REVIEW

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Traditional Chinese medicine in antiviral treatment

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Highlights

Traditional Chinese medicine (TCM) regards infectious diseases caused by viruses as “plagues”, and TCM has played an important role in the fight against various epidemics for thousands of years. In TCM theory, it was the first description of infectious diseases such as smallpox, plague, pertussis and measles; TCM treatment pays attention to the balance of the human body, which can improve and enhance the human body's ability of immunity and disease resistance. Therefore, it can effectively prevent and control of plague. In this paper, the classification, mechanism, existing problems and the prospect of traditional Chinese medicine in antiviral treatment has been summarized.

Abstract

The Novel Coronavirus (COVID-19), which broke out in Wuhan, China in December 2019, attracted worldwide attention. With a long incubation period and strong infectiousness, COVID-19 poses a great threat to the life and health worldwide with high incidence, high pathogenicity and low sensitivity to antibiotics. At present, there are less kinds of antiviral drugs, including rimantadine hydiochloride, acyclovir, interferon, zidovudine, ribavirin, etc., which maybe lead to severe adverse reactions of the nervous system, hematopoietic system, liver and kidney system, as well as side effects such as nausea, vomiting, upper abdominal discomfort and diarrhea. Meanwhile, the development of antiviral drugs requires huge investment and time, the development of effective antiviral drugs and vaccine lags far behind the rapidly developed disease. Traditional Chinese medicine has played an important role against the infection, especially in the fight against severe acute respiratory syndrome, H1N1 influenza, H7N9 flu virus, middle east respiratory syndrome and Ebola virus infection. In this paper, the classification, mechanism, existing problems and the prospect of traditional Chinese medicine in antiviral treatment has been summarized in order to provide certain reference for the research and prescription screening of traditional Chinese medicine anti-COVID-19 drugs.

Keywords: Traditional Chinese medicine, Antiviral treatment, Mechanism, Research status, Prospect

***Abbreviations*:**

COVID-19, Novel Coronavirus; TCM, traditional Chinese medicine; NK, natural killer cells; INF-1, interferon-1; IL-2, interleukin-2.

***Competing interests*:**

The authors declare that there is no conflict of interest.

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Background

Novel Coronavirus (COVID-19) broke out in Wuhan, China in December 2019, followed by a global outbreak. The COVID-19 has a high disease rate, high pathogenicity and high susceptibility to drug resistance, making antiviral strategies a major scientific issue facing human [1–2]. At present, the antiviral drugs are few, the effect is not ideal, and the development of antiviral drugs requires a huge investment; meanwhile, vaccine development obviously lags behind, which will make antiviral efforts uncontrollable.

Traditional Chinese medicine (TCM) regards infectious diseases caused by viruses as “plagues”, and TCM has played an important role in the fight against various “epidemics” (infectious diseases) encountered for thousands of years [3–4]. Especially since 2003, TCM has played an effective role in fighting against viral diseases such as against severe acute respiratory syndrome, H1N1 influenza, H7N9 flu virus, middle east respiratory syndrome and Ebola virus infection[5–6]. In this paper, the classification, mechanism, existing problems and the prospect of traditional Chinese medicine in antiviral treatment has been summarized in order to provide certain reference for the research and prescription screening of traditional Chinese medicine anti-COVID-19 drugs.

