



## Review

## Carry forward advantages of traditional medicines in prevention and control of outbreak of COVID-19 pandemic

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## ABSTRACT

Members of the China-ASEAN Joint Laboratory for International Cooperation in Traditional Medicine Research used the video conference platform to exchange and discuss the advantages of traditional medicine through the form of score exchange and report, and research and develop the amount and issues of the therapeutic COVID-19 products of concern. This paper mainly reviews the achievements of the implementation of the epidemic prevention and control plan, advances of scientific basic studies on SARS-CoV-2, analysis and screening of potential targets and pathways of antiviral compounds based on network pharmacology and development of antiviral food dual-use products. The authors believe that the declaration of the (10 + 3) special meeting of national leaders on epidemic prevention and control should raise the medical and pharmaceutical issues of common concern. It is the responsibility of our joint laboratory members to accelerate the development of traditional medicine research and industry. Also the authors believe that this exchange will certainly promote the development of the cause of cooperation.

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## 1. Introduction

The world is facing unprecedented health threats, social and economic shocks from COVID-19. World Health Organization (WHO) is to address the global impact of the COVID-19 pandemic. WHO reported that the world has now been more than 3.5 million cases of COVID-19 (WHO, 2020). Around the world, the pandemic has caused severe disruption to essential health services, including to community-based health care, and in many countries trained members of the community play a vital role in delivering essential health services like vaccination, drug screening, clinical detection, prevention and management of the diseases. We must address this now and in the long-term by prioritizing diagnosis and care for those who are most at risk. The WHO will help communities most at risk by scaling up local medical and public health efforts and better protect people around the world from future pandemics. At this grim time, the timely convening of the Asia-Pacific (10 + 3) special video-meeting demonstrates the responsibility of countries in the Asia-Pacific region. The statement and declaration of the special session pointed the way to how our co-laboratory could exploit the advantages of traditional medicines.

The Joint Statement of the Special ASEAN Plus Three (APT) Summit on Coronavirus Disease 2019 (COVID-19) (10 + 3 Summit) was held on 14 April 2020 (China Daily, 2020). At the Special ASEAN Summit of ASEAN's highest-level commitment for collective response to the outbreak of COVID-19. The summit published the ASEAN Chairman's Statement and the Declaration.

The commitment to strengthen solidarity, enhance cooperation and mutual support among the APT countries to control and contain the spread of the pandemic, addressing the adverse impact of the pandemic on our societies and economies. The ASEAN countries hereby resolve to 18 terms. The Strengthen 5 points out that "scientific cooperation in epidemiological research, including through the APT Field Epidemiology Training Network, coordination, including with the private sector, towards rapid, research, development, manufacturing and distribution of diagnostics anti-viral medicines and vaccines, adhering to the objectives of efficiency, safety, equity accessibility and affordability", and the Strengthen 15 points out that "efforts to stabilize the manufacturing and supply of essential goods and services, including vital medical supplies, critical agricultural products, maintain necessary flow of goods and services and sustain supply . . . . . in order to support economic development, reaffirming our commitment described in the Joint Leader's Statement on the Regional Comprehensive Economic Partnership released in 2019" (China Daily, 2020).

We learned from the conference documents that the two articles had great responsibilities for experts in joint laboratories engaged in the research, development and application of traditional medicines. We are also holding a joint laboratory work meeting on this important day (5th May) to share research advances and innovations in the fight against the epidemic using traditional drug services in the Asia-Pacific region. During the epidemic, we also carried out some theoretical and applied studies and published several papers (Han et al., 2020; Liu, 2020a, 2020b; Liu, Wang, Zang, Tian, et al., 2020; Liu, Wang, & Yan, 2020; Liu, Wang, Zang, & Wu, 2020; Liu, Yi, Wang, & Yan, 2020; Qin et al., 2020). This article will focus on the expert discussion and reports contents.

## 2. Basic studies on SARS-CoV-2

Nankai University was involved in the development of diagnostic reagents and techniques to combat with COVID-19, and developed COVID-19 IgM/IgG antibody detection kit. By integrating AI technology and CT images, the new diagnostic technique was successfully used in clinical detection of COVID-19.

