

Antiviral Properties of Traditional Chinese Medicine against Coronavirus: Research Clues for Coronavirus Disease-2019

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Abstract

The objective of this study was to provide research clues for the prevention and treatment of coronavirus disease-2019 (COVID-19) and coronavirus (CoV) infection using Traditional Chinese Medicine (TCM). A review on research and clinical trials that using TCM extracts and active ingredients against CoV was performed, and a table of TCM agents and their effects on CoV were summarized. Relevant analysis was performed and visual expression of the data included summarizing the types of TCM and treatment methods for COVID-19. TCM fighting against CoV is mainly used in the lung and heart channels, and its medicinal properties are mainly cold and mild, while its taste is mainly bitter and sweet. The majority of research focused on treatments that clear away heat and toxic materials and those that strengthen body resistance and tonify deficiencies. TCM has unique advantages to fight against CoV. The development of new anti-CoV therapy using TCM is of great significance for the prevention and treatment of COVID-19 pneumonia and various viral infectious diseases.

Keywords: 2019-novel coronavirus, coronavirus, coronavirus disease-19, novel coronavirus pneumonia, severe acute respiratory syndrome-coronavirus-2, Traditional Chinese Medicine

INTRODUCTION

Coronavirus (CoV) is an enveloped positive-sense single-stranded RNA virus of the family *Coronaviridae* and is of the order *Nidovirales*. It is named because of the pleomorphic Corolla process observed on the surface of this kind of virus. CoV is a pathogen that causes diseases in a variety of wild animals, livestock, and human beings. CoV is divided into four genera (α , β , γ , and δ) according to gene sequence, serotype relationships, and natural hosts by the International Committee on Taxonomy of Viruses. Severe acute respiratory syndrome (SARS)-CoV, SARS-CoV-2 (2019-novel CoV [nCoV]), and Middle East respiratory syndrome (MERS)-CoV belong to the β genus.

Notably, there are a large number of variable translations in the genome of beta-CoV (β -CoV), which is characterized by high diversity and rapid variation. Nevertheless, studies have shown that 2019-nCoV has more than 85% homology with bat-SL-CoVZC45 and bat-SL-CoVZXC21, and about 79% homology with SARS-CoV, and both have similar receptor-binding domains (ACE2 receptors). In addition, there

is a highly conserved sequence (Nankai CDS) in the genome of β -CoV, which rarely mutates.^[1,2]

Therefore, research on the SARS-CoV, MERS-CoV, and other coronaviruses can be beneficial for the development of clinical treatments for coronavirus disease-2019 (COVID-19) patients and may inform us of the prevention and treatment methods to inhibit this kind of novel CoV.

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SUMMARY OF ANTICORONAVIRUS TRADITIONAL CHINESE MEDICINE AND RELATED PREPARATIONS

Since the outbreak of SARS, research and treatment for various coronaviruses have rapidly emerged, among which the research on antiviral components of natural drugs is prevalent. Practice has proved that treatment with Traditional Chinese Medicine (TCM) can interfere with respiratory diseases caused by CoV in varying degrees. Moreover, a variety of effective components contained in TCM can inhibit the replication of CoV. The author summarizes and analyzes the research in recent years on the use of TCM to treat CoV, which can provide a basis for the discovery of novel anti-CoV drugs.

Types of Chinese medicine effective against severe acute respiratory syndrome coronavirus

SARS-associated CoV is highly pathogenic and belongs to the subgroup B of β -CoV. It has the epidemiological characteristics of being highly infectious, rapidly progressing, and causing severe disease in human beings. From 2002 to 2003, SARS-CoV spreads to more than 30 countries and regions around the world with more than 8000 people being infected and a fatality rate of approximately 10%.^[3] After the outbreak of SARS, governments and organizations in various countries began to attach great importance to research on this kind of CoV. The whole genome of SARS-CoV was rapidly deciphered, and research and development of antiviral drugs and vaccines were promoted. However, due to many unfavorable factors such as virus mutation, this problem could not be solved completely. Because the practice of syndrome differentiation is effective in the treatment of SARS, the health department of China has always incorporated these methods into treatment plans. A large number of studies have proved that a variety of TCM treatments have an inhibitory effect on SARS-CoV, as detailed in Table 1.