Classification of antiviral TCM

According to different antiviral efficacies, TCM herbs can be divided into Qing Re (clearing heat) herbs, Jie Biao (relieving exterior syndrome) herbs, Bu Xu (curing deficiency) herbs and Huoxue Huayu (invigorate the circulation of blood) herbs, etc., as shown in Table 1 [7, 8]. The Qing re herbs have the functions of clear internal heat, discharging fire, and relieving internal heat or fever, which mainly includes Lianqiao (*Forsythiae Fructus*), Huangqin (*Scutellariae Radix*), Chishao (*Paeoniae Radix Rubra*), Huangbai (*Phellodendri Chinensis Cortex*), etc. The antiviral active ingredients are mainly alkaloids, glycosides, etc., and their antiviral mechanisms are mostly direct-action pathways that inhibit viral adsorption, replication, etc. The Jie biao herbs generally refer to the different degrees of sweating, antipyretic, antiviral, diuretic and other effects, viral diseases such as rubella, influenza and other initial onset, all external symptoms are urgent. Mahuang (*Ephedrae Herba*), Guizhi (*Cmnamomi Mmulus*), Xixin (*AsariRadix Et Rhizoma*), Jingjie (*Schizonepetae Herba*), etc are this kind of herbs. The antiviral active components are essential oil, glycosides, etc, and their antiviral mechanisms includes the direct effect of inhibiting virus penetration, adsorption, replication, and the indirect effect of regulating interferon and cytokine. Bu xu herbs are a kind of TCM which has the effect of supporting vital energy to dispel pathogenic factors. It can enhance the immune function of the body and produce the effect of supporting vital energy and dispelling pathogenic factors. It mainly includes Huangqi (*Astmgali Radix*), Renshen (*Ginseng Radix Et Rhizoma*), Gancao (*Radix Rhizoma Glycyrrhizae*), Baizhu (*Macrocephalae Rhizoma*), etc. The antiviral active components mainly include glycosides, polysaccharides, flavonoids, etc. and antiviral mechanism includes the direct effect of inhibiting virus replication, and the indirect effect of regulating the immune function of the body such as cytokines. Huoxue Huayu herbs can promote the recovery of pathological changes, improve metabolic function, reduce inflammation and adjust immunity. The application of Huoxue Huayu herbs is helpful to remove pathological products and ensure the normal operation of *Qi* and blood in the body. The TCM for Huoxue Huayu herbs mainly include Danshen (*Salviae Miltiorrhizae*), Niuxi (*Radix Achyranthis Bidentatae*), Daji (*Cirsii Japonici Herba Carbonisata*), Chuanxiong (*Ligusticum chuanxiong Hort*) and so on. Xie xia herbs is a kind of TCM with antibacterial, anti-inflammatory and enhancing the collective immune function, which often has both purgative and purgative functions. It mainly includes Dahuang (*Rhei Radix Et Rhizoma*), Luhui (*Aloe*), Shanglu (*Phytolaccae Radix*), Gansui (*Kansui Radix*), etc., and its antiviral mechanism is the directly inhibitory effect against virus' replication.

Antiviral mechanism of TCM

The mechanisms of TCM antiviral treatment can be divided into two ways: direct antiviral and indirect antiviral. Some herbs have direct inhibition or damage effects on virus; while, some herbs can strengthen immune function. TCM has many ways to resist virus, the key to controlling virus infection lies in giving play to the body's restrictive mechanism and inhibiting virus replication [9–13] (Table 2).

Direct antiviral pathway

The direct antiviral treatments play direct roles in all aspects of virus proliferation. The process of virus proliferation can be roughly divided into adsorption, penetration, uncoating, genome transcription, genome replication and gene expression, assembly, maturation and release (Figure 1). The direct antiviral effects around it can be divided into the following categories: (1) Inhibiting virus adsorption and invasion. The cell membrane is the first barrier for viruses to enter the cell. Adsorption and invasion are when the virus attaches to the surface of susceptible cells and then the viral nucleic acid or infectious nucleocapsid crosses the membrane and enters the cytoplasm, which is the initial stage of infection. Flavonoids, triterpenes, polysaccharides and their derivatives can inhibit the absorption of virus. (2) Inhibiting virus replication. Because nucleic acid is the genetic material of viruses,

