

# A Review of Antiviral Research on Tibetan Medicine Triphala

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### Abstract

Corona virus disease 2019 (COVID-19), 2012 Middle East Respiratory Syndrome (MERS) and 2003 severe respiratory syndrome (SARS) are all caused by coronavirus, COVID-19 has become a global epidemic, becoming a major public health problem and bringing great harm to the physical and mental health of people worldwide, and there are no effective drugs or vaccines to inhibit it. The evidence that traditional Chinese medicine has achieved good results in fighting against COVID-19 and prompts researchers to explore the evidence of traditional medicine to inhibit virus from a broader point of view and provide more possible ways for the treatment of COVID-19.

**Keywords:** Tibetan Medicine; Triphala; Antivirus

### Introduction

Tibetan Medicine Triphala (THL) is a recognized and highly effective multi-herbal Ayurvedic drug, which is composed of *Terminalia chebula* Retz. (*T. chebula*), *Terminalia bellerica* (Gaertn.) Roxb. (*T. bellerica*), *Phyllanthus emblica* L. (*emblica*), and it can be used as an expectorant, antispasmodic and bronchodilator [1]. After publication in "Tang Ben Cao", THL was also found in "Four Classic Books of Tibetan Medicine" which records "indicating the epidemic, chaotic fever, and promoting fever syndrome". THL was already officially reported in "Drug Standards of Ministry of Health of the People's Republic of China, Tibetan medicine version in 1995". The researchers found that the most common compounds of THL are phenolic acids and tannins, and modern pharmacology has shown that they can resist fatigue and antioxidants. Research has found that COVID-19 has multiple pathological mechanisms, such as inflammatory storms, immune disorders, and lung injury [2-5].

This paper reviews the antiviral effects of THL and its constituent herbs and its common compounds, to provide some ideas for the antiviral effect of THL and the treatment of COVID-19.

### THL antiviral immunity

THL is an effective astringent, and studies have shown that it has antiviral, antibacterial, antiallergic, and anti-allergic activity [6] and has no obvious toxic side effects. THL can play an antiviral role by regulating immunity. As a potential immune stimulant and/or immunosuppressant, it can significantly prevent the increase in interleukin-4 (IL-4), increase the decrease in interleukin-2 (IL-2) and interferon  $\gamma$  (IFN- $\gamma$ ) levels, and inhibit cellular immunity, mitogen-induced T lymphocyte proliferation and humoral immunity under

inflammatory stress [7]. THL and its three different constituents contain compounds with different activities such as gallic acid (GA), tannin phenols, chebulagic acid (CHLA), ellagic acid (EA), etc. and can also become a plant-based Ayurvedic immunomodulator [7]. Immunomodulatory drugs or herbal preparations to improve cellular immune function to treat human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) have become a hot topic of research, and serum of THL-treated volunteers was found in Phase I clinical research Interleukin-6 (IL-6), IFN- $\gamma$  and tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) were not significantly increased; cytotoxic T cells (CD3<sup>-</sup>, CD8<sup>+</sup>) and natural killer cells (CD16<sup>+</sup>, CD56<sup>+</sup>) have obvious immune stimulating effects. The increase of the absolute number of these cells may provide a new adjuvant treatment for HIV/AIDS positive patients in terms of immune improvement [8]. THL water and alcohol extracts have antibacterial activity against *Klebsiella pneumoniae* strains obtained from HIV-infected patients [9]. THL extracts affect lymphocyte and natural killer T cell (NKT) functions, can significantly reduce bronchial reactivity, change the distribution of immune cells, and exert antioxidant properties, thereby reducing lung injury [10], reducing lung damage and facilitating the treatment of viral pneumonia. In addition, it has anti-inflammatory effects. Studies have found that in lipopolysaccharide-stimulated macrophages, THL can inhibit IL-6, TNF- $\alpha$ , interleukin- $\beta$  (IL-1 $\beta$ ) and human monocytes. protein 1 (MCP-1), vascular endothelial growth factor (VEGF), nitric oxide (NO) and prostaglandin E2 (PGE2) and other inflammatory mediators, intracellular free radicals, inflammatory enzymes and lysosomal enzyme release [11] (Figure 1).



