REVIEW
TMR Integrative Medicine 2023;7:e23014. https://doi.org/10.53388/TMRIM202307014

Recent advances in the antiviral activity of *Forsythiae Fructus*

Dong-Kai Tang[1, 2], Zi-Bin Lu[1, 2*]

[1]Third Level Research Laboratory of State Administration of Traditional Chinese Medicine, School of Traditional Chinese Medicine, Southern Medical University, Guangzhou 510515, China. [2]Guangdong Provincial Key Laboratory of Chinese Medicine Pharmaceutics, Southern Medical University, Guangzhou 510515, China.

[*]**Corresponding to:** Zi-Bin Lu, School of Traditional Chinese Medicine, Southern Medical University, No.1023, South Shatai Road, Baiyun District, Guangzhou 510515, China. E-mail: huang624@smu.edu.cn.

Author contributions

Dong-Kai Tang: Writing - Original Draft; Zi-Bin Lu: Writing - Review & Editing

Competing interests

The authors declare no conflicts of interest.

Acknowledgments

This work was supported by the Guangdong Basic and Applied Basic Research Foundation (2023A1515011106), General Project of Guangdong Provincial Enterprise Joint Fund (2022A1515220066), and Project of Guangzhou Municipal Science and Technology Bureau (2023A04J1825).

Peer review information

TMR Integrative Medicine thanks Xiao-Li Li and Xue-Ping Lei for their contribution to the peer review of this paper.

Abbreviations

RSV, respiratory syncytial virus; FF, *Forsythiae Fructus*; TCM, Traditional Chinese medicine; LHQW, Lianhua Qingwen capsule; JHQG, Jinhua Qinggan granules; TRQ, Tanreqing injection; FFYH, Fufang Yinhua Jiedu granules; KD-1, phillyrin; FA, forsythoside A.

Citation

Tang DK, Lu ZB. Recent advances in the antiviral activity of *Forsythiae Fructus*. *TMR Integr Med.* 2023;7:e23014. doi: 10.53388/TMRIM202307014.

Executive editor: Xin-Yun Zhang.

Received: 31 March 2023; **Accepted:** 08 May 2023; **Available online:** 16 May 2023.

Abstract

Forsythiae Fructus, a well-known traditional Chinese medicine preparation derived from the dried fruits of *Forsythia suspensa* (Thunb.) Vahl, has been historically utilized for its heat-clearing and detoxification properties. *Forsythiae Fructus* has been reported to exhibit antiviral activity such as against SARS-CoV-2 and influenza virus. This review highlights the recent updates on the effects and underlying action mechanisms of compounds in and active fractions from *Forsythiae Fructus* and Chinese formulae containing *Forsythiae Fructus*.

Keywords: *Forsythiae Fructus*; traditional Chinese medicine; anti-viral activity

Introduction

Viruses are small, obligate, intracellular parasites that contain genetic material, which can be either RNA or DNA, surrounded by a protective protein coat. They cannot reproduce on their own and use the host's cellular machinery to replicate their genetic material and produce more virus particles [1]. Viral infection is the process by which viruses invade the body through various routes and proliferate in susceptible host cells [2]. Infectious diseases are characterized by their diversity, high infectivity, morbidity, and mortality, all of which pose a significant risk to human health. Owing to the diversity of virus species and physiological conditions, viral infections frequently result in a wide range of diseases with varying degrees of severity. The common symptoms of viral infections include but are not limited to fever, headache, and cough.

With the global spread of viruses, particularly the SARS-CoV-2 that was identified in 2019 and is still mutating and continues to be highly infectious, antiviral drugs are urgently needed. The key to combating SARS-CoV-2 is the development of safe and effective medications [3, 4]. At present, oseltamivir [5] (effective against influenza virus), ribavirin [6] (effective against respiratory syncytial virus (RSV)), interferon-α [7] (effective against hepatitis B virus), and other antiviral medications are commonly used in clinical practice [8]. Additionally, immunizations prevent virus infections. However, these drugs are known to cause serious side effects such as gastrointestinal (oseltamivir) [9] and hemolytic anemia (ribavirin) [10]. The H275Y mutation confers resistance to oseltamivir [11], lacking immune regulation [12]. Therefore, the major challenges associated with viral diseases should be identified to aid in the development of antiviral medications [13].

Traditional Chinese medicine (TCM) is characterized by few side effects and exceptional healing benefits. TCM is quite distinct from western medicine in the prevention, diagnosis, and treatment of diseases because it uses multiple targets, multiple pathways, and multiple linkages, which can effectively reduce symptoms and shorten the course of therapy [14, 15].

Unfortunately, due to the complex matrix and undefined active components, the underlying mechanisms of TCM are still largely unknown, which impedes its globalization. However, unlike western medicine, TCM is effective in treating complex diseases with immune imbalance, such as influenza.

Forsythiae Fructus (FF), an effective heat-clearing and detoxicating herb in Chinese medicine, is derived from the dried fruits of *Forsythia suspensa* (Thunb.) Vahl. Depending on the harvest time, FF is classified into Qingqiao (when the fruits are green) and Laoqiao (when the fruits are ripe). Both are commonly used in clinical and pharmaceutical studies on TCM. FF and its active ingredients can inhibit various viruses, including SARS-CoV-2, influenza A virus, RSV, herpes simplex virus, and human cytomegalovirus [16]. In this review, we highlight the recent updates on the antiviral research of FF and explore the literature regarding its underlying molecular mechanisms.

