metabolism by inhibiting ATP citrate lyase (ACLY) and enhancing the expression of peroxisome proliferator-activated receptor alpha (PPARα). Western blot and immunohistochemistry analyses further demonstrated that Qingfei Oral Liquid promotes fatty acid oxidation and remodels fatty acid metabolism by downregulating ACLY and upregulating PPARα, thereby regulating macrophage polarization and facilitating the transition from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, effectively mitigating inflammation [49].

These studies provide important theoretical foundations and practical support for the application of Traditional Chinese Medicine in the treatment of respiratory viral diseases, while also offering new perspectives for future clinical research and therapeutic strategies.

In summary, during RSV infection and the resulting pulmonary inflammation, natural products can intervene at multiple stages of the viral lifecycle, inhibit inflammatory pathways, and promote the expression of antiviral genes, thereby directly or indirectly alleviating inflammation caused by RSV infection (Table 2).

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

Table 2. Host Immune/Inflammatory Modulation Pathways

Pathway	Intervention Agents	Mechanism of Action	Key Effects
TLR4/NF-κB Pathway	Astragalus Polysaccharides Grape Seed Proanthocyanidins	Inhibits TLR4 activation → Blocks NF-κB nuclear translocation	↓ IL-6, TNF-α, and other pro-inflammatory factors
IFN Signaling Pathway	Gegen Decoction (GGT) Andrographolide	Induces IFN-β secretion → Activates ISGs (Interferon-Stimulated Genes)	↑ Antiviral state
Cell Death Regulation	Andrographolide Gastrodin	Inhibits apoptosis (↓ Caspase-3) Promotes pyroptosis (↑ GSDMD)	Clearance of infected cells + Inflammation modulation
Metabolic Reprogramming	Quercetin Qingfei Oral Liquid	Regulates purine metabolism (↓ Uric acid) Activates PPARα → Promotes fatty acid oxidation	↓ M1 macrophage polarization
Oxidative Stress	Protocatechuic Acid Garlic Polysaccharides	Scavenges ROS	↓ Lung epithelial cell damage

4. Prospects and Challenges

As RSV continues to pose a significant global health threat, natural products have emerged as a promising avenue for antiviral therapy, attracting increasing attention. Due to their unique chemical structures and diverse bioactivities, natural products often exhibit lower toxicity and higher efficacy, making them an important resource for the development of anti-RSV drugs. Studies have demonstrated that natural products can inhibit multiple stages of the RSV life cycle, including viral attachment, entry, replication, and release. Furthermore, they may alleviate virus-induced respiratory damage by modulating host immune responses and suppressing inflammation.

However, the translation of natural products from laboratory research to clinical application still faces considerable challenges. Firstly, the complex sources and extraction processes, coupled with variability in purity and stability, necessitate the use of advanced purification technologies and synthetic biology approaches for optimization. Secondly, the mechanisms of action of many natural products remain incompletely understood, requiring deeper investigation into their molecular targets, signaling pathways, and potential side effects to ensure safety and efficacy. Additionally, clinical application demands addressing issues related to dosing, pharmacokinetics, and drug interactions. Therefore, future research should emphasize the screening and optimization of natural products while exploring their metabolism and toxicity profiles in vivo.

Plant-derived bioactive compounds offer an attractive solution to the current shortage of effective clinical RSV therapeutics, owing to their rich chemical diversity, unique multi-target mechanisms (direct inhibition of key viral life cycle stages and modulation of host immune defenses), and relatively low toxicity risks. Although challenges such as component complexity, poor bioavailability, insufficient mechanistic elucidation, and translational bottlenecks persist, rapid advancements and integration of cutting-edge technologies—including modern separation techniques, structural biology, nanotechnology, multi-omics analyses, and artificial intelligence—hold promise for overcoming these obstacles. Through continuous deepening of mechanistic understanding, structural optimization of lead compounds, innovative drug delivery strategies, and rigorous clinical evaluation, plant-derived high-efficiency and low-toxicity anti-RSV drugs are expected to emerge in the near future. Such therapeutics could serve as important complements or even alternatives to existing treatments, ultimately benefiting patients worldwide who suffer from RSV infection.

CRediT authorship contribution statement

Bingyao Wang: Conceptualization, Literature research, Data curation, Writing – Original Draft, Visualization.

Daishun Liu: Conceptualization , Supervision, Critical revision, Writing – Review & Editing, Project administration, Corresponding Author.

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. This study does not involve any human subjects/patient data or experimental animals, and therefore ethical approval and informed consent were not required.