**Figure 1:** THL (*T. chebula*, *T. bellerica*, *emblica*=1:1:1).

### ***Terminalia chebula* Retz antiviral**

The fruit of *T. chebula* has anti-asthma, anti-tumor, stomach strengthening, expectorant, sore throat, and dyspnea effects and it is usually used to treat infectious diseases in traditional Chinese medicine. Pharmacological studies have shown that *T. chebula* has an inhibitory effect on viral infections such as human immunodeficiency virus type 1 (HIV-1) [12], herpes simplex virus type 1 (HSV-1) [13], cytomegalovirus (CMV) and influenza A virus (IAV) [14]. *T. chebula* are rich in hydrolyzable tannins with good antiviral activity. It is generally believed that it adsorbs HSV and HIV viruses to the host cell membrane, affecting the reverse transcriptase activity of HIV [15]. It has been reported that the hydrolyzable tannins extracted from fructus *T. chebulae* have the effect of anti-hepatitis C virus (HCV) [16] and the isolated hydrolyzed tannins have an inhibitory effect on HSV-1 and HSV-2 [17]. In addition, the ethanol extract of fruits of *T. chebula* 50% and the purified active component CHLA and chebulinic acid (CHLI) have anti-herpes simplex virus type 2 (HSV-2) activity. Compared with acyclovir, the extract and CHLA and CHLI have higher direct antiviral activity against HSV-2 and inhibit virus adhesion and penetration into host cells, but acyclovir can more effectively inhibit virus replication [18]. Moreover, the combination of *T. chebula* and

acyclovir has recombinant *in vitro* anti-HSV-1 activity, and when taken orally at a human dose equivalent to each other, it can significantly inhibit the development of skin lesions and/or prolong the average survival time of infected HSV-1 mice ( $P < 0.01$  or  $0.05$ ) [13] (Figure 2).



**Figure 2:** Dried fruits of *T. chebulae*.

### ***Phyllanthus emblica* L. antiviral**

The fruit of emblica has the functions of diuresis, invigorating stomach, and can be used for diarrhea. The literature survey shows that emblica has many pharmacological activities, namely, anti-diabetic, antioxidant, anti-microbial, anti-fungal, anti-allergic, anti-viral and anti-cancer properties. Porcine reproductive and respiratory syndrome (PRRS) caused by PRRS virus (PRRSV) causes economic loss to the global pig industry. The antiviral activity of seven Thai medicinal plant extracts against PRRSV was studied, and the ethanol extract of *Phyllanthus emblica* showed the highest cytotoxicity ( $78.1 \mu\text{g/ml}$ ) [19]. The extract of fructus emblica inhibited the DNA binding activity of inherent activity activator protein-1 (AP-1) in human papillomavirus 16 (HPV 16)-positive and HPV18-positive (HeLa) cervical cancer cells in a dose-and time-dependent manner [20]. The extracts of 41 kinds of Egyptian folk medicinal plants were screened to inhibit human HIV reverse transcriptase. It was found that emblica had obvious inhibitory activity, and the GA extracted by methanol had strong activity [12]. Other studies have shown that methanol and water extracts of emblica fruit can resist HIV reverse transcription [21]. The researchers developed four herbal gels containing *T. chebula* and emblica prepared with 50% ethanolic, which have the ability to resist HSV-2 and HIV infection. Some studies have shown that emblica has an anti-bronchial pneumonia effect [21] and the methanol extract of its leaves can repair pulmonary fibrosis. In addition, the methanol extract of *Ipomoea prostrata* has a good inhibitory effect on carbapenem-resistant strains (RS-307) that can cause bacteremia, urinary tract infections, meningitis and pneumonia [22]. Emblica treatment can significantly reduce the number of nodules on the surface of the lungs and reduce the levels of  $\text{TNF-}\alpha$ , IL-6 and IL-1 $\beta$  in benzopyrene-induced lung tissue proinflammatory cytokines [23].