Table 1 Classification of antiviral TCM

Classification	Name of traditional Chinese medicine
QingRe herbs (Clearing heat herbs)	Lianqiao (Forsythiae Fructus), Huangqin (*Scutellariae Radix*), Chishao (*Paeoniae Radix Rubra*), Huangbai (*Phellodendri Chinensis Cortex*), Zicao (*Arnebiae Radix*), Shegan (*Belamcandae Rhizoma*), Zhizi (*Fructus Gardeniae*), Qinghao (*Artemisiae Annuae Herba*), Zaoxiu (*Manyleaf Paris Rhizome*), Banzhilian (*Scutellariae Barbatae Herba*), Mabo (*Lasiosphaera*), Kugua (*Fructus Momordicae Charantiae*), Niuhuang (*Bovis Calculus*), Xishu (*Anemarrhenae Rhizoma*), Guanzhong (*Rhizoma Woodwardiae Seu Osmundae Seu Cyrtomii*), Kushen (*Sophorae Flavescentis Radix*), Digupi (*Lycii Cortex*), Mudanpi (*Moutan Cortex*), Jinyinhua (*Lonicerae Japonicae Flos*), Pugongying (*Taraxaci Herba*), Chuanxinlian (*Andrographis Herba*), Tianhuafen (*Radix Trichosanthis*), Daqingye (*Folium Isatidis*), Kuiding (*Corydalis Bungeanae Herba*), Machixian (*Portulacae Herba*), Shandougen (*Radix Sophorae Tonkinensis*), Banlangen (*Indigowoad Root*), Yejuhua (*Chrysanthemi Indici Flos*), Danzhuzye (*Lophatheri Herba*), Rendongteng (*Lonicerae Japonicae Caulis*), Yadanzi (*Bruceae Fructus*), Pugongying (*Taraxaci Herba*), Yexiazhu (*Herba Phyllanthi Urinariae*), Baijiangcao (*Herba Patriniae*), Yuxingcao (*Houttuynia cordata Thunb*), Xiakucao (*Prunellae Spica*), Baitouweng (*Pulsatillae Radix*), Zihuadiding (*Violae Herba*), Baihuasheshecao (*Hedyotis diffusa Willd*).
Jie Biao herbs (Relieving exterior syndrome herbs)	Mahuang (*Ephedrae Herba*), Guizhi (*Cmnamomi Mmulus*), Xixin (*AsariRadix Et Rhizoma*), Jingjie (*Schizonepetae Herba*), Xiangru (*Moslae Herba*), Chaihu (*Radix Bupleuri*), Muzei (*Equiseti Hiemalis Herba*), Juhua (*Chrysanthemi Flos*), Zisuye (*Perillae Folium*), Baishao (*Saposhnikoviae Radix*), Bohe (*Menthae Haplocalycis Herba*), Xinyi (*Magnoliae Flos*), Qianghuo (*Notopterygii Rhizoma Et Radix*), Qingdai (*Indigo Naturalis*), Huoxiang (*Herba Agastaches*), Shengma (*Cimicifugae Rhizoma*), Cangerzi (*Siberian Cocklour Fruit*), Niubangzi (*Great Burdock Achene*).
Bu Xu herbs (Curing deficiency herbs)	Huangqi (*Astmgali Radix*), Renshen (*Ginseng Radix Et Rhizoma*), Gancao (*Radix Rhizoma Glycyrrhizae*), Baizhu (*Macrocephalae Rhizoma*), Dangshen (*Codonopsis Radix*), Shihu (*Dendrobii Caulis*), Baishao (*Paeoniae Radix Alba*), Danggui (*Angelicae Sinensis Radix*), Duzhong (*Eucommiae Cortex*), Ningmeng (*Lemon*), Xuanshen (*Scrophulariae Radix*), Maidong (*Radix Ophiopogonis*), Tiandong (*Asparagi Radix*), Niuxi (*Radix Achyranthis Bidentatae*), Huangjing (*Polygonati Rhizoma*), Xianggu (*Shiitake Mushroom*), Sangjisheng (*Talxilli Herba*), Buguzhi (*Psoraleae Fructus*), Xiyangshen (*Panacis Quinquefolii Radix*), Ziheche (*Hominis Placenta*), Wuweizi (*Schisandrae Chinensis Fructus*), Baqitian (*Morindae Officinalis Radix*), Yinyanghuo (*Epimedii Folium*), Dongchongxiacao (*Cordyceps*).
Lishui Shenshi herbs (Diuresis-removing dampness herbs)	Haiyun (*Natural Sea Beauty*), Haizao (*Sargassum*), Shiwei (*Pyrrosiae Folium*), Zhuling (*Polyporus*), Mutong (*Akebiae Caulis*), Qinjiao (*Gentianae Macrophyllae Radix*), Sangzhi (*Mori Ramulus*), Peilan (*Eupatorii Herba*), Cangzhu (*Atractlodis Rhizoma*), Aiye (*Artemisiae Argyi Folium*), Caoguo (*Fructus Tsaoko*), Xiqiancao (*Siegesbeckiae Herba*), Qiannianjian (*Homalomenae Rhizoma*), Yazhicao (*Commelinae Herba*), Baimaogen (*Imperatae Rhizoma*), Jixuecao (*Centellae Herba*), Leigongteng (*Radix Et Rhizoma Tripterygii Wilfordii*).