Ethics approval and consent to participate

This review article did not involve any studies with human participants or animals performed by any of the authors. Therefore, ethical approval and consent to participate are not applicable.

Patient consent for publication

Not applicable. This study does not involve any individual patient data or images requiring consent for publication.

Consent for Publication

All authors consent to the submission and publication of this manuscript.

Competing Interests

All authors declare that have no competing interests.

Data availability

The data that support the findings of this study are available from the corresponding authors upon reasonable request.

Funding Information

This study was financially supported by the National Natural Science Foundation of China (No.82360001).

Acknowledgements

The authors gratefully acknowledge the contributions of colleagues and institutions that provided support during the preparation of this review. We also thank all the researchers whose work is cited in this manuscript for their valuable contributions to the field.

References

[1] BAUM S G. Respiratory Syncytial Virus: Another Serious Respiratory Infection [J]. Clin Infect Dis, 2021, 73(1): e164-e5.
[2] HU M, BOGOYEVITCH M A, JANS D A. Impact of Respiratory Syncytial Virus Infection on Host Functions: Implications for Antiviral Strategies [J]. Physiol Rev, 2020, 100(4): 1527-94.
[3] LANGEDIJK A C, HARDING E R, KONYA B, et al. A systematic review on global RSV genetic data: Identification of knowledge gaps [J]. Rev Med Virol, 2022, 32(3): e2284.
[4] LI Y, JOHNSON E K, SHI T, et al. National burden estimates of hospitalisations for acute lower respiratory infections due to respiratory syncytial virus in young children in 2019 among 58 countries: a modelling study [J]. Lancet Respir Med, 2021, 9(2): 175-85.
[5] LI Y, WANG X, BLAU D M, et al. Global, regional, and national disease burden estimates of acute lower respiratory infections due to respiratory syncytial virus in children younger than 5 years in 2019: a systematic analysis [J]. Lancet, 2022, 399(10340): 2047-64.