The compounds extracted from emblicas also have antiviral functions. The study found that 1,2,4,6-tetra-O-galloyl- $\alpha$ -D-glucose (1246TGG) extracted from emblica can significantly resist infection with HSV-1 and HSV-2 at nontoxic concentrations. The antiviral mechanism may be to prevent extracellular infection by inactivating free virus particles, reduce virus attachment, penetration, and inhibit intracellular biosynthesis of the virus [24]. The sesquiterpene glycosides extracted from emblica lanceolata and the main tannin compound Phyllaemblicin B. Euglycoside B has strong activity against Coxsackievirus B3 (CVB3) [25] (Figure 3).



**Figure 3:** Dried fruits of emblica.

#### ***Terminalia bellerica* (Gaertn.) Roxb. antivirus**

A review of the early literature shows that *T. bellerica* fruits have the function of convergence, digestion, defecation, deworming, treatment of bronchitis, asthma, ophthalmopathy, diarrhea and so on. *T. bellerica* is effective against all three HIV-1 pseudoviruses with the least cytotoxicity and the greatest antiviral potential [26]. The compounds extracted from *T. bellerica* can be used as HIV reverse transcriptase and have anti-HIV-1, antimalarial and antifungal activities [12] (Figure 4).



**Figure 4:** Dried fruits of *T. Bellerica*.

#### **Chemical compounds**

### Ellagic acid

EA has antiviral activity, and EA has anti-HBV, HCV and HIV effects. EA can inhibit the secretion of HBeAg in HBV-infected cell lines and HBeAg transgenic mice, overcome the host immune tolerance induced by HBeAg in the process of HBV infection [27]. EA showed dose-dependent inhibition of HCV NS3/4A protease activity *in vitro* and HCV RNA levels were significantly reduced in infectious cell culture systems containing HCV subgenomic HCV-JFH1 (genotype 2a) virus and H77s (genotype 1a) RNA [28]. EA can inhibit HIV reverse transcriptase and cellular DNA polymerase activity, inhibit HIV-1 replication in target cells without cytotoxicity, and play a key role in anti-HIV-1 infection in early and late stages [29]. In addition, EA has different inhibitory effects on a variety of viruses. The triple combination of oseltamivir, isoprinosine and EA and the dual combination of EA, oseltamivir and isoprinosine have significant protective effects on mice infected with H3N2 influenza virus, indicating that EA has the potential of anti-IAV [30]. EA has antiviral activity against human rhinovirus (HRV) and Ebola virus (EV) [31]. The structure is shown in figure 5.

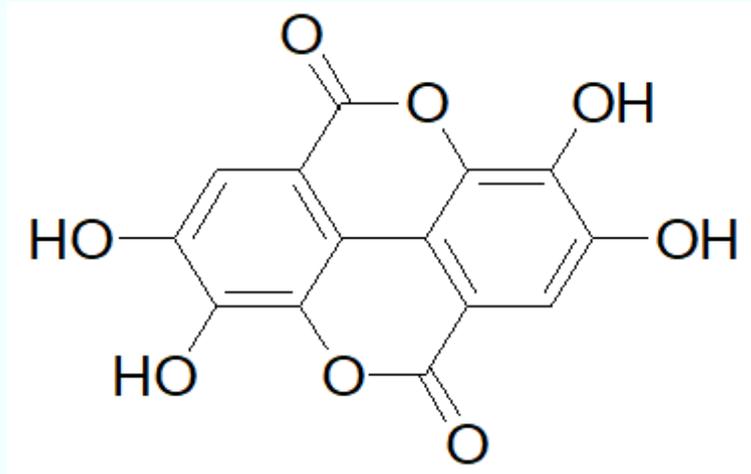


Figure 5: Structural formula of EA.