Antiviral effect of FF prescriptions

According to ancient Chinese classic literature such as *Treatise on Cold Damage Diseases* (Zhong-Jing Zhang, 205 C.E.), *Compendium of Materia Medica* (Shi-Zhen Li, 1552–1578 C.E.), *Shennong's Classic of Materia Medica* (Nong Shen, 25–220 C.E.), and *Prescriptions of Peaceful Benevolent Dispensary* (Shi-Wen Chen, 1107–1110 C.E.), FF has heat-clearing and detoxification properties, eliminates mass, relieves swelling, and dispels wind and heat [17]. It can also treat stranguria, edema, Qi (Qi refers to the basic substance that constitutes the human body and maintains life activities, and is the unity of substance and function)-stagnation, and blood stasis. FF is believed to have anti-inflammatory, antibacterial, and antiviral properties, which may make it useful in treating conditions such as furuncles and influenza. It is also believed to have a diuretic effect, which can help to reduce edema and relieve symptoms such as swelling and bloating. In addition, FF is thought to have a protective effect on the liver and may be useful in the treatment of liver injury and related conditions. It is also believed to have a mild antiemetic effect, which can help to relieve nausea and vomiting. According to Chinese pharmacopoeia, preparations containing FF are mainly used for clearing heat and detoxification. Compounds and active fractions from FF and formulae containing FF have antiviral effects, particularly against SARS-CoV-2 and influenza virus. Prescriptions and Chinese patent medicines are summarized in Table 1.

Table 1 Summary of traditional and modern *FF prescriptions* in China

Prescription name	Composition	Treatment	Records
Liangge powder	*Forsythiae Fructus*, *Rhei Radix et Rhizoma*, Natrii Sulfas, *Gardeniae Fructus*, *Menthae Herba*, *Scutellariae Radix*, *Glycyrrhizae Radix et Rhizoma*, *Lophatheri Herba*.	Herpangina in children [18]; acute suppurative tonsillitis in children [19, 20].	*Prescriptions of Peaceful Benevolent Dispensary*, 1511
Yinqiao powder	*Forsythiae Fructus*, *Lonicerae Japonicae Flos*, *Armeniacae Semen Amarum*, *Menthae Herba*, *Lophatheri Herba*, *Platycodonis Radix*, *Glycyrrhizae Radix*, *Schizonepetae Spica*, *Sojae Preparatum Semen*, *Arctii Fructus*.	Influenza A virus infection [21–23]; H1N1 virus infection [24]; Reduces the level of M1 protein [25].	*Detailed Analysis of Epidemic Warm Diseases*, 1798
Lianhua Qingwen capsule	*Forsythiae Fructus, Lonicerae Japonicae Flos*, *Ephedrae Herba*, *Armeniacae Semen Amarum*, Gypsum Fibrosum, *Isatidis Root*, *Dryopteridis Crassirhizomatis Rhizoma*, *Houttuyniae Herba*, *Pogostemonis Herba*, *Rhei Radix et Rhizoma*, *Rhodiolae Crenulatae Radix et Rhizoma*, L-Menthol, *Glycyrrhizae Radix et Rhizoma*.	Severe viral-bacterial pneumonia [26]; Influenza A virus infection [27, 28]; COVID-19 [29].	*Pharmacopoeia of the People's Republic of China*, 2010
Jinhua Qinggan granule	Ephedrae Herba, Gypsum Fibrosum, *Armeniacae Semen Amarum*, *Lonicerae Japonicae Flos*, *Scutellariae Radix*, *Forsythiae Fructus*, *Fritillariae Thunbergii Bulbus*, *Anemarrhenae Rhizoma*, *Arctii Fructus*, *Artemisiae Annuae Herba*, *Menthae Herba*, *Glycyrrhizae Radix et Rhizoma*.	Influenza A virus infection [30]; COVID-19 [31–33].	China Academy of Traditional Chinese Medicine, 2009
Tanreqing injection	*Scutellariae Radix*, Bear Bile, Goat Horn, *Lonicerae Japonicae Flos*, *Forsythiae Fructus*, Propylene Glycol.	RSV pneumonia [34–36]; COVID-19 [37].	China's National Drug Standards, 2009
Fufang Yinhua Jiedu granule	*Artemisiae Annuae Herba*, *Lonicerae Japonicae Flos*, *Schizonepetae Herba*, *Menthae Herba*, *Chrysanthemi Indici Flos*, *Isatidis Folium*, *Forsythia Fructus*, *Commeline Communis*, *Sojae Preparatum Semen, Peucedani Radix*.	Influenza A virus infection [38].	China's National Drug Standards, 2007

RSV, respiratory syncytial virus.

Liangge powder

Liangge powder, a popular TCM formula documented in *Formulary of Peaceful Benevolent Dispensary* [39] comprises FF, Natrii Sulfas, *Rhei Radix et Rhizoma*, *Gardeniae Fructus*, *Scutellariae Radix*, *Glycyrrhizae Radix et Rhizoma*, Menthae Haplocalycis Herba, and *Lophatheri Herba*. It is prescribed for pharyngitis, stomatitis, acute tonsillitis, biliary tract infection, and acute icteric hepatitis. Liangge powder has been reported to have antiviral activity and when combined with Kaihoujian spray, was effective in reducing the duration of various symptoms associated with herpangina in children, such as antipyretic time, pain improvement time, salivation disappearance time, and herpes resolution time [18]. Similarly, combination of Liangge powder and the anti-inflammatory oral liquid Pudilan improved clinical symptoms such as pharyngeal congestion, sore throat, loss of appetite, halitosis, and stool characteristics in children [19]. Furthermore, Liangge powder was found to be effective in the treatment of acute suppurative tonsillitis in children with excessive lung and stomach heat, with an effective rate of 93.33% [20].

Yinqiao powder

Yinqiao powder is commonly used for the treatment of warm diseases, particularly at the initial stages of the disease. It was first described in *Detailed Analysis of Epidemic Warm Diseases*, which was written by Tang Wu.

Yinqiao powder comprises FF, *Lonicerae Japonicae Flos*, *Armeniacae Semen Amarum*, *Menthae Herba*, *Lophatheri Herba*, *Platycodonis Radix*, *Glycyrrhizae Radix et Rhizoma*, *Schizonepetae Spica*, *Sojae Semen Praeparatum*, and *Arctii Fructus*. Clinical applications include the treatment of influenza, acute tonsillitis, initial symptoms of measles, encephalitis B, meningitis, mumps, pharyngitis, and angina. Yinqiao powder extracted in 50% ethanol had the best effect against influenza A virus and outperformed ribavirin in this regard [21]. Moreover, Wang et al. [24] found that Maxing Shigan decoction-Yinqiao powder resulted in faster resolution of fever in 410 people (aged from 15 to 69) with laboratory-confirmed H1N1 influenza. In the absence of oseltamivir, Maxing Shigan decoction-Yinqiao powder can be utilized as an alternate treatment for H1N1 virus infection. In addition, Law et al. [25] discovered that forsythoside A, the main component of Yinqiao powder, lowered the level of influenza virus M1 protein, which may aid in inhibiting viral replication. Network pharmacological prediction and experimental verification revealed that Yinqiao powder combined with Xijiao Dihuang decoction can alleviate the inflammatory response of influenza virus infection by inhibiting the TLR4/TRAF5/NF-κB pathway [22]. By promoting the autophagy of macrophages in influenza virus-infected mice, it down-regulated the level of mtROS, thereby reducing the inflammatory response [23].