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

[6] ROSAS-SALAZAR C, CHIRKOVA T, GEBRETSADIK T, et al. Respiratory syncytial virus infection during infancy and asthma during childhood in the USA (INSPIRE): a population-based, prospective birth cohort study [J]. Lancet, 2023, 401(10389): 1669-80.
[7] FALSEY A R, HENNESSEY P A, FORMICA M A, et al. Respiratory syncytial virus infection in elderly and high-risk adults [J]. N Engl J Med, 2005, 352(17): 1749-59.
[8] YOUNG M, SMITHERMAN L. Socioeconomic Impact of RSV Hospitalization [J]. Infect Dis Ther, 2021, 10(Suppl 1): 35-45.
[9] BILLOWRIA K, ALI R, RANGRA N K, et al. Bioactive Flavonoids: A Comprehensive Review on Pharmacokinetics and Analytical Aspects [J]. Crit Rev Anal Chem, 2024, 54(5): 1002-16.
[10] FONSECA W, MALINCZAK C A, SCHULER C F, et al. Uric acid pathway activation during respiratory virus infection promotes Th2 immune response via innate cytokine production and ILC2 accumulation [J]. Mucosal Immunol, 2020, 13(4): 691-701.
[11] SUN Y-L, ZHAO P-P, ZHU C-B, et al. Integrating metabolomics and network pharmacology to assess the effects of quercetin on lung inflammatory injury induced by human respiratory syncytial virus [J]. Scientific Reports, 2023, 13(1): 8051.
[12] FENG Z, XU L, XIE Z. Receptors for Respiratory Syncytial Virus Infection and Host Factors Regulating the Life Cycle of Respiratory Syncytial Virus [J]. Front Cell Infect Microbiol, 2022, 12: 858629.
[13] XIONG Y, TAO K, LI T, et al. Resveratrol inhibits respiratory syncytial virus replication by targeting heparan sulfate proteoglycans [J]. Food & function, 2024.
[14] KAUL T N, MIDDLETON E, JR., OGRA P L. Antiviral effect of flavonoids on human viruses [J]. J Med Virol, 1985, 15(1): 71-9.
[15] FENG A, LI J, HU Y, et al. Cichoric acid aerosol for inhalation therapy in respiratory syncytial virus [J]. Heliyon, 2023, 9(5): e15789.
[16] SAKAI S, KAWAMATA H, KOGURE T, et al. Inhibitory effect of ferulic acid and isoferulic acid on the production of macrophage inflammatory protein-2 in response to respiratory syncytial virus infection in RAW264.7 cells [J]. Mediators Inflamm, 1999, 8(3): 173-5.
[17] ZI-KAI G, YA-QUN L I, et al. Characterization of chemical components of Gegen decoction based on HPLC-QTOF-MS and study on spectrum-effect relationship of different polar parts against RSV (in Chinese), 2019 [C].
[18] RUAN P, DAI P, MAO Y, et al. The in vitro and in vivo antiviral effects of IGF1R inhibitors against respiratory syncytial virus infection [J]. J Biomol Struct Dyn, 2024: 1-12.
[19] LEE J W, KIM Y I, IM C N, et al. Grape Seed Proanthocyanidin Inhibits Mucin Synthesis and Viral Replication by Suppression of AP-1 and NF-κB via p38 MAPKs/JNK Signaling Pathways in Respiratory Syncytial Virus-Infected A549 Cells [J]. J Agric Food Chem, 2017, 65(22): 4472-83.
[20] LI Z, XIANG J, HU D, et al. Naturally potential antiviral agent polysaccharide from Dendrobium nobile Lindl [J]. Pesticide Biochemistry and Physiology, 2020, 167: 104598.
[21] LIANG Y Y, LI K W, NIU F J, et al. Salvia plebeia R. Br. polysaccharides (SPP) against RSV (respiratory syncytial virus) infection: Antiviral effect and mechanisms of action [J]. Biomed Pharmacother, 2021, 141: 111843.
[22] LI J J, LIU M L, LV J N, et al. Polysaccharides from Platycodonis Radix ameliorated respiratory syncytial virus-induced epithelial cell apoptosis and inflammation through activation of miR-181a-mediated Hippo and SIRT1 pathways. Int Immunopharmacol, 2022, 104: 108510.
[23] Z-B Wu, S-R Shu, H-Y Chen. Antiviral effect of astragalus polysaccharide on respiratory syncytial virus-induced lung infection in young mice and its mechanism (in Chinese). 2022, 47(04): 346-52.
[24] Ni Zhu, J-G Sun, M-Z Deng, et al. In vitro inhibitory effect of garlic polysaccharide on respiratory syncytial virus and its mechanism (in Chinese). Journal of Hubei University of Science and Technology, 2018, 32(05): 376-9.
[25] BARBOZA M G L, DYNA A L, LIMA T F, et al. In vitro antiviral effect of sulfated pectin from Mangifera indica against the infection of the viral agent of childhood bronchiolitis (Respiratory Syncytial Virus - RSV) [J]. Int J Biol Macromol, 2024, 280(Pt 1): 135387.
[26] CHEN W, CHEN Y-H, LIAO Y-C, et al. Effect of hot water extracts of Arthrospira maxima (spirulina) against respiratory syncytial virus [J]. Phytomedicine, 2023, 110: 154611.
[27] WANG Q, ZHAO X, JIANG Y, et al. Functions of Representative Terpenoids and Their Biosynthesis Mechanisms in Medicinal Plants [J]. Biomolecules, 2023, 13(12): 1725.
[28] ZENG B, WEI A, ZHOU Q, et al. Andrographolide: A review of its pharmacology, pharmacokinetics, toxicity and clinical trials and pharmaceutical researches [J]. Phytother Res, 2022, 36(1): 336-64.
[29] CHE S, ZHOU N, LIU Y, et al. Andrographolide exerts anti-respiratory syncytial virus activity by up-regulating heme oxygenase-1 independent of interferon responses in human airway epithelial cells