In order to rapidly discover lead compounds for clinical use, researchers identified a mechanism-based inhibitor, N3, by computer-aided drug design and subsequently determined the crystal structure of COVID-19 virus Mpro (3CLpro) in complex with this compound. An initiated program of combined structure-assisted is used for drug design, virtual drug screening and high-throughput screening to identify new drug leads that target the COVID-19 virus main protease was designed (Jin, Du, & Xu, 2020).

The RNA-dependent RNA polymerase (RdRp, also named nsp12) is the central component of coronaviral replication/transcription machinery and appears. Researchers also report the cryo-EM structure of COVID-19 virus full-length nsp12 in complex with cofactors nsp7 and nsp8 at 2.9-Å resolution. A comparative analysis model shows how Remdesivir binds to this polymerase. The structure provides a basis for the design of new antiviral therapeutics targeting viral RdRp (Gao, Yan, & Huang, 2020).

By actively carrying out joint research, the structure of COVID-19 key proteases, 3CLpro and RdRp have been published in *Science* and *Nature*. A series of lead compounds were screened for COVID-19 related targets from natural product compound library.

Mangiferin is well-known xanthone in mango fruits, barks, peel, leaves and stone. The compound has potential pharmacological effects, such as antioxidant, antiaging, antiviral, hepatoprotective, analgesic and immunomodulatory activities (Imran, Arshad, & Butt, 2017). Mangiferin is a natural miracle bioactive compound against lifestyle related disorders. Baicalin is derived compound from the plant *Scutellaria baicalensis* Georgi. It is famous in many countries, including the Russian Federation, European countries and several East Asian countries, for its potential pharmacological properties including anti-inflammation effect, apoptosis modulation, autophagy induction, cell cycle arrest, metastasis suppression and oxidative stress inhibition and so on (Li, Qiao, & Hu, 2019). From the pharmacological actions of them, we suggested that the two compounds maybe have relation with antiviral of SARS-CoV-2.

Prof. Bai's team at Nankai University in China used the PyMOL software to display the 3D map of the interaction of mangiferin with Mpro (PDB: 6LU7). The interactions between the mangiferin and the protein include hydrogen bond interactions with LEU141, SER-144, GLN-192 and THR-190 (Fig. 1). The software was also used to display the 3D map of the interaction of baicalin (Fig. 2) with 3CLpro (PDB:6LU7), RdRp (PDB:6NUR), and angiotensin-converting enzyme 2 (ACE2) (PDB:1R4L).

Guangxi University of Chinese Medicine (GXUCM) has been committed to the ethnic medicine research for many years, discovering new therapeutic application through its plant resources, chemical and pharmacological research (Qin et al., 2020). According to the traditional usage and clinical practice of Yao medicine, the research team of GXUCM took Yao medicine (Xidong in Chinese) as the candidate drug, and collected and sorted out the

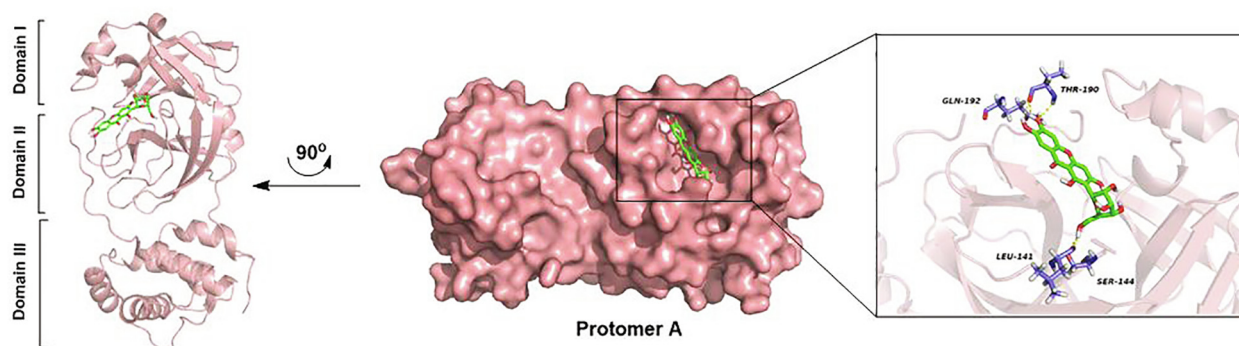


Fig. 1. Molecular docking of mangiferin with Mpro from COVID-19 virus.