Lianhua Qingwen capsule (LHQW)

LHQW was listed in the Diagnosis and Treatment Program for COVID-19 (Trial version 6) of the National Health Commission of the People's Republic of China in February 2020. LHQW was approved by the State Food and Drug Administration in treating COVID-19 patients with mild symptoms such as fever, cough, and fatigue, with a course of treatment ranging from 7 to 10 days in April 2020. The LHQW formula is composed of FF, *Lonicerae Japonicae Flos*, Ephedrae Herba, *Armeniacae Semen Amarum*, Gypsum fibrosum, *Isatidis Root*, *Dryopteridis Crassirhizomatis Rhizoma*, *Houttuyniae Herba*, *Pogostemonis Herba*, *Rhei Radix et Rhizoma*, *Rhodiolae Crenulatae Radix et Rhizoma*, L-menthol, and *Glycyrrhizae Radix et Rhizoma*. It has heat clearing and detoxification properties. According to network pharmacology analysis, LHQW may regulate the inflammatory process, have antiviral properties, and alleviate lung injury [40]. Zhao's [41] findings suggest that LHQW can inhibit the inflammatory response mediated by lipopolysaccharide and modify the AGE-RAGE pathway via IL-6. LHQW inhibited influenza-induced bacterial adhesion by downregulating adhesion molecules, thereby inhibiting severe pneumonia, indicating that LHQW, rather than being administered as a single agent, could be utilized as an adjuvant in the treatment of severe viral-bacterial pneumonia [26]. Additionally, a meta analysis [28] revealed that the incidence of side effects in LHQW group was lower than that in conventional drug group in treating influenza A and H1N1 virus infections. According to Xu [27], LHQW is effective in treating pneumonia caused by influenza A virus and the mechanism is related to inhibiting the TLR4/NF-κB signaling pathway in the lung. More importantly, several LHQW components such as forsythoside A, rhein, forsythoside I, and neochlorogenic acid can inhibit SARS-CoV-2 by significantly affecting the binding of ACE-2 to the S protein, which is a vital pathway to prevent virus infection [29].

Jinhua Qinggan granules (JHQG)

Oseltamivir (Tamiflu) was the first choice of drug during the global outbreak of influenza (H1N1) in 2009. However, owing to its high cost and limited supply, JHQG, a new prescription based on Maxing Shigan decoction and Yinqiao powder was developed; JHQG is composed of Ephedrae Herba, Gypsum fibrosum, *Armeniacae Semen Amarum*, *Lonicerae Japonicae Flos*, *Scutellariae Radix*, FF, *Fritillariae Thunbergii Bulbus*, *Anemarrhenae Rhizoma*, *Arctii Fructus*, *Artemisiae Annuae Herba*, *Menthae Herba*, and *Glycyrrhizae Radix et Rhizoma*. JHQG is one of the three TCM prescriptions listed in the Diagnosis and Treatment Plan (Trial Third Edition), which was jointly released by the China Health Commission and the Administration of Traditional Chinese Medicine on January 22, 2020. It has the effect of dispersing wind, ventilating lungs, clearing heat, and detoxifying in the treatment of infections caused by all types of influenza, especially influenza A. Shi [30] found that JHQG targets viral life cycle and regulates host immune responses and inflammation. Several studies on COVID-19 have reported that the main active ingredients of JHQG could down-regulate IL-6 [32]. Furthermore, Wu [33] found that JHQG alleviates cough in COVID-19 patients. In addition, JHQG effectively shortened the time required to clear SARS-CoV-2 and improved the absorption of inflammatory exudates from pneumonia without apparent side effects [31].

Tanreqing injection (TRQ)

TRQ has been available since 2003. It has been listed in the clinical guidelines or Diagnosis and Treatment Plan by the Health Commission of China and the Administration of Traditional Chinese Medicine for the prevention and control of major epidemics such as human avian influenza, influenza A (H1N1), influenza A (H7N9), dengue, Ebola, and Middle East respiratory syndrome. In addition, TRQ capsule was listed as the recommended medication for common, severe, and critical cases in the "Expert Consensus on the Prevention and Treatment of COVID-19 with Chinese Patent Medicine". TRQ is extracted and processed from *Scutellariae Radix*, bear bile, goat horn, *Lonicerae Japonicae Flos*, FF, and propylene glycol. Its functions include clearing heat, dissipating phlegm, and detoxification. It is used for the treatment of respiratory tract infections, particularly those characterized by phlegm-heat blocking the lung with wind-heat or lung-heat syndrome. In China, TRQ was utilized in combination with ganciclovir in the treatment of RSV pneumonia in children [34]. Moreover, Wang [35, 36] discovered that TRQ could directly inactivate RSV, inhibit its replication, and prevent RSV from infecting Hep-2 cells with an obvious dose-effect relationship. In addition, based on network pharmacology analysis, Han et al. [37] found that the main active ingredients in TRQ capsules interfere with the IL-17 signaling pathway, the cAMP signaling pathway, the T cell receptor signaling pathway, and arachidonic acid metabolism, all of which play a role in treating COVID-19 by acting on vital proteins such as TNF, NOS3, EGFR, IL2, and PTGS2.