Types of Chinese medicine effective against beta-coronavirus

The genomic structure of β -CoV is relatively complex and includes four subgroups (A, B, C, and D).^[20] Subgroup A includes two kinds of human CoV (HCoV-OC43 and HCoV-HKU1), mouse hepatitis virus, bovine CoV, etc.; Subgroup B includes SARS-CoV and SARS-Rh-BatCoV-HKU3; Subgroup C includes MERS-CoV and two bat coronaviruses; Subgroup D contains Ro-BatCoV-HKU9. At present, five of the seven known human coronaviruses belong to the β -genus, of which three are highly pathogenic coronaviruses, namely, SARS-CoV, MERS-CoV, and SARS-CoV-2. These viruses have a high fatality rate when they infect humans, with MERS-CoV reaching rates as high as 36%.^[21]

Because of the high homology among the viruses of the same genus, there is no specific treatment for this kind of infection and an effective preventive vaccine has not yet been developed. Thus, understanding this genus is key to solving many problems associated with coronaviruses. Countries around the world have attached great importance to this by performing

extensive research and exploration including TCM treatments, as detailed in Table 2.

Types of Chinese medicine effective against alpha-coronavirus

Alpha CoV (α -CoV) can be divided into two subgroups: α 1 and α 2. α 1 subgroup includes feline infectious peritonitis virus, canine CoV, etc., and α 2 Subgroup includes two kinds of hCoV (HCoV-NL63 and HCoV-229E), porcine epidemic diarrhea virus (PEDV), etc.

HCoV-229E is the earliest isolated hCoV, and it is a common CoV strain with global distribution currently. Like HCoV-NL63, the respiratory symptoms caused by the two viruses are mild, the course of disease is short, and clinical treatment can effectively control the development of the disease.^[24,25] PEDV is a type of enterovirus and the mortality rate of piglets is very high after infection. Spread of this virus has occurred in many countries and caused serious economic losses.^[26] The study of α -CoV is also very necessary, and the ingredients contained in TCM are capable of inhibiting it, as detailed in Table 3.

Types of Chinese medicine effective against gamma-coronavirus

Gamma-CoV mainly infects birds and some marine mammals and includes infectious bronchitis virus (IBV) and beluga whale coronavirus (SW1). IBV is a highly infectious pathogen for poultry. Poultry infected with IBV will develop serious respiratory symptoms resulting in death that has led to significant economic losses to the poultry industry.^[32] The nucleotide sequence homology of IBV and SARS-CoV is close, and there is a certain genetic relationship, which has led some scholars to use IBV as a model for CoV in studies measuring the inhibition capacity of TCM, as shown in Table 4.

DATA ANALYSIS AND VISUAL EXPRESSION

Treatments were analyzed based on syndrome differentiation of disease caused by CoV and details from the theory of TCM. In order to make the data in the [Tables 1-4] more intuitive, we synthesized the known data in the above literature using the ancient and modern medical record cloud platform Personal Edition version 2.2.1 as well as the Cytoscape 3.7.2 (U.S. National Institute of General Medical Sciences (NIGMS)) drawing software to carry out the relevant statistical analysis and visual expression of the data.

Properties of Traditional Chinese Medicine against coronavirus

The results of Chinese medicinal nature and flavor show that the medicinal properties are mainly cold and plain, and the flavor of these medicines is mainly bitter and sweet. The results of channel tropism showed that this kind of TCM is mostly in the meridians of the lung and heart [Figures 1-3].

Efficacy of Traditional Chinese Medicine against coronavirus

From the analysis using the ancient and modern medical record

Table 1: Active ingredients and effects of Traditional Chinese Medicine on severe acute respiratory syndrome-related coronavirus