### Chebulagic acid and chebulinic acid

CHLA and CHLI inhibit replication during the IAV replication cycle and inhibit virus release mediated by neuraminidase (NA), which is expected to be further developed as a new antiviral drug against IAV. In addition, CHLA and CHLI showed a high inhibitory effect on an oseltamivir-resistant IAV strain [32]. It has been reported that the anti-HIV activity of CHLA, and CHLI can prevent recombinant HIV gp120 from binding to CD4 and inhibit HIV-1 RT and integrase. CHLA treatment of lethal human enterovirus 71 (EV71)-attacking mice can effectively reduce mortality and relieve symptoms by inhibiting virus replication. It may be a potential therapeutic agent for EV71 infection [33]. CHLA can inhibit the activity of HSV-1 glycoprotein and exert antiviral effects [17]. Chebulic acid (CA) on urban particulate matter (UPM) UPM-mediated inflammation (detection of the expression of TNF- $\alpha$ , IL-6 and IL-8 in alveolar epithelial cells) has a protective effect on the collapse of alveolar epithelial cells (NCI-H441) exposed to UPM [32]. The structure is shown in figure 6.

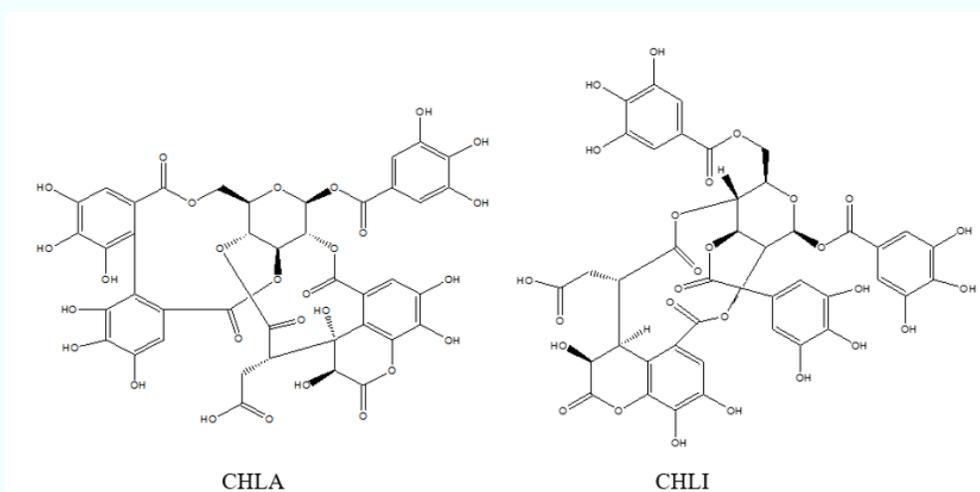
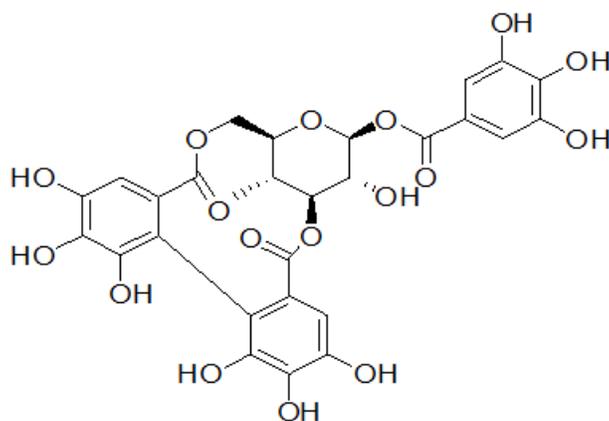


Figure 6: Structural formula of CHLA and CHLI.

## Corilagin

Excoecariphenol D, corilagin, geraniin and CHLA show potential inhibitory effects on HCV NS3-4A protease, and corilagin has significant inhibitory effects on HCV NS3 protease and NS5B RNA polymerase, effectively inhibiting infectious cell culture systems virus replication; in chimeric mice infected with HCV carrying human hepatocytes, corilagin may limit serum HCV RNA levels, reduce collagen deposition and liver cell degeneration [33]. Moreover, Corilagin found *in vivo* and *in vitro* experiments that it significantly inhibited the increase in Toll-like receptor 2 (TLR2) and its downstream mediator levels after macrophage-activated lipopeptide-2 (MALP-2) or HSV-1 challenge and inhibited HSV-stimulated migraine cells Release TNF- $\alpha$ , IL-1 $\beta$  and NO play a protective role against HSV-1 encephalitis [34]. In addition, corilagin inhibits HBV [13], reduces the cytotoxicity of EV71 or Coxsackie virus A16 to Vero cells [35], has a protective effect against Japanese encephalitis virus (JEV)-induced Parkinson's disease, and HIV viral infection shows high antiviral activity [37]. The structure is shown in figure 7.