ISSN 2618-1584 Vol. 7, Issue 4: 91-100, DOI: 10.25236/FMSR.2025.070412

[J]. Mol Biol Rep, 2023, 50(5): 4261-72.
[30] CHE S, XIE X, LIN J, et al. Andrographolide Attenuates RSV-induced Inflammation by Suppressing Apoptosis and Promoting Pyroptosis after Respiratory Syncytial Virus Infection In Vitro [J]. Comb Chem High Throughput Screen, 2024, 27(12): 1776-87.
[31] ZHAO L, XIANG K-L, LIU R-X, et al. Anti-inflammatory and anti-viral labdane diterpenoids from the fruits of Forsythia suspensa [J]. Bioorganic Chemistry, 2020, 96: 103651.
[32] KHOMENKO T M, SHTRO A A, GALOCHKINA A V, et al. Monoterpene-Containing Substituted Coumarins as Inhibitors of Respiratory Syncytial Virus (RSV) Replication [J]. Molecules, 2021, 26(24).
[33] ZHONG H, WANG L, XIONG S, et al. Cassaine diterpenoid glycosides from the seeds of Erythrophleum fordii Oliv. and their antiviral and anti-inflammatory activities [J]. Fitoterapia, 2022, 163: 105348.
[34] AL-BELTAGI S, PREDA C A, GOULDING L V, et al. Thapsigargin Is a Broad-Spectrum Inhibitor of Major Human Respiratory Viruses: Coronavirus, Respiratory Syncytial Virus and Influenza A Virus [J]. Viruses, 2021, 13(2).
[35] SAINI A, SENI K, CHAWLA P A, et al. An insight into recent updates on analytical techniques for bioactive alkaloids [J]. Phytochem Anal, 2024, 35(3): 423-44.
[36] KUANG G K, WANG L, YANG L L, et al. One new sesquiterpene pyridine alkaloid from the stems and leaves of Euonymus fortunei [J]. J Asian Nat Prod Res, 2021, 23(4): 399-406.
[37] PENG J, WANG Q, GUO M, et al. Development of Inhalable Chitosan-Coated Oxymatrine Liposomes to Alleviate RSV-Infected Mice [J]. Int J Mol Sci, 2022, 23(24).
[38] AGGARWAL M, LESER G P, LAMB R A. Repurposing Papaverine as an Antiviral Agent against Influenza Viruses and Paramyxoviruses [J]. J Virol, 2020, 94(6).
[39] Tao Peng, Y-J Yang, Wei Fu, Min Xiang, RY Zhang. Effects of pentoxifylline on TNF-α expression in human alveolar macrophages infected with respiratory syncytial virus (in Chinese). 2001, (03): 190-2.
[40] SONG D, LU C, CHANG C, et al. Natural Binary Herbal Small Molecules Self-Assembled Nanogel for Synergistic Inhibition of Respiratory Syncytial Virus [J]. ACS Biomater Sci Eng, 2024, 10(10): 6648-60.
[41] VALIPOUR M, ZAKERI KHATIR Z, ABDOLLAHI E, et al. Recent Applications of Protoberberines as Privileged Starting Materials for the Development of Novel Broad-Spectrum Antiviral Agents: A Concise Review (2017-2023) [J]. ACS Pharmacol Transl Sci, 2024, 7(1): 48-71.
[42] L-X Xue, B-X Li, Z-G Zhag. Effects of gastrodin on lung tissue damage and Th17/Treg cell balance in rats infected with respiratory syncytial virus by inhibiting Notch/NF-κB signaling pathway (in Chinese). 2023, 18(01): 6-11.
[43] LIU Z, MA N, ZHONG Y, et al. Antiviral effect of emodin from Rheum palmatum against coxsakievirus B5 and human respiratory syncytial virus in vitro [J]. J Huazhong Univ Sci Technolog Med Sci, 2015, 35(6): 916-22.
[44] LI X Y, JIANG J, SHU B, et al. Anti-inflammatory naphthoquinone-monoterpene adducts and neolignans from Eugenia caryophyllata [J]. Fitoterapia, 2024, 175: 105982.
[45] CHANG J S, WANG K C, SHIEH D E, et al. Ge-Gen-Tang has anti-viral activity against human respiratory syncytial virus in human respiratory tract cell lines [J]. J Ethnopharmacol, 2012, 139(1): 305-10.
[46] HUANG Z, GAO L, ZHAO X, et al. Effect of Gubenfangxiao decoction on respiratory syncytial virus-induced asthma and expression of asthma susceptibility gene orosomucoid 1-like protein 3 in mice [J]. J Tradit Chin Med, 2016, 36(1): 101-6.
[47] LI M, FAN X, ZHOU L, et al. The effect of Ma-Xin-Gan-Shi decoction on asthma exacerbated by respiratory syncytial virus through regulating TRPV1 channel [J]. J Ethnopharmacol, 2022, 291: 115157.
[48] YAO B, LIU J L, WANG M Q, et al. [Active components and mechanism of Wuhu Decoction in intervening RSV-induced asthma based on network pharmacology and in vivo experiment] [J]. Zhongguo Zhong Yao Za Zhi, 2024, 49(15): 4148-57.
[49] AN L, LU M, XU W, et al. Qingfei oral liquid alleviates RSV-induced lung inflammation by promoting fatty-acid-dependent M1/M2 macrophage polarization via the Akt signaling pathway [J]. J Ethnopharmacol, 2022, 298: 115637.