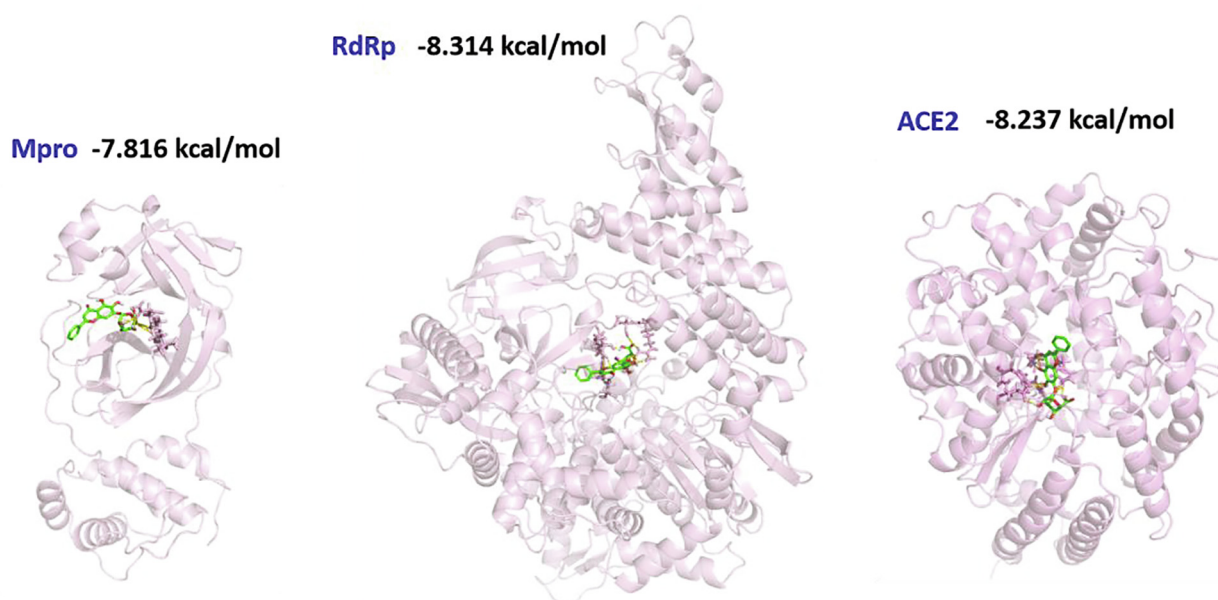


Fig. 2. Incorporation model of baicalin in COVID-19 virus Mpro, RdRp and ACE2 receptor.

chemical components of the Yao medicine through literature mining and TCMSP, ETCM, TCMID and NPASS databases. The collected ingredients were molecular-bonded with SARS-cov-2 3CL hydro-lase (Mpro) and angiotensin-converting enzyme 2 (ACE2), respectively. In order to optimize the active ingredients and predict the key Yao drugs, the network graph of TCM-component-target was constructed by collecting the components with the top 50 points. A total of 902 chemical components were obtained through literature mining and TCM database collection, of which 875 components that could be combined with Mpro. Also 902 components that could be combined with ACE2 were obtained through molecular docking. Among them, quercetin 3-O-koo-L-arabinofuranoside, kaempferol 3-O-koo-D-arabinopyranoside, tannins, coccinic acid, chlorogenic acid, rutin, cyanidanol and other medicinal herbs such as double hook drill (Shuanggouzuan in Chinese), betel nut drill (Binlangzuan in Chinese), big drill (Dazuan in Chinese), ground drill (Dizuan in Chinese), white drill (Baizuan in Chinese), small red drill (Xiaohongzuan in Chinese), small drill, Kowloon drill (Jiulongzuan in Chinese) and square drill (Sifangzuan in Chinese) (*Uncaria rhy-nchophylla* (Miq.) Miq. ex Havil, *Sargentodoxa cuneata* (Oliv.) Rehd. et Wils, *Kadsura coccinea* (Lem.) A.C. Smith, *Flemingia philippinensis* Merr. et Rolfe or *Flemingia macrophylla* (Willd.) Prain, *Schisandra viridis* A.C. Smith, *Kadsura oblongifolia* Merr, *Bauhinia championii*