Source	Active ingredient	Experimental model	Efficacy and Mechanism	References
<i>Glycyrrhiza uralensis Fisch</i>	Glycyrrhizin	Vero cells	Inhibits SARS-CoV replication, and also inhibits virus adsorption and transmembrane invasion into host cells in the early stages of replication	[4]
	Glycyrrhizic Acid Derivatives	Vero cells	Inhibits SARS-CoV replication.	[5]
	Compound Glycyrrhizin	Clinical patient	Improve the clinical symptoms of SARS patients, protect liver function, reduce hormone dose, shorten hormone treatment time.	[6]
<i>Gentiana scabra</i>	Extract GSH	Vero E6 cells	Inhibits SARS-CoV replication.	[7]
<i>Cassia tora</i>	Extract CTH	Vero E6 cells	Inhibits SARS-CoV replication.	[7]
<i>Dioscorea batatas</i>	Extract DBM	Vero E6 cells	Inhibits SARS-CoV replication while inhibiting 3CL protease activity. (3CL pro)	[7]
<i>Cibotium barometz</i>	Extract CBE	Vero E6 cells	Inhibits SARS-CoV replication.	[7]
	Extract CBM	Vero E6 cells	Inhibits SARS-CoV replication while inhibiting 3CL protease activity. (3CL pro)	[7]
<i>Taxillus chinensis</i>	Extract TCH	Vero E6 cells	Inhibits SARS-CoV replication.	[7]
<i>Lycoris radiata</i>	Lycorine	Vero E6 cells	Inhibits SARS-CoV-induced cytopathic effects.	[8]
<i>Artemisia annua</i>	Extract	Vero E6 cells	Inhibits SARS-CoV-induced cytopathic effects.	[8]
<i>Pyrrosia lingua</i>	Extract	Vero E6 cells	Inhibits SARS-CoV-induced cytopathic effects	[8]
<i>Lindera aggregata</i>	Extract	Vero E6 cells	Inhibits SARS-CoV-induced cytopathic effects.	[8]
<i>Broussonetia papyrifera</i>	Polyphenols	Escherichia Coli BL21	Inhibits SARS-CoV papain-like protease (PL pro) and 3C-like protease (3CL pro) activity, of which Papyriflavonol A has the best inhibitory effect on PL pro.	[9]
<i>Tribulus terrestris</i>	Cinnamic Amides	Escherichia Coli BL21	Inhibits SARS-CoV papain-like protease (PL pro) activity.	[10]
<i>Boenninghausenia sessilicarpa</i>	Coumarins	Vero E6 cells	Inhibits SARS-CoV activity and reduces SARS-CoV-induced cytopathic effects.	[11]
<i>Toona sinensis</i>	Extract TSL-1	Vero cells (CCL-81)	Inhibits SARS-CoV replication.	[12]
<i>Isatis indigotica root</i>	Hesperetin & Aloe emodin	Vero cells	Inhibits SARS-CoV 3C-like protease (3CL pro) activity	[13]
<i>Galla chinensis</i>	TGG	Vero E6 cells	Interfering with SARS-CoV and cell fusion process. (Predicted to be related to S2 subunit of SARS virus S protein)	[14]
<i>Rhodiola kirilowii</i>	Luteolin	Vero E6 cells	Interfering with SARS-CoV and cell fusion process. (Predicted to be related to S2 subunit of SARS virus S protein)	[14]
<i>Scutellaria baicalensis</i>	Baicalin	FRhK-4 cells	Inhibits SARS-CoV replication.	[15]
<i>Houttuynia cordata</i>	Extract	Balb/c mice	Inhibits SARS-CoV 3C-like protease (3CL pro) and RNA-dependent RNA polymerase (RdRP) activities; stimulates mouse lymphocyte proliferation (CD4+, CD8+), and promotes lymphocyte secretion of IL-2 and IL-10.	[16]
<i>Radix et Rhizoma Rhei</i>	Emodin	Escherichia Coli BL21	Prevent the virus from invading host cells by inhibiting the SARS-CoV S protein from binding to the ACE2 receptor.	[17]
<i>Radix Polygoni multiflori</i>				
<i>Caulis Polygoni multiflori</i>				
<i>Litchi chinensis Sonn</i>	Flavonoids	Escherichia Coli BL21	Inhibits SARS-CoV 3C-like protease (3CL pro) activity,	[18]
<i>Semen Sojae Praepatum</i>	Curcumin	SARS-CoV fluorescent substrate	Inhibits SARS-CoV 3C-like protease (3CL pro) activity.	[19]
<i>Schisandrae Chinensis Fructus</i>	Lignin (Dibenzocyclooctadiene)	SARS-CoV fluorescent substrate	Inhibits SARS-CoV 3C-like protease (3CL pro) activity.	[19]