Fufang Yinhua Jiedu granules (FFYH)

FFYH is a modified and optimized formula derived from Yinqiao powder, which has been used in the clinical treatment of influenza for approximately 20 years [42, 43]. FFYH is a well-known Chinese patent medicine including *Artemisiae Annuae Herba*, *Lonicerae Japonicae Flos*, *Schizonepetae Herba*, *Menthae Herba*, *Chrysanthemi Indici Flos*, *Isatidis Folium*, FF, *Commeline communis*, *Sojae Preparatum Semen*, and *Peucedani Radix*. Previous studies shown that FFYH [38]

significantly inhibited the replication of influenza A viruses, including H1N1, H3N2, H5N1, H7N9, and H9N2 in vitro. FFYH protects against influenza virus-induced acute lung injury in vivo by inhibiting inflammatory response via suppression of the TLR7-MyD88 signaling pathway. Zheng [44] discovered that the combination of FFYH and oseltamivir provided superior protection against influenza A viruses in mice than either oseltamivir or FFYH alone through inhibition of the TLR7-MyD88 signaling pathway.

Antiviral effect of FF extract

FF extract is obtained from dried fruits by using different solvents, the most common of which being water and alcohol. FF extracts exerted obvious antiviral activity. FF aqueous extract inhibited the replication of the avian influenza viruses H5N1 and H9N2 in DF-1 cells [45]. It inhibited the inflammatory response of RSV-infected A549 cells and lowered the inflammatory response of RSV-infected mice in vivo [46]. Su et al. discovered that the 80% ethanol extract of FF protected MDCK cells infected with the H1N1 virus at a minimum inhibitory concentration of 1:8192 mg/mL [47]. Moreover, Ko [48] discovered that 95% ethanol extract of FF exerted both a positive and negative impact on the production of MCP-1 in virus-stimulated macrophages, which is concentration dependent. However, both 50% ethanol and aqueous extract of FF increased virus-induced MCP-1 secretion. Above of them, the extracts of FF exhibited a consistent inhibitory effect on the activation of virus-stimulated T cells at the non-cytotoxic doses. Additionally, the extract of FF also decreased the viral load, alleviated the pathological damage of brain tissues, and reduced the expression levels of TNF-α, IL-1β, IFN-α, and other inflammatory factors in brain tissue from mice infected with herpes simplex virus type 1 [49].

Antiviral effect of compounds from FF

The chemical composition of FF is complex; it consists of lignans, phenylethanol glycosides, flavonoids, terpenoids, among other compounds. The main active constituents are lignans and phenylethanol glycosides. Wang et al. summarized that FF contained at least 237 ingredients [50]. Among them, phillyrin (KD-1) [51], forsythoside A (FA) [52], and some new compounds exert significant antiviral effect. The specific chemical structures are shown in Figure 1.

KD-1

KD-1 (Figure 1), a type of bisepoxylignan, is a representative ingredient of FF. Chinese Pharmacopoeia lists KD-1 as an important indicator for the quality control of FF [17]. KD-1 has anti-inflammatory, lipid-lowering, hepatoprotective, antibacterial, antiviral, and neuroprotective activities [53]. Qu [54] showed that KD-1 protects influenza A virus-infected mice by inhibiting virus replication. Duan et al. [55] showed that KD-1 could reduce the copy number of nucleoprotein (NP) gene of influenza A virus, which may be related to the inhibition of NP and viral RNA binding to form NP complex, thereby inhibiting the production of the influenza A virus's NP gene after transfection. In addition, by upregulating the expression of IFITM3 and IFN-β, KD-1 promotes the clearance of influenza A (H1N1) virus and lowers the amount of NP [56].

KD-1 can also play a critical role in the treatment of COVID-19 [57]. Based on bioinformatics analysis [58], 192 common core targets and 25 biological pathways for FF were found in the treatment of COVID-19 and influenza coinfection, including HIF-1, RAS, and PI3K-AKT, which were the key signaling pathways implicated in its antiviral activity, offering new perspectives for the subsequent treatment of COVID-19. In vitro, Ma found that KD-1 could significantly inhibit SARS-CoV-2 and HCoV-229E replication [59]. Moreover, network pharmacology and molecular docking analysis revealed that KD-1 blocked the SARS-CoV-2 S protein binding and Gln325 in ACE2 [60]. In addition, KD-1 had a significant anti-RSV effect; in vitro experiments showed that KD-1 could effectively in improving the survival rate of cells infected with RSV, increasing the expression of PI3K, and decreasing the expression of AKT [61].

FA

FA (Figure 1) is the main component of FF and has antiviral, anti-inflammatory, antipyretic, and antioxidant properties. Deng found that FA inhibits the replication of influenza A virus by down-regulating the mRNA expression of TLR7, TRAF6, MyD88, and IRAK4 in the TLR7 signaling pathway as well as NF-κB [62]. Zheng [63] discovered that FA could down-regulating of the RLRs signaling pathway in mouse lung immune cells, thereby reducing the inflammation caused by influenza A virus infection in mouse lungs and improve the prognosis of infection. Law et al. found that FA could lower the quantity of influenza virus M1 protein, potentially limiting viral replication [25]. FA was able to directly inhibit the infectious bronchitis virus in vitro in a dose-dependent manner. When chicken embryonic kidney cells were pretreated with high doses of FA, the infectivity of infectious bronchitis virus was significantly inhibited [64].