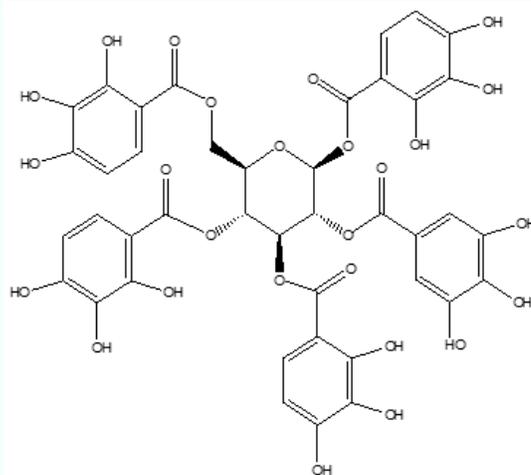
**Figure 7:** Structural formula of corilagin.

### 1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucopyranose

THL contains a variety of acyl glucose and has a variety of antiviral effects, such as HIV, and antiviral drugs for severe acute respiratory syndrome coronavirus (SARS-CoV) [38]. 1,2,6-Trigalloyl- $\beta$ -D-glucose and 1,2,3,6-tetra-O-galloyl- $\beta$ -D-glucose have a significant inhibitory effect on HCV NS3 protease [39].

1,2,3,4,6-penta-O-galloyl- $\beta$ -D-glucopyranose (PGG) is a more common tannin compound in THL, and there are many reports of antiviral effects. PGG is a generic HCV entry inhibitor with high bioavailability, does not destroy the integrity of HCV virions, and mainly functions during virus attachment. When PGG is used in combination with the well-characterized HCV inhibitor dalatavi, it shows an additive effect and has an inhibitory effect on NS3 protease inhibition [40]. PGG delays the nuclear transport process of HSV-1 particles by inhibiting the upregulation of dynein (a cellular major motor protein) induced by HSV-1 infection, affecting the outflow of HSV-1 core-shell; it is the first time that PGG is resistant to acyclovir *in vitro* antiviral activity of drug viruses, further confirming that PGG can be used as a candidate for HSV therapy, especially for the treatment of drug-resistant strains [41]. PGG can also prevent the adsorption and release of HSV-1. PGG strongly inhibits rabies virus (RABV) virus titer (50-fold) and viral mRNA expression (up to 90%) and protein synthesis *in vitro* and PGG not only inhibits virus adsorption and entry but also mediates mTOR-dependent autophagy signals Activation of the pathway inhibits autophagy and directly inactivates RABV; *in vivo* PGG (10 mg/kg) reduces clinical symptoms and reduces the mortality