SARS-CoV: Severe acute respiratory syndrome-related coronavirus, GSH: Glutathione, *E. Coli*: *Escherichia Coli*, *G. uralensis*: *Glycyrrhiza uralensis*, *G. scabra*: *Gentiana scabra*, *C. tora*: *Cassia tora*, *D. batatas*: *Dioscorea batatas*, *C. barometz*: *Cibotium barometz*, *T. chinensis*: *Taxillus chinensis*, *L. radiata*: *Lycoris radiata*, *A. annua*: *Artemisia annua*, *P. lingua*: *Pyrrosia lingua*, *L. aggregata*: *Lindera aggregata*, *B. papyrifera*: *Broussonetia papyrifera*, *T. terrestris*: *Tribulus terrestris*, *B. sessilicarpa*: *Boenninghausenia sessilicarpa*, *T. sinensis*: *Toona sinensis*, 3CL pro: 3C-like protease, PL pro: Papain-like protease, CTH: extract from *Cassia Semen* (the dried seed of *Cassia tora*), DBM: extract from *Dioscoreae Rhizoma* (the tuber of *Dioscorea batatas*), CBE and CBM: extract from *Rhizoma Cibotii* (the dried rhizome of *Cibotium barometz*), TCH: extract from *Loranthi Ramus* (the dried stem, with leaf of *Taxillus chinensis*), TSL-1: The fraction of crude extract from the tender leaf of *Toona sinensis* Roem

Table 2: Active ingredients and effects of Traditional Chinese Medicine targeting β coronavirus

Source	Active ingredient	Experimental model	Efficacy and mechanism	References
<i>B. papyrifera</i>	Polyphenols	<i>E. Coli</i> BL21	Brousochalcone B inhibits MERS-CoV 3C pro activity. Kazinol F had the best effect on MERS-CoV PL pro	[9]
N/R	Resveratrol	Vero E6 cells	Inhibits MERS-CoV replication and reduces MERS-CoV virus N protein expression	[22]
<i>A. sativum</i> L.	Allitridin injection	Balb/c mice	Inhibition of MHV-3 replication	[23]
<i>L. japonica</i> Thunb., <i>S. baicalensis</i> Georgi, <i>F. suspensa</i>	Shuanghuanglian injection	Balb/c mice	Inhibition of MHV-3 replication	[23]
<i>H. cordata</i>	Injection	Balb/c mice	Inhibition of MHV-3 replication	[23]

3CL pro: 3C-like protease, PL pro: Papain-like protease, MERS-CoV: Middle east respiratory syndrome coronavirus, *B. papyrifera*: *Broussonetia papyrifera*, *A. sativum*: *Allium sativum*, *L. japonica*: *Lonicera japonica*, *S. baicalensis*: *Scutellaria baicalensis*, *F. suspensa*: *Forsythia suspensa*, *H. cordata*: *Houttuynia cordata*, *E. Coli*: *Escherichia Coli*, MHV: Mouse hepatitis virus, N/R: No specific drugs mentioned

Table 3: Active ingredients and effects of anti- α coronavirus Traditional Chinese Medicine

Source	Active ingredient	Experimental model	Efficacy and mechanism	References
<i>Sambucus Formosana</i> Nakai	Caffeic acid	LLC-MK2 cells	Inhibits HCoV-NL63 replication and blocks virus attachment.	[27]
<i>Euphorbia nerifolia</i>	β -Friedelanol	MRC-5 cells	Inhibits HCoV-229E replication	[28]
<i>R. kirilowii</i>	Extract	Vero cells (CCL-81)	Inhibits HCoV-229E replication	[12]
<i>C. chinensis</i> Franch	Extract	Vero cells (CCL-81)	Inhibits HCoV-229E replication	[12]
6 herbal decoctions	Chinese medicine compound	Vero cells (CCL-81)	Inhibits HCoV-229E replication	[12]
<i>H. cordata</i>	Q7R	Vero cells (CCL-81)	Inhibits PEDV-induced cytopathic effects and blocks viral mRNA production	[29]
<i>E. cava</i>	Phlorotannins	Vero cells	By inhibiting the binding of PEDV virus hemagglutinin to the host SA receptor to produce antiviral activity, phlorofucofuroeckol and dieckol have a good effect on inhibiting the invasion and replication of PEDV virus	[30]
<i>A. turbinata</i> Blume.	Escin	Vero cells	Inhibits PEDV replication	[31]