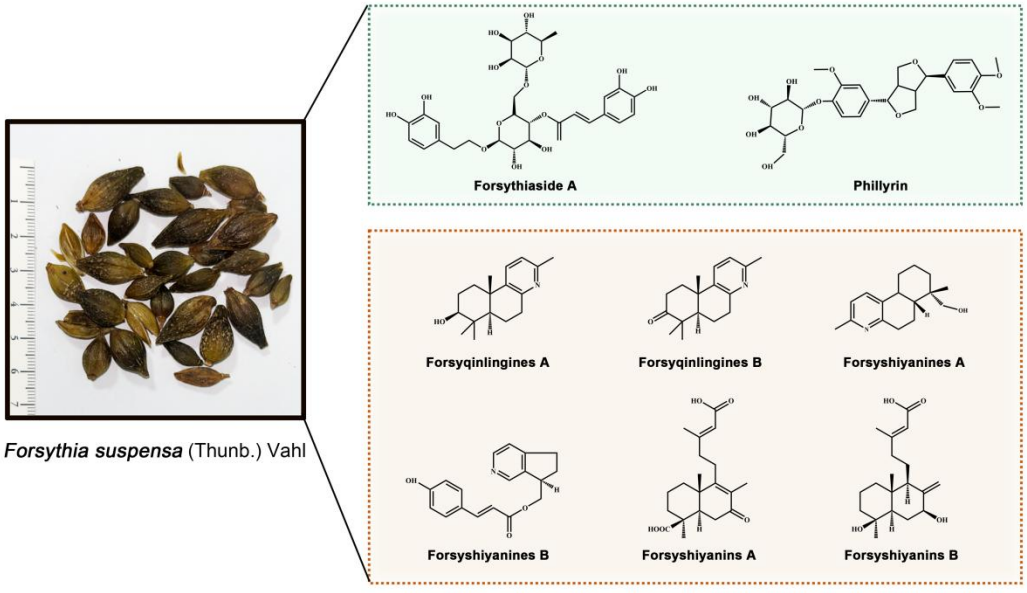

Figure 1 Structure of antiviral compounds from FF. FF, *Forsythiae Fructus*.

Others

In addition to KD-1 and FA, there are other novel compounds in FF that exert antiviral effects. By inhibiting the release of β-glucuronidase in rat polymorphonuclear leukocytes, two novel C17-labdane diterpenoid alkaloids, forsyqinlingine A and B (Figure 1), were shown to have antiviral and anti-inflammatory activities against the influenza A (H1N1) virus and RSV [65]. Zhao [66] found that eight labdane diterpenoids, including two new labdane diterpenoids named forsyshiyanins A and B (Figure 1), showed antiviral activities against influenza A (H1N1) virus and RSV, with IC50 values ranging from 18.4–26.2 μM and EC50 values ranging from 10.5–14.4 μM in vitro. Two alkaloids not previously described, forsyshiyanins A and B (Figure 1), as well as three known alkaloids, had antiviral activity against influenza A and RSV, with IC50 values ranging from 7.3–32.5 μM and EC50 values ranging from 3.7–14.1 μM [67].

Conclusion and future perspectives

TCM has a well-documented history for treating virus infectious diseases. As a traditional antipyretic TCM preparation, FF is effective against various viral infections. During the fight against COVID-19 in China, TCM prescriptions of LHQW, JHQG, TRQ, and FFYH were utilized. Maxing Shigan decoction, Liangge powder, and Yinqiao powder have demonstrated clinical efficacy against influenza virus.

Nevertheless, there are still some issues that remain unclarified. Although TCM has demonstrated important clinical value as an antiviral medication, similar to FF, is difficult to promote the application of TCM worldwide due to the complexity of its components and unclear underlying mechanisms. Firstly, systematic investigation of difference between Qingqiao and Laoqiao in the clinic is still limited. In addition, thorough understanding of the activity of FF, appropriate quality control standards, and exploration of the underlying mechanism are lacking. Although further research on FF is needed, we believe that it has potential for clinical application.

References

1. Gorbalenya AE, Krupovic M, Mushegian A, et al. The new scope of virus taxonomy: partitioning the virosphere into 15 hierarchical ranks. *Nat Microbiol* 2020;5(5):668–674. Available at: http://doi.org/10.1038/s41564-020-0709-x
2. Kellogg C, Kouznetsova VL, Tsigelny IF. Implications of viral infection in cancer development. *Biochim Biophys Acta Rev Cancer* 2021;1876(2):188622. Available at: http://doi.org/10.1016/j.bbcan.2021.188622
3. Rahimi F, Talebi Bezmin Abadi A. Tackling the COVID-19 Pandemic. *Arch Med Res* 2020;51(5):468–470. Available at: http://doi.org/10.1016/j.arcmed.2020.04.012
4. Indari O, Jakhmola S, Manivannan E, Jha HC. An Update on Antiviral Therapy Against SARS-CoV-2: How Far Have We Come?. *Front Pharmacol* 2021;12:632677. Available at: http://doi.org/10.3389/fphar.2021.632677
5. Doshi P, Heneghan C, Jefferson T. Oseltamivir for influenza. *Lancet* 2016;387(10014):124. Available at: http://doi.org/10.1016/S0140-6736(15)01282-9
6. Nam HH, Ison MG. Respiratory syncytial virus infection in adults. *BMJ* 2019;366:l5021. Available at: http://doi.org/10.1136/bmj.l5021
7. Chen J, Li Y, Lai F, et al. Functional Comparison of Interferon-α Subtypes Reveals Potent Hepatitis B Virus Suppression by a Concerted Action of Interferon-α and Interferon-γ Signaling. *Hepatology* 2021;73(2):486–502. Available at: http://doi.org/10.1002/hep.31282
8. Meganck RM, Baric RS. Developing therapeutic approaches for twenty-first-century emerging infectious viral diseases. *Nat Med* 2021;27(3):401–410. Available at: http://doi.org/10.1038/s41591-021-01282-0