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Table 1 Classification of antiviral TCM (*continued*)

Huoxue Huayu herbs (Invigorate the circulation of blood herbs)	Danshen (*Salviae Miltiorrhizae*), Niuxi (*Radix Achyranthis Bidentatae*), Daji (*Cirsii Japonici Herba Carbonisata*), Chuanxiong (*Ligusticum chuanxiong Hort*), Jianghuang (*Curcumae Longae Rhizoma*), Ezhu (*Curcumae Rhizoma*), Huzhang (*Giant Knotweed Rhizome*), Banmao (*Mylabris*), Hongyaozi (*Girald Pteroxygonum Root*), Zijinpi (*Kadsura Root-bark*), Heidadou (*Semen Sojae Atricolor*), Jixueteng (*Spatholobi Caulis*), Tubiechong (*Eupolyphaga*).
Huatan Zhike herbs (Relieve phlegm and cough herbs)	Xingren (*Apricot Kernel*), Jiegeng (*Platycodonis Radix*), Baibu (Stemonae Radix), Sangbaipi (*Mori Cortex*), Cebaiye (*Platycladi Cacumen*), Madouling (*Aristolochiae Fructus*), Tubeimu (*Bolbostemmatis Rhizoma*), Xuanfuhua (*Inulae Flos*), Pipaye (*Eriobotryae Folium*).
Xie Xia herbs (Purgative herbs)	Dahuang (*Rhei Radix Et Rhizoma*), Luhui (*Aloe*), Shanglu (*Phytolaccae Radix*), Gansui (*Kansui Radix*), Yuanhua (*Genkwa Flos*), Jiachacai (*Chondrus ocellatus*), Bimazi (*Ricini Semen*).
Pinggan Xifeng herbs (Calming liver-wind herbs)	Wugong (*Scolopendra*), Jiegumu (*Sambucus williamsii*), Jiangcan (*Bombyx Batryticatus*), Ebushicao (*Small Centipeda Herb*), Wushaoshe (Zaocys).
Li Qi herbs (Qi regulating herbs)	Meiguihua (*Rosae Rugosae Flos*), Zhishi (*Aurantii Fructus Immaturus*), Ezhu (*Curcumae Rhizoma*), Chenpi (*Citrus Reticulata Blanco*), Houpo (*Magnoliae Officmalis Cortex*), Jianghuang (*Curcumae Longae Rhizoma*).
Wen Li herbs (Warming the internal herbs)	Dasuan (*Garlic*), Rougui (*Cinnamomi Cortex*), Gaoliangjiang (*Alpiniae Officmarum Rhizoma*), Lizhihe (*Litchi Semen*).
Shou se herbs (astringent agent herbs)	Hongqi (*Hedysari Radix*), Jingyingzi (*Fructus Rosae Laevigatae*), Wubeizi (*Galla Chinensis*).
Qu Chong herbs (Anthelmintic herbs)	Changshan (*Dichroae Radix*), Binlang (*Arecae Semen*).

viruses can be divided into DNA viruses and RNA viruses according to different genetic materials. Preventing viral nucleic acid replication is an effective target of antiviral drugs. (3) Inhibiting virus assembly and release. The assembly and release of the virus is the last step of virus replication. Mature virus particles are released from host cells by exocytosis and budding, and there are few reports of TCM acting at this stage.

Indirect antiviral pathway

This approach mainly refers to indirectly play the role of anti-virus by enhancing the immunity and stimulating the immune defense system. The direct antiviral effects around it can be divided into the following categories: (1) Promoting the development of immune organs. Immune organ is the organization that produces immune response and performs immune function. The quality of immune organ is closely related to immune function. (2) Enhancing the role of immune cells. TCM immune enhancer can act on thymic lymphatic system, induce T cell differentiation and proliferation, form effector cells, and produce lymphoid factors. (3) Enhancing humoral immunity. The main factor of antiviral humoral immunity is antibody. The secreted IgA can prevent the local invasion of the virus, and IgG and IgM can interrupt the already invaded virus to spread through blood circulation. (4) Enhancing the phagocytosis of macrophages and the killing effect of NK cells. (5) Induced interferon. Interferon is an inducible protein controlled by the cell genome. It has a variety of biological activities such as anti-virus reproduction and

tumor growth. It is a kind of defensive substance produced by oneself inside organism to resist foreign virus invasion and maintain organism or cell function self-stable. (6) Comprehensive regulation of various cytokines. Natural killer cells (NK), interferon-1 (IFN-1) and interleukin-2 (IL-2) interact in the body to form an immune network and enhance antiviral and immunomodulatory effects.