(Benth.) Benth, *Cissus pteroclada* (Hayata) have potential inhibitory effects on SARS-CoV-2.

### 3. Achievements of implementation of epidemic prevention and control plan

#### 3.1. Anti-epidemic project of CAE2, development of anti-epidemic product “Lanzhi Bacteriostatic liquid”

Chinese Academy of Engineering (CAE) to protest the development of a major project “Lanzhi Bacteriostatic Solution” (Research and development of new Chinese medicine sprayers based on COVID-19 TCM prevention and control strategies) has been approved by Academician Chang-xiao Liu and the Chinese medicine team of Tianjin Institute of Pharmaceutical Research (TJIPR). Based on the epidemic characteristics and prevention and control countermeasures and traditional Chinese medicine for external use in fire prevention theory and experience, design suppresses environmental pathogenic microorganisms and human conditioning *qi* activity for the principle formula, in raw materials, logistics, testing, processing is very difficult to special circumstances, complete Chinese medicine epidemic prevention and control product



“Lanzhi Antibacterial Liquid (spray type)”, complete the production of 20,000 bottles of products, and giving the epidemic area.

### 3.2. Achievements of regional epidemic prevention and control plans

After the outbreak of COVID-19, the research team of GXUCM responded actively, and the application for two special science and technology projects to prevent and control pneumonia caused by SARS-CoV-2 in Guangxi in 2020 was approved, including *Sino-Singapore cooperation for evaluating the effectiveness and application of Guangxi Zhuang/Yao medicines against COVID-19* and *Anti-COVID-19 drug study based on natural Chinese and Thai medicinal materials* undertook sub-topics.

#### 3.2.1. Qingyi fragrant flower tea bag

Qingyi fragrant flower tea bag was produced with modern preparation technology. South and Yao medicines such as *Patchouli Oil*, *Lonicerae Flos*, *Coicis Semen* (*Pogostemon cablin* (Blanco) Benth, *Lonicera japonica* Thunb., *Coix lacryma-jobi* L.) etc. were selected to form the prescription based on the fully analysis of dampness pathogenic characteristics. Following the TCM theory of preventive treatment of disease and TCM theory of constitution, the prescription referenced the *Diagnosis and Treatment Protocol for COVID-19* issued by the national ministries and combined with the Guangxi Zhuang and Yao living epidemic characteristics. This product has the function of aromatizing dampness, invigorating spleen and removing stagnation, and can be used as preventive tea for people with phlegm dampness and damp and hot constitution, people who have contact with infectious source but have no symptoms, people who are susceptible to body weakness and so on. The project team cooperated with enterprises to mass produce the product and send it to Nanning, Qinzhou, Beihai, Beijing, Fangchenggang, Wuhan and other places for drinking to prevent COVID-19.

#### 3.2.2. Qingyi three ginseng recovery tea

Promulgated by the project team according to the *National Health Commission's COVID-19 Therapy* and 7th trial version in the recovery of the recommended prescription, comprehensive recovery of common symptoms, with safe, effective and universality for the principle, with flat regulating *yin* and *yang*, gentle figure, nourished with hydrophobic lag for drug characteristics, using medicine edible Chinese medicines such as American ginseng, *Codonopsis Radix*, *Adenophorae Radix* (*Panax quinquefolium* L., *Codonopsis pilosula* (Franch.) Nannf, *Adenophora tetraphylla* (Thunb.) Fisch.) formula, carefully makes a drug phase to phase, supplement each other.