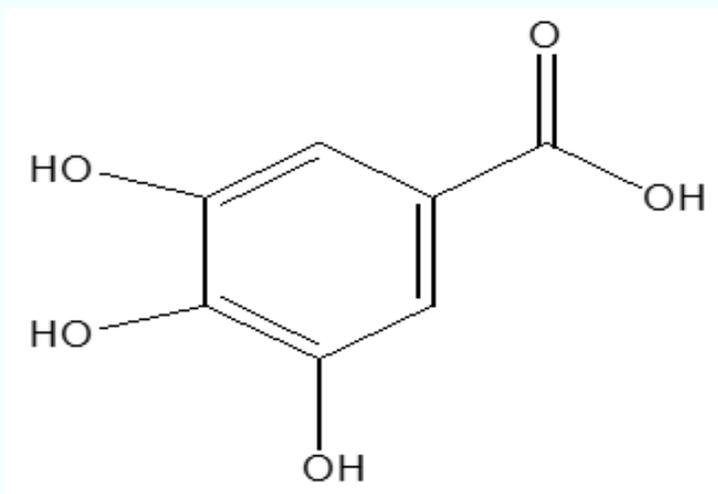
of infected mice by 27.3% [42]. PGG significantly inhibited the activation of c-Jun N-terminal kinase (JNK) induced by varicella-zoster virus (VZV), that is, early expression of viral 62 (IE62) protein and VZV replication [43]. Finally, PGG has IAV activity, and its mechanism can reduce the accumulation of plasma membranes of NP protein in the late replication cycle by interacting with viral hemagglutinin, significantly reducing virus sprouting and progeny viruses from infected cells release, thereby inhibiting IAV infection, PGG regulates Hsp90 induction and the mTOR/p70S6K signaling pathway to enhance autophagy, thereby inhibiting IAV growth and viral protein synthesis [44]. In addition, it has been reported that in HepG2.2.15 cell culture, PGG also reduces extracellular HBV in a dose-dependent manner [45]. In addition, PGG can also inhibit HIV, respiratory syncytial virus (RSV), and HRV [43]. Its antiviral mechanisms include direct inactivation, inhibition of virus adsorption on host cells and expression of viral genes, and protein translation inhibition of replicated viral genomes. The structure is shown in figure 8.



**Figure 8:** Structural formula of PGG.

### Gallic acid

GA is a natural phenolic compound with various biological activities such as antioxidant, anti-inflammatory, antibacterial, anticancer, antiviral and cardiovascular protection. Human coronavirus NL63 (HCoV-NL63) is one of the major HCoVs worldwide, and can cause respiratory diseases such as runny nose, cough, bronchiolitis and pneumonia. In *in vitro* experiments, GA, caffeic acid and chlorogenic acid can reduce the production of progeny HCoV-NL63 particles and have an antiviral effect [46]. GA down-regulates the expression of NS5A-HCV protein (~55%) and HCV-RNA (~50%) in a time-dependent manner, reducing the production of ROS in cells that express HCV protein early, suggesting that GA reduces oxidative stress and downregulates liver cancer HCV replication [47]. When GA is used in combination with other anti-inflammatory agents, it may help to incorporate it into a multi-component combination fungicide that targets the HIV virus and promotes the host factor of HIV transmission [48]. GA only destroys virus particles against A and B Influenza virus shows broad-spectrum antiviral activity and is a promising drug source for targeting viral particles. It exhibits concentration-dependent inhibition at higher concentrations. Moreover, GA, methyl gallate (MG) and pentagalloyl glucose can inhibit the replication of IAV in MDCK cells, which may be a sensitive agent for inhibiting influenza A H1N1 influenza virus infection [49]. Ultrasound-induced rapid reduction of GA yields highly monodisperse gold nanoparticles (GAunps), which interfere with virus attachment in a dose- and time-dependent manner, and inhibit HSV proliferation in VERO cells, and its cytotoxicity to VERO cells (CC50 is 972.4  $\mu\text{M}$ ) was significantly lower than that of acyclovir (CC50 was 561.7  $\mu\text{M}$ ) [50]. GA and ethyl gallate inhibit the binding of Norovirus (NoVs) P protein to saliva (IC 50  $\approx$  0.1  $\mu\text{M}$ ), thereby inhibiting infection [51]. In addition, GA is also resistant to dengue virus (DENV), HBV, EV71 and EV [52-54]. The structure is shown in figure 9.



**Figure 9:** Structural formula of GA.

## Conclusion

In summary, THL is the most commonly used prescription for Tibetan medicine, with a history of corrected ancient plague treatment. THL and its main components and common phenolic tannin compounds have different degrees of antiviral effects, which can inhibit DNA viruses, such as HBV and HSV and have inhibitory effects on many RNA viruses, such as HIV-1, RSV, HCV, HRV and IAV and human coronavirus, etc. Moreover, THL has obvious antioxidative stress and antiviral immunity, and promotes hypoxia tolerance and lung injury repair. Therefore, this manuscript is the basis for the treatment of new coronary pneumonia. In the future, further treatment applications will prove the antiviral effect of THL, especially new coronary pneumonia.

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## Conflict of Interest

The authors declare no conflicts of interest.

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