HCoV: Human coronavirus, PEDV: Porcine epidemic diarrhea virus, *E. nerifolia*: *Euphorbia nerifolia*, *R. kirilowii*: *Rhodiola kirilowii*, *C. chinensis*: *Coptis chinensis*, *H. cordata*: *Houttuynia cordata*, *E. cava*: *Ecklonia cava*, *A. turbinata*: *Aesculus turbinata*, SA: Sialic acid

cloud platform software, we know that most of the above drugs belong to two categories: eliminating pathogenic factors and strengthening vital qi. The most common antipathogenic drugs are involved in “clearing heat and removing toxicity”, “cooling blood and clearing heat” and “removing phlegm and relieving cough. In contrast, the drugs for strengthening vital qi are “nourishing liver and kidney,” “relieving pain” and “tonifying spleen qi.”

Active components of Traditional Chinese Medicine against coronavirus

Next, we collected the information from different TCM treatments for CoV along with the effective ingredients of these therapies. Using the drawing software Cytoscape 3.7.2 (<https://cytoscape.org/>) to integrate the effective components of TCM with the viruses that they inhibit, we created a Network Diagram of Efficacy and Drug Composition [Figure 4].

DISCUSSION

The antiviral mechanisms of TCM include viral replication inhibition in host cells, inhibition of virus adsorption or invasion into host cells, and regulation of the human immune system. The active components of each TCM interfere with

unique steps in the process of viral invasion into host cells.^[38] At present, the research on the antiviral activity of TCM extracts and their active components is mainly focused on the mechanism of action at the cellular and molecular level *in vitro*,^[39] which can be used for reference in clinic; however, it should be correctly distinguished from the actual use of drugs and *in vivo* treatments or clinical trials.

Strengthening vital qi to eliminate pathogenic factors

Combined with the above analysis, most of the TCMs with antiviral properties are mainly “clearing heat and removing toxicity” with some medicines acting by “Strengthening vital qi and consolidating body resistance.” According to the latest research, in the diagnosis and treatment programs of TCM for the prevention and treatment of pneumonia caused by SARS-CoV-2 infection, COVID-19 pneumonia has mainly been identified as an epidemic disease caused by the evil of “dampness-heat toxicity and blood stasis.” Importantly, the recommended prescriptions of TCM and proprietary Chinese medicine for COVID-19 pneumonia are compound prescriptions for clearing heat and removing toxicity. However, at the same time, the disease does great damage to the vital qi of patients, and “deficiency” is also one of the main characteristics of this epidemic disease.^[40] Through the accurate prescription