9. Lehnert R, Pletz M, Reuss A, Schaberg T. Antiviral Medications in Seasonal and Pandemic Influenza. *Dtsch Arztebl Int* 2016;113(47):799–807. Available at: http://doi.org/10.3238/arztebl.2016.0799
10. Balassa K, Salisbury R, Watson E, et al. Treatment stratification of respiratory syncytial virus infection in allogeneic stem cell transplantation. *J Infect* 2019;78(6):461–467. Available at: http://doi.org/10.1016/j.jinf.2019.04.004
11. Webster D, Li Y, Bastien N, Garceau R, Hatchette TF. Oseltamivir-resistant pandemic H1N1 influenza. *Can Med Assoc J* 2011;183(7):E420–E422. Available at: http://doi.org/10.1503/cmaj.100313
12. Beaucourt S, Vignuzzi M. Ribavirin: a drug active against many viruses with multiple effects on virus replication and propagation. Molecular basis of ribavirin resistance. *Curr Opin Virol* 2014;8:10–15. Available at: http://doi.org/10.1016/j.coviro.2014.04.011
13. Lu L, Su S, Yang H, Jiang S. Antivirals with common targets against highly pathogenic viruses. *Cell* 2021;184(6):1604–1620. Available at: http://doi.org/10.1016/j.cell.2021.02.013
14. Qiu J. When the East meets the West: the future of traditional Chinese medicine in the 21st century. *Natl Sci Rev* 2015;2(3):377–380. Available at: http://doi.org/10.1093/nsr/nwv049
15. Huang K, Zhang P, Zhang Z, et al. Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: Efficacies and mechanisms. *Pharmacol Ther* 2021;225:107843. Available at: http://doi.org/10.1016/j.pharmthera.2021.107843
16. Xiong X, Wang P, Su K, Cho WC, Xing Y. Chinese herbal medicine for coronavirus disease 2019: A systematic review and meta-analysis. *Pharmacol Res* 2020;160:105056. Available at: http://doi.org/10.1016/j.phrs.2020.105056
17. National Pharmacopoeia Committee. *Pharmacopoeia of the People's Republic of China.* Part I. Beijing, China Medical Science and Technology Press; 2020. (Chinese) Available at: https://www.nmpa.gov.cn/xxgk/ggtg/qtggtg/20200702151301219.html
18. Ou XH. To investigate the clinical effect of Liangge powder combined with Kaihoujian spray in the treatment of herpangina in children. *Inn Mong J Tradit Chin Med* 2022;41(03):56–57. Available at: http://dx.doi.org/10.16040/j.cnki.cn15-1101.2022.03.049
19. Jiang W. *Clinical Observation of Modified Lianggesan on Treating Infantile Herpangina(Accumulating Heat in Spleen and Stomach Pattern*. Chengdu Univ Tradit Chin Med 2020. (Chinese) Available at: http://dx.doi.org/10.26988/d.cnki.gcdzu.2020.000255
20. He ZQ. *Clinical observation of odorized cold diaphragm powder in the treatment of acute purulent tonsillitis in children.* Heilongjiang Univ Chin Med 2020. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C475KOm_zrgu4lQARvep2SAkWfZcByc-RON98J6vxPv10ReJXvqrQ2Y2tw2CvBKJwqLiRtGC0FYfBikYltUnmps8&uniplatform=NZKPT
21. Wang X, Hao O, Wang W, Ying X, Wang H. Evaluation of the Use of Different Solvents to Extract the Four Main Components of Yinqiaosan and Their In Vitro Inhibitory Effects on Influenza-A Virus. *Kaohsiung J Med Sci* 2010;26(4):182–191. Available at: http://doi.org/10.1016/S1607-551X(10)70027-9
22. Deng D, Ma LY, Liu TY, et al. Network pharmacological prediction and experimental verification of the effect of Xijiao Dihuang decoction and Yinqiao powder on macrophage inflammation induced by influenza virus infection. *J Beijing Univ Tradit Chin Med* 2023;46(01):57–64. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=8q8G1i9Uapfh-a68v6tA-8Q8oEOlo9cq4gzvvtyw4C_vtd0THwtPR3efnIYXcH-N86s9M8pb26CXCUANtN2sxA8l1wpFIZRhjQ3ljjaj4DLLllsQ_uKt8MGgyMYAnDWs&uniplatform=NZKPT