Table 2 Mechanism of antiviral action by multiple pathways of TCM

Mechanism of action	Name of traditional Chinese medicine
Inhibiting virus adsorption and inhalation	Huangqi (*Astmgali Radix*), Huangqin (*Scutellariae Radix*), Danghen (*Codonopsis Radix*), Fuling (*Poria*), Baizhu (*Macrocephalae Rhizoma*), Chazao (*Thea Saponin*), Yuganzi (*Phmllanthi Fructus*), Heshouwu (*Polygoni Multiflori Radix*), Banlangen (*Indigowoad Root*), Yejuhua (*Chrysanthemi Indici Flos*), Dureping Injection, Qilan Anti-toxic Drink, Compound Shenzhu Soup, Compound Lianweng Soup, Compound ShenFu Soup.
Inhibiting virus replication	Huanglian (*Coptidis Rhizoma*), Huangqin (*Scutellariae Radix*), Dihuang (*Rehmanniae Radix*), Pugongying (*Taraxaci Herba*), Xixin (*AsariRadix Et Rhizoma*), Huangqi (*Astmgali Radix*), Lianqiao (*Forsythiae Fructus*), Juhua (*Chrysanthemi Flos*), Yandaji (*Euphorbiae Pekinensis Radix*), Baililu (*Radix Et Rhizoma Veratri Nigri*), Jinyinhua (*Lonicerae Japonicae Flos*), Shanyinhua (*Lonicerae Flos*), Banlangen (*Indigowoad Root*), Yinqiao Powder, Yupingfeng Powder.
Inhibiting virus assembly and release	Yangdihuang (*Digitalis*), Yuganzi (*Phmllanthi Fructus*), Choulingdan (*Laggera pterodonta*).
Immunological regulation	Daqingye (*Folium Isatidis*), Chuanxinlian (*Andrographis Herba*), Yuxingcao (*Houttuynia cordata Thunb*), Baililu (*Radix Et Rhizoma Veratri Nigri*), Compound Recipe Andrographitis, Haoqin Qingdan Decoction, Wujia Jianzhengqi Powder, Kudingcha (*Folium Ilecis Latifoliae*), Zhongsheng Pill, Jinyin Qingre Oral Liquid, Fuzheng Qudu Recipe, Shugan Jianpi Bushen Recipe, Compound Longqincao, Maxingshigan Decoction, Longdan Xiegan Formula Granule, Hericium Erinaceus, Dureping Injection, Gegen Decoction, Niubangziyuan Compound, Jiawei Xuanfei Transdermal Agent, Phyllanthus Compound.
Targeting host cells	Lianqiao (*Forsythiae Fructus*), Chaihu (*Radix Bupleuri*), Guizhi (*Cmnamomi Mmulus*), Hezi (*Terminalia Chebula Retz*), Huangqi (*Astmgali Radix*), Chonglou (*Paridis Rhizoma*), Jiegeng (*Platycodonis Radix*), Baishao (*Paeoniae Radix Alba*), Xuanshen (*Scrophulariae Radix*), Gancao (*Radix Rhizoma Glycyrrhizae*), Chazao (*Thea Saponin*), Jinyinhua (*Lonicerae Japonicae Flos*), Banlangen (*Indigowoad Root*), Yinyanghuo (*Epimedii Folium*), Compound Shenzhu Soup, Compound Lianweng Soup, Compound ShenFu Soup, Qishao Wuweizi Compound Preparation, Yangxin Huoxue Jiedu Decoction.
Inhibiting oxidative stress	Yinyanghuo (*Epimedii Folium*), Sanqi (*Notoginseng Radix Et Rhizoma*), Juhua (*Chrysanthemi Flos*), Banlangen (*Indigowoad Root*), Huangqi (*Astmgali Radix*).
Anti-inflammatory effect	Huangqi (*Astmgali Radix*), Jingjie (*Schizonepetae Herba*), Guizhi (*Cmnamomi Mmulus*), Xijiao Dihuang Decoction, Yinqiao Powder, Jinyin Qingre Oral Liquid, Qingre Toubiao Recipe, Tianlong Kechuanling, Dureping Injection.