This formula can be used to treat the deficiency of spleen and lung, deficiency of *qi* and *yin*, shortness of breath, tiredness, tolerance and vomiting, or low heat, dry cough with less phlegm, dry mouth, thirst, palpitations, excessive sweat, insufficient sleep, weak stool and irritated stools during the recovery period after discharge. Tongue light fat or dry tongue less fluid, moss white greasy or less moss, veins fine or weak and so on. It can also be used as a source of *qi-yin* deficiency or *yin* deficiency holding wet constitution people daily conditioning drinking.

#### 3.2.3. Traditional Chinese and ethnic medicine preparations

The early symptoms SARS-CoV-2 infection was fever, dry cough, sore throat, fatigue, etc. At the beginning, patients were mainly with the plague rage infringement throat, causing acute inflammation. At present, the oral preparations are the preferential therapy. The Guangxi project team developed a contain gargle solution “antipyretic wet nurse liquid”, for the epidemic prevention and control. Using six kinds of traditional Chinese and ethnic medicines including *Arctylodis Rhizoma* (*Artemisia annua* L. and

*Arctylodes lancea* (Thunb.) DC.) etc., in Chinese medicine and national medicine formula.

The preparation is given locally in the mouth, which can increase the contact surface between the drug and the lesion, enhance the efficacy of clearing heat, changing humidity, and improving pharyngeal protection. Currently, the product prescription and process research have been completed, and the simple archival materials of traditional Chinese medicine and ethnic medicine preparations have been submitted to the food and drug administration of Guangxi Zhuang Autonomous Region, China.

## 4. Analysis and screening of potential targets and pathways of antiviral compounds based on network pharmacology

### 4.1. Research platform construction

The National University of Singapore has established the state of the art BSL3-Core facility in the Yong Loo Lin School of Medicine as a screening technology platform for drug discovery research against SARS-CoV-2. The BSL-3 Core Facility, led by Associate Professor Justin Chu, has successfully isolated and cultured the SARS-CoV2 from COVID-19 patients from the hospitals. In view of the coronavirus replication cycle, 54 chemical components in the library of GXUCM and 461 chemical components in the library of ACE2 receptor inhibitors are being screened for anti-SARS-CoV-2 virus activity.

After screening the active compounds, a human ACE2 transgenic mouse model will be established to study the anti-SARS-CoV-2 virus activity *in vivo*. With this platform, target prediction was carried out to achieve high-throughput screening (Fig. 3) and screening scheme design (Fig. 4) to obtain valuable information.

### 4.2. Target – pathway – activity screening

The project team searched the domestic and foreign literatures, screened the reported compounds with anti-coronavirus, influenza

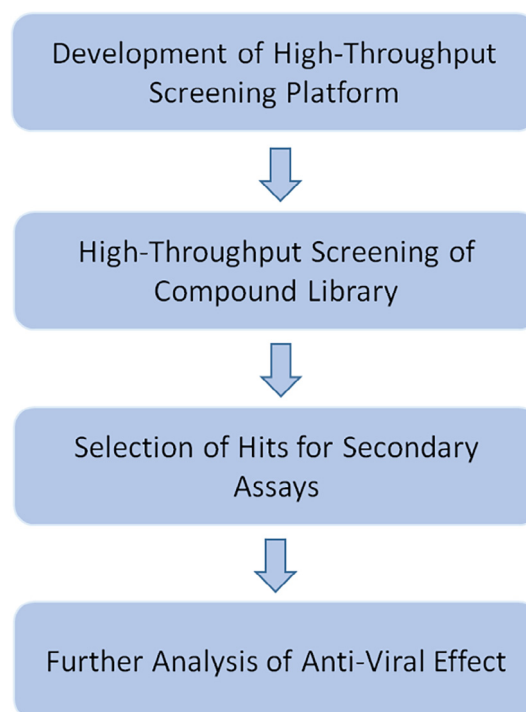


Fig. 3. High-throughput screening for antiviral activity.