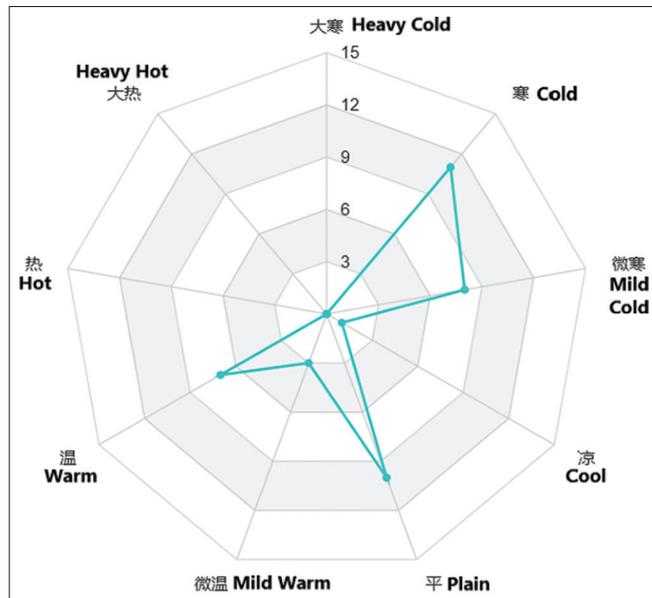


Figure 1: Four natures of Traditional Chinese Medicine

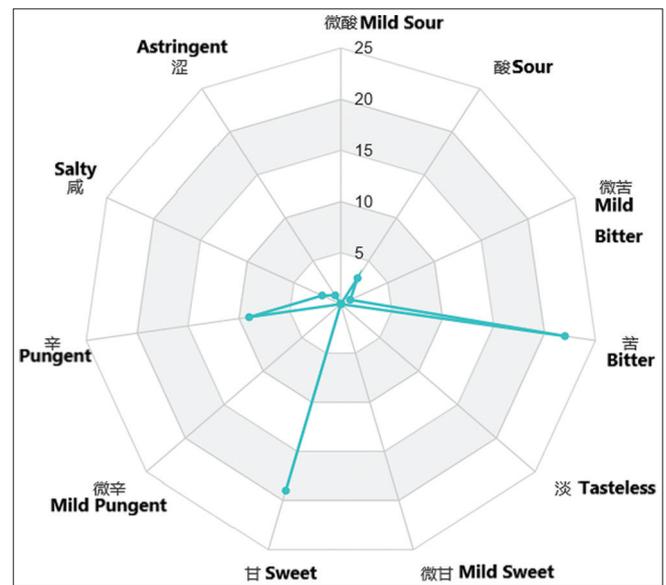


Figure 2: Five flavors of Traditional Chinese Medicine

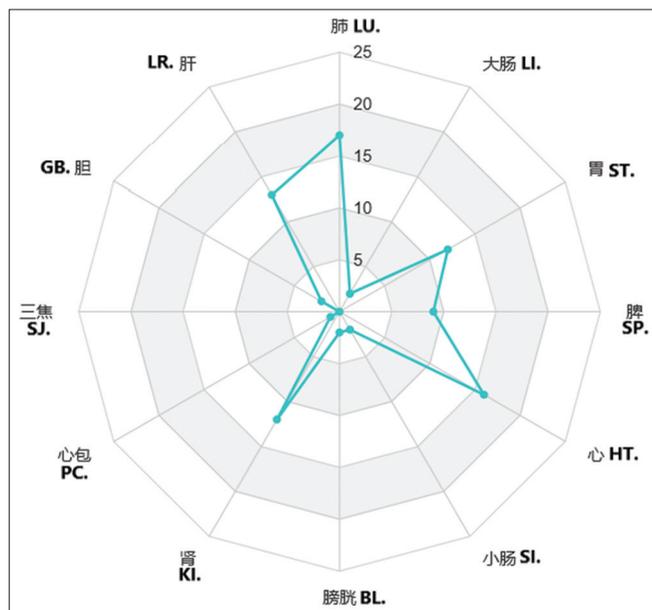


Figure 3: Channel and collateral of Traditional Chinese Medicine

of treatment based on syndrome differentiation, we can improve the human body’s ability to resist the invasion of external illness and maintain a healthy qi in the inner body. We hope to prevent the epidemic as well as avoid the creation of pathogenic qi. Thus, it can be seen that “strengthening vital qi to eliminate pathogenic factor” is the basic antiviral treatment mechanism in TCM.

Comprehensive analysis of data gained by two effects

“Two effects” refers to both effective antivirals and effective clinical syndrome differentiation. The external symptoms of different diseases vary, and the manifestation of the same disease may differ from one individual to the next. It

is necessary to use the overall concept of time, place, and personal conditions. For the treatment of all infectious diseases in TCM, we must adhere to treating through the principle of comprehensive analysis based on data from the four diagnostic methods and treatment based on syndrome differentiation. On this basis, it may be more beneficial to the overall clinical effect to add TCM, which has been proven to have antiviral capacity, to modern pharmacology.

CONCLUSION

The antiviral mechanism of TCM is the result of many factors. As a natural form of medicine, most TCM treatments have the advantage of broad-spectrum antiviral coverage, good curative effect, and low side effect profiles. The field of TCM antiviral treatments has broad prospects. The research and development of these treatments is of great significance for the prevention and treatment of COVID-19 pneumonia other sequelae caused by SARS-CoV-2.

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Conflicts of interest

There are no conflicts of interest.

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