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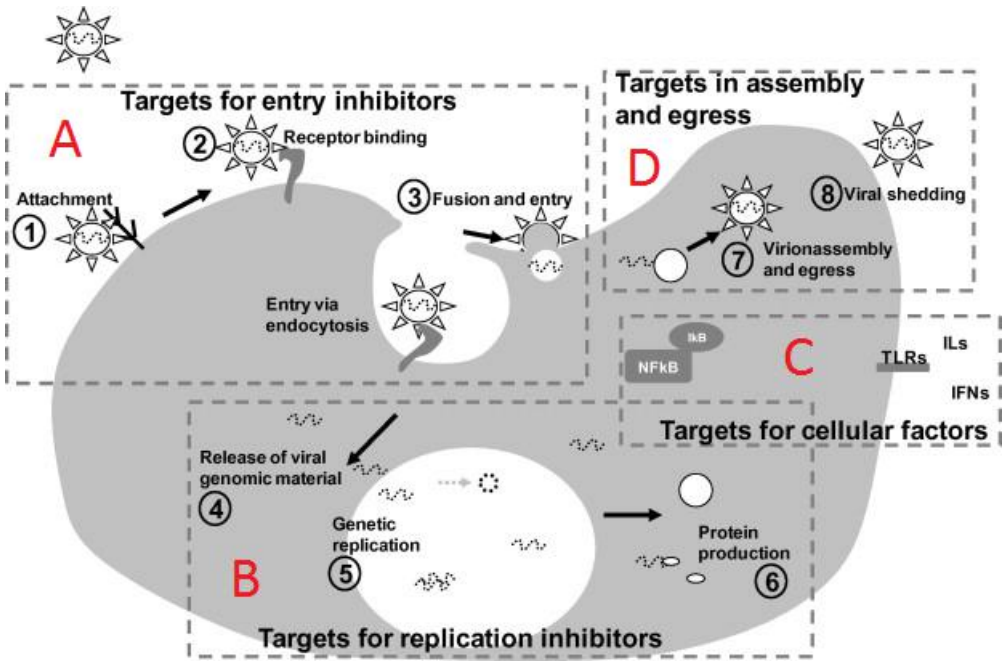

Figure 1 Major steps in the generalized viral life cycle. A: Targets for entry inhibitors (*Astmgali Radix, Scutellariae Radix, Codonopsis Radix*), **B:** Targets for replication inhibitors(*Coptidis Rhizoma, Scutellariae Radix, Rehmanniae Radix*), **C:** Targets for cellular factors(*Forsythiae Fructus, Radix Bupleuri, Cmnamomi Mmulus*), **D:** Targets in assembly and egress(*Digitalis, Phmllanthi Fructus, Laggera pterodonta*).

Problems in antiviral research of TCM

At present, some achievements have been made in antiviral research of TCM, but there are still some problems as follows. (1) Antiviral researches of TCM mainly focus on single herb, antiviral spectrum and mechanism of action of TCM. Most of them are laboratory researches, and lack of syndrome basis and standardized animal model of disease and syndrome combination, which makes antiviral researches of TCM divorced from clinical practice of TCM. (2) The lack of guidance from the corresponding TCM prescription theory in the treatment of diseases caused by viral diseases restricts the rapid development of antiviral research in TCM. (3) The lack of in-depth anti-virus research on integrated Chinese and Western medicine makes it difficult to achieve new breakthroughs and restrict its development. (4) The research technology and methods are not advanced enough, and there is a lack of systematic screening system for antiviral TCM.

Research prospects

In view of the current anti-virus research of TCM, the following aspects should be implemented. (1) It is necessary to adhere to the theory of TCM, but also to integrate the latest researches of modern biological science. (2) Establishing the diagnosis and treatment system of “combination of syndrome and disease”, give full play to the advantages and characteristics of TCM. (3) Through artificial intelligence-assisted design, the selection system of TCM for antiviral should be established, and the classical prescriptions with potential antiviral effects should be vigorously explored. (4) The research on antiviral of TCM must reasonably introduce modern bioscience, promote the modernization of TCM by using the latest technologies, such as genomics, proteomics, metabolomics, immunology and other technologies.

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