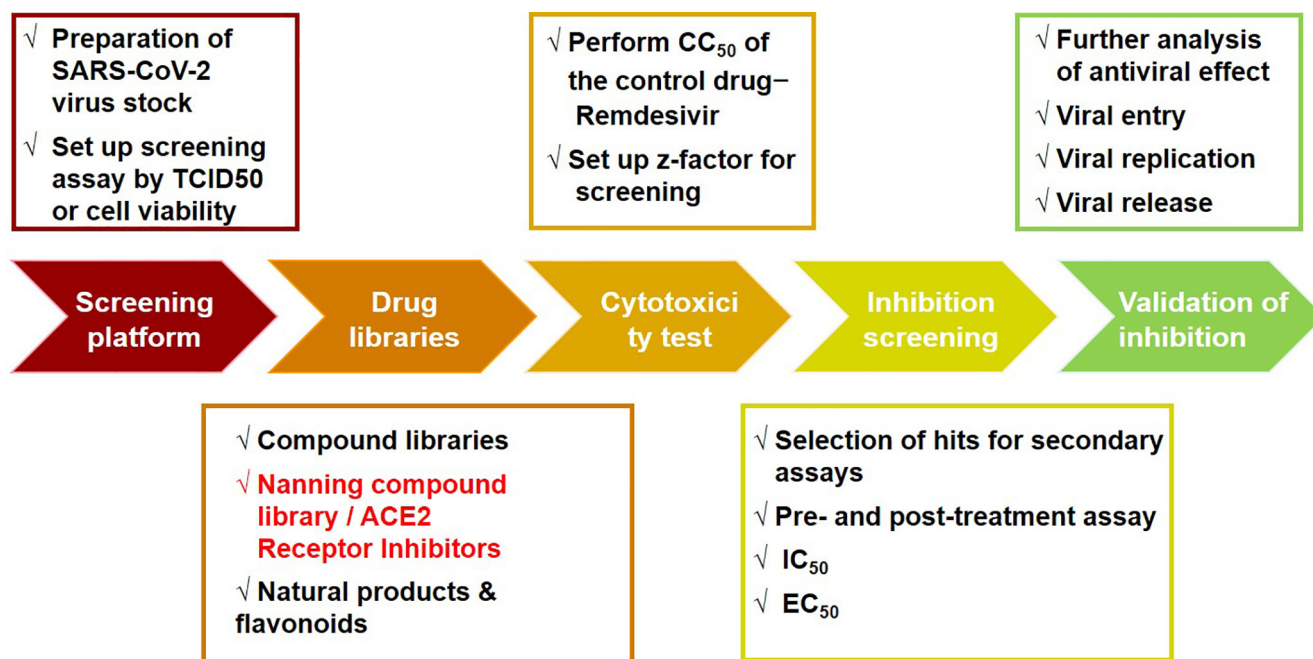


Fig. 4. Screening scheme design.

virus and HIV, and prepared 54 active chemical components through purchase and isolation. The team studied the chemical composition analysis of potential targets and pathways of 54 potential antiviral preparations, and screened and found the total of 87 potential targets in the database. They also obtained information on the protein and the protein interaction network, download protein–protein interaction information using Cytoscape software, according to the network topology parameters selected is greater than 2 times the average degree of targets, the targets play a pivotal role in the network, key targets for received 49.

The network topological parameters of compounds and targets were visualized by Cytoscape software. The results showed that the top five compounds were resveratrol, genistein, estradiol, berberine and baicalein. The top five targets were TP53, AKT1, BCL2, NOS3 and CDKN1A. They also detected the neutralization activity of the pseudovirus, and initially found four compounds with potential antiviral activity, and one compound extract of traditional Chinese medicine. Currently, a cell based assay is being used for activity validation in the NUS Medicine Biosafety Level 3 Research Facility, a research unit in the National University of Singapore.