23. Mao Q, Ma LY, Liu TY, et al. Xijiao Dihuang decoction and Yinqiao powder can reduce mitochondrial ROS level by promoting autophagy of macrophages in mice infected with influenza virus. *Chin J Pathophysiol* 2022;38(04):704–711. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=8q8G1i9Uapdc8AKqRIksxK6zARXUfxuQEEdNTUNy-U9qo4u0zQCAcPxM_MB_VrCXHfkMOiB2jLPJM4WJlV-gFd1_mEX3VOxFUOC7JW1dFNxXjDOZbeK2oarwfQHYLvns&uniplatform=NZKPT
24. Wang C, Cao B, Liu Q-Q, et al. Oseltamivir Compared With the Chinese Traditional Therapy Maxingshigan–Yinqiaosan in the Treatment of H1N1 Influenza. *Ann Intern Med* 2011;155(4):217. Available at: http://doi.org/10.7326/0003-4819-155-4-201108160-00005
25. Law AH-Y, Yang CL-H, Lau AS-Y, Chan GC-F. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit against influenza A virus through reduction of viral M1 protein. *J Ethnopharmacol* 2017;209:236–247. Available at: http://doi.org/10.1016/j.jep.2017.07.015
26. Du Q, Huang W, Zhao J, et al. Lianhuaqingwen capsule inhibits influenza-induced bacterial adhesion to respiratory epithelial cells through down-regulation of cell adhesion molecules. *J Ethnopharmacol* 2021;280:114128. Available at: http://doi.org/10.1016/j.jep.2021.114128
27. Xu P, Yang Z, Du S, Hong Z, Zhong S. Intestinal microbiota analysis and network pharmacology reveal the mechanism by which Lianhua Qingwen capsule improves the immune function of mice infected with influenza A virus. *Front Microbiol* 2022;13:1035941. Available at: http://doi.org/10.3389/fmicb.2022.1035941
28. Hu C, He B, Gong F, Liang M, Zhao D, Zhang G. The Adverse Reactions of Lianhua Qingwen Capsule/Granule Compared With Conventional Drug in Clinical Application: A Meta-Analysis. *Front Pharmacol* 2022;13:764774. Available at: http://doi.org/10.3389/fphar.2022.764774
29. Chen X, Wu Y, Chen C, et al. Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. *Acta Pharm Sin B* 2021;11(1):222–236. Available at: http://doi.org/10.1016/j.apsb.2020.10.002
30. Shi M, Peng B, Li A, et al. Broad Anti-Viral Capacities of Lian-Hua-Qing-Wen Capsule and Jin-Hua-Qing-Gan Granule and Rational use Against COVID-19 Based on Literature Mining. *Front Pharmacol* 2021;12:640782. Available at: http://doi.org/10.3389/fphar.2021.640782
31. Liu Z, Li X, Gou C, et al. Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients. *J Tradit Chin Med* 2020;40(3):467–472. Available at: http://journaltcm.com/EN/10.19852/j.cnki.jtcm.2020.03.016
32. Niu W, Wu F, Cao W, et al. Network pharmacology for the identification of phytochemicals in traditional Chinese medicine for COVID-19 that may regulate interleukin-6. *Biosci Rep* 2021;41(1):BSR20202583. Available at: http://doi.org/10.1042/BSR20202583
33. Wu J, Sun B, Hou L, et al. Prospective: Evolution of Chinese Medicine to Treat COVID-19 Patients in China. *Front Pharmacol* 2021;11:615287. Available at: http://doi.org/10.3389/fphar.2020.615287
34. Li H, Wu KX, Shi KH, Tang L, Liang CY. Research progress on chemical constituents, pharmacological activities and clinical application of Bolbostemma paniculatum. *China J Chin Mater Med* 2021;46(17):4314–4322. (Chinese) Available at: http://dx.doi.org/10.19540/j.cnki.cjcmm.20210325.601
35. Wang L, Tao YL, Chen WS. Research progress on chemical constituents, pharmacological effects and clinical application of Tanreqing Injection. *Chin Tradit Herbal Drugs* 2020;51(12):3318–3328. (Chinese) Available at: http://qikan.cqvip.com/Qikan/Article/Detail?id=7102307280
36. Wang YQ, Xi ZQ, Feng GZ. Study on the inhibition of Tanreqing on respiratory syncytial virus in vitro. *Hebei Med J* 2010;32(24):3447–3448. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLTlOAiTRKgchrJ08w1e7_IFawAif0myniXGjphO0GcQ5BA4H9_QbJCjTs8TG8sNWASPnkLJ4s7jIBj1lDhHy&uniplatform=NZKPT
37. Han YQ, Liu YC, Wu Q, et al. To study the mechanism of Tanreqing capsule in the treatment of COVID-19 based on network pharmacology. *Chin Tradit Herbal Drugs* 2020;51(11):2967–2976. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLTlOAiTRKibYlV5Vjs7i8oRR1PAr7RxjuAJk4dHXomDMAykjOojxCJ2BMMmcdxu48s_JP2IOAC4JVJngxbyA&uniplatform=NZKPT
38. Zhang Y, Wang R, Shi W, et al. Antiviral effect of fufang yinhua jiedu (FFYH) granules against influenza A virus through regulating the inflammatory responses by TLR7/MyD88 signaling pathway. *J Ethnopharmacol* 2021;275:114063. Available at: http://doi.org/10.1016/j.jep.2021.114063
39. Lu Z, Cao H, Liu D, et al. Optimal combination of anti-inflammatory components from Chinese medicinal formula Liang-Ge-San. *J Ethnopharmacol* 2021;269:113747. Available at: http://doi.org/10.1016/j.jep.2020.113747
40. Zheng S, Baak JP, Li S, et al. Network pharmacology analysis of the therapeutic mechanisms of the traditional Chinese herbal formula Lian Hua Qing Wen in Corona virus disease 2019 (COVID-19), gives fundamental support to the clinical use of LHQW. *Phytomedicine* 2020;79:153336. Available at: http://doi.org/10.1016/j.phymed.2020.153336
41. Tianyu Z, Xiaoli C, Yaru W, et al. New tale on LianHuaQingWen: IL6R/IL6/IL6ST complex is a potential target for COVID-19 treatment. *Aging (Milano)* 2021;13(21):23913–23935. Available at: http://doi.org/10.18632/aging.203666
42. Lu JP, Jiang JH, Zhang H. Clinical study of Yinhuajiedu Granules for influenza with wind-heat type. *Chin Tradit Pat Med* 2003(02):41–43. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLTlOAiTRKgchrJ08w1e7ZCYsl4RS_3gZq7ALqfwXqVP1S_oQS1-iDdOmtp5-HMm0FgyRd8piR6OOacanH6Em&uniplatform=NZKPT
43. Jiang M, Xiong NN, Xi ZQ, Zhou JD. Clinical Trial for Treating Wind-heat Syndrome of Upper Respiratory Infection and Influenza with Yinhua Jiedu Granule. *Tradit Chin Drug Res Clini Pharmacol* 2003(04):270–272. (Chinese) Available at: http://dx.doi.org/10.19378/j.issn.1003-9783.2003.04.018
44. Zheng Z, Zhang Y, Li M, et al. In vitro and in vivo antiviral effect of Fufang Yinhua Jiedu granules (FFYH) combined with oseltamivir against influenza A virus. *Phytomedicine Plus* 2023;3(1):100386. Available at: http://doi.org/10.1016/j.phyplu.2022.100386
45. Zhao BQ, Luo C, Liu JX, et al. Inhibitory effect of forsythia water extract on avian influenza virus proliferation and expression of inflammatory factors. *Acta Vet Zootechnica Sin* 2020;51(06):1466–1474. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C44YLTlOAiTRKibYlV5Vjs7i8oRR1PAr7RxjuAJk4dHXorUCCFie5gjavOHNZAgnylymih3imM9uU7tJ84OcnDVr&uniplatform=NZKPT
46. Wang P, Ma YR, Zhang HM. To study the anti-RSV effects of different extracts of Forsythia suspensa based on network pharmacology and in vitro and in vivo experiments. *J Hunan Univ Chin Med* 2022;42(07):1121–1128. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=8q8G1i9UapdFDl0_0zBipURw5ckzpFywbiX6vgnJRuV_9JGTZOA9Mqwa8zxxXA6CIlsBrQxDtITM5y2Yojhgb_6tY5KXWuXfZmM6jj46jFUaHW5lGRSz6s9cNCTrHU-S&uniplatform=NZKPT
47. Su W, Xu H, Huang H. Effects of the extract of Forsythia suspensa on influenza A H1N1 infection in vitro. *J Med Plants*

Res 2010;4:1455–1458. Available at: https://academicjournals.org/journal/JMPR/article-abstract/02B600617380
48. Ko HC, Wei BL, Chiou WF. Dual regulatory effect of plant extracts of Forsythia suspense on RANTES and MCP-1 secretion in influenza A virus-infected human bronchial epithelial cells. *J Ethnopharmacol* 2005;102(3):418–423. Available at: http://doi.org/10.1016/j.jep.2005.06.029
49. Wang Y, Zhou J, Yuan MM, Zheng SH, Zhang L. Protective effect of forsythia extract on mice with herpes simplex virus encephalitis. *China J Chin Mater Med* 2022;47(11):3023–3028. (Chinese) Available at: http://dx.doi.org/10.19540/j.cnki.cjcmm.20220124.401
50. Wang Z, Xia Q, Liu X, et al. Phytochemistry, pharmacology, quality control and future research of Forsythia suspensa (Thunb.) Vahl: A review. *J Ethnopharmacol* 2018;210:318–339. Available at: http://doi.org/10.1016/j.jep.2017.08.040
51. Tang K, Zhong B, Luo Q, et al. Phillyrin attenuates norepinephrine-induced cardiac hypertrophy and inflammatory response by suppressing p38/ERK1/2 MAPK and AKT/NF-kappaB pathways. *Eur J Pharmacol* 2022;927:175022. Available at: http://doi.org/10.1016/j.ejphar.2022.175022
52. Kim, Shin, Chung, Lee, Baek, Lee. Anti-Inflammatory Mechanisms of Koreanaside A, a Lignan Isolated from the Flower of Forsythia koreana, against LPS-Induced Macrophage Activation and DSS-Induced Colitis Mice: The Crucial Role of AP-1, NF-κB, and JAK/STAT Signaling. *Cells* 2019;8(10):1163. Available at: http://doi.org/10.3390/cells8101163
53. Zhao P. Research progress of forsythia and predictive analysis of quality markers. *Chin Arch Tradit Chin Med* 2022;40(04):19–27. (Chinese) Available at: http://dx.doi.org/10.13193/j.issn.1673-7717.2022.04.005
54. Qu X, Li Q, Zhang H, et al. Protective effects of phillyrin against influenza A virus in vivo. *Arch Pharm Res* 2016;39(7):998–1005. Available at: http://doi.org/10.1007/s12272-016-0775-z
55. Duan LJ, Zhang Q, Wang NR, Yang B, He SQ, Sun J. Effect of phillyrin on the expression of nucleoprotein gene of influenza A virus. Chin Gen Pract 2012;15(18):2082–2084. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=8q8G1i9UapczxRQ90vBceequXqTaWlLOLd7gDxdDAVrWibaovR3FgZFuSq7RSalT-KPnK2CjTvJvgftUFGRIMPZ7WKFuv7rUznNr-53qwcIJ7fYgs_PJlw==&uniplatform=NZKPT
56. Chen H. *The role of mitochondrial Mfn2/MAVS antiviral signaling pathway in antiviral oral solution reducing influenza virus "susceptibility" in restraint stress mice.* Jinan Univ 2016. (Chinese) Available at: https://kns.cnki.net/kcms2/article/abstract?v=3uoqIhG8C475KOm_zrgu4lQARvep2SAkkyu7xrzFWukWIylgpWWcEnK8mi4x8XnUDIIvcOJuL4K0fAoWjU5P4ae3pCHMfl1m&uniplatform=NZKPT
57. Hensel A, Bauer R, Heinrich M, et al. Challenges at the Time of COVID-19: Opportunities and Innovations in Antivirals from Nature. *Planta Med* 2020;86(10):659–664. Available at: http://doi.org/10.1055/a-1177-4396
58. Lai Y, Han T, Lao Z, Li G, Xiao J, Liu X. Phillyrin for COVID-19 and Influenza Co-infection: A Potential Therapeutic Strategy Targeting Host Based on Bioinformatics Analysis. *Front Pharmacol* 2021;12:754241. Available at: http://doi.org/10.3389/fphar.2021.754241
59. Ma Q, Li R, Pan W, et al. Phillyrin (KD-1) exerts anti-viral and anti-inflammatory activities against novel coronavirus (SARS-CoV-2) and human coronavirus 229E (HCoV-229E) by suppressing the nuclear factor kappa B (NF-κB) signaling pathway. *Phytomedicine* 2020;78:153296. Available at: http://doi.org/10.1016/j.phymed.2020.153296
60. Yu J, Wang L, Bao L. Exploring the active compounds of traditional Mongolian medicine in intervention of novel coronavirus (COVID-19) based on molecular docking method. *J Funct Foods* 2020;71:104016. Available at: http://doi.org/10.1016/j.jff.2020.104016
61. Wang X, Wang P, Du H, et al. Prediction of the Active Components and Mechanism of Forsythia suspensa Leaf against Respiratory Syncytial Virus Based on Network Pharmacology. *Evid Based Complement Alternat Med* 2022;2022:5643345. Available at: http://doi.org/10.1155/2022/5643345
62. Deng L, Pang P, Zheng K, et al. Forsythoside A Controls Influenza A Virus Infection and Improves the Prognosis by Inhibiting Virus Replication in Mice. *Molecules* 2016;21(5):524. Available at: http://doi.org/10.3390/molecules21050524
63. Zheng X, Fu Y, Shi SS, et al. Effect of Forsythiaside A on the RLRs Signaling Pathway in the Lungs of Mice Infected with the Influenza A Virus FM1 Strain. *Molecules* 2019;24(23):4219. Available at: http://doi.org/10.3390/molecules24234219
64. Wang X, Li X, Wang X, et al. Experimental study of Forsythoside A on prevention and treatment of avian infectious bronchitis. *Res Vet Sci* 2021;135:523–531. Available at: http://doi.org/10.1016/j.rvsc.2020.11.009
65. Li W, Zhao L, Sun LT, et al. Trinorlabdane diterpenoid alkaloids featuring an unprecedented skeleton with anti-inflammatory and anti-viral activities from Forsythia suspensa. *RSC Adv* 2021;11(47):29684–29689. Available at: http://doi.org/10.1039/D1RA05760J
66. Zhao L, Xiang KL, Liu RX, Xie ZP, Zhang SM, Dai SJ. Anti-inflammatory and anti-viral labdane diterpenoids from the fruits of Forsythia suspensa. *Bioorg Chem* 2020;96:103651. Available at: http://doi.org/10.1016/j.bioorg.2020.103651
67. Zhao L, Li W, Dai SJ, et al. Alkaloids bearing rare skeletons from Forsythia suspensa with anti-inflammatory and anti-viral activities in vitro. *Phytochemistry* 2021;186:112739. Available at: http://doi.org/10.1016/j.phytochem.2021.112739