#### 4.3. Data mining was carried out for the prevention and treatment of COVID-19 by traditional Chinese medicine

During January 20, 2020 to March 23, 2020, the project team has collected 25 guiding documents, such as the latest version of diagnosis and treatment plans, prevention and treatment plan, and technical guidelines, which have been published by the National Health Commission and the health commissions of 24 provinces, autonomous regions and municipalities directly under the central government. Collection of treatment prescription information in each program, the establishment of a database, including prescription name, drug name, efficacy classification, sexual taste, efficacy indications, treatment, disease stage and other information. Using EXCEL, Graphpad 8.0, SPSS Modeler18.0 and other software, the paper made a statistical analysis on the usage frequency,

classification frequency, properties and compatibility characteristics of all kinds of traditional Chinese medicines.

A total of 137 prescriptions of traditional Chinese medicine for treating COVID-19 were collected, and 178 herbs were included. Chinese medicine with the functions of clearing heat, tonifying deficiency, resolving phlegm, relieving cough and asthma, relieving exterior syndrome, resolving dampness, clearing damp and promoting diuresis were the mainly used Chinese medicine, in which types of resolving phlegm, relieving cough and asthma, resolving dampness, clearing damp and promoting diuresis accounted for 35.78%. There were also a considerable number of medicines with the function of removing dampness in the types of clearing heat, tonifying deficiency and relieving exterior syndrome. It can be seen that the medicines with the function of removing dampness was the first choice in the treatment of COVID-19 with Chinese medicine. The Chinese medicine with the function of aromatic resolving dampness, clearing heat and drying dampness, drying dampness and tonifying spleen *qi*, drying dampness and removing phlegm, promoting diuresis and relieving swelling, promoting diuresis and relieving exterior syndrome were mainly used Chinese medicine for removing dampness. Among them, the most frequently used medicine was *Ephedrae Herba*, which frequency up to 52, and the frequencies of *Citri Reticulatae Pericarpium*, *Pogostemonis Herba*, *Pinelliae Rhizoma*, *Poria*, *Scutellariae Radix* and *Atractylodis Rhizoma* were up to 40. The results of this study have referenced and guided significance for the treatment of COVID-19 with Chinese medicine.

#### 4.4. Study on the mechanism of treating COVID-19 with Tanreqing capsule based on network pharmacology

The results showed that the 19 compounds could intervene 68 key signaling pathways by acting on 163 related targets, such as IL-17 signaling pathway, T-cell receptor signaling pathway, arachidonic acid metabolism, cAMP signaling pathway, and pi3k-akt signaling pathway. It mainly involves anti-inflammatory, immune regulation, antipyretic, phlegm elimination, anti-tussive, anti-asthmatic, analgesic, antibacterial, antiviral, sedation, etc. The

network of compound-target-pathway-pharmacological action-efficacy of Tanreqing Capsules was constructed. Phlegm heat (Tanreqing) capsule in the main chemicals in baicalin, laminated paper element-7-O-glucuronic acid glycosides, chrysin-7-O-glucuronic acid glycosides, forsythia glycosides, forsythia ester glucoside E, chlorogenic acid, caffeic acid, chlorogenic acid A, glycine, alanine, arginine, lysine, tyrosine, bear to oxygen cholic acid, such as chenodeoxycholic acid may through the role to TNF, EGFR, NOS3, PTGS2, IL2, GABBR1, MAPK14, ADRB2, REN, VCAM1, ACHE, PTPRC and other key proteins interfere with a number of biological processes related to heat clearing, phlegm elimination and detoxification, thus exerting the therapeutic effect on COVID-19.

## 5. Development of antiviral food dual-use products

### 5.1. Development of special medical food “Yiyiyuan”

Tianjin Institute of Pharmaceutical Research carried out the development of special medical food. According to the needs of covid-19 nutrition support, the institute seizes the time to develop new special medical food “Yiyiyuan” during the epidemic and has completed the production of 20,000 boxes of finished products that was donated to Hubei epidemic areas, China.

### 5.2. Development of immunomodulatory products

Dr. Panee Sirisa-ard, associate professor, University of Chiang-mai, Thailand, studied a kind of medicinal mushroom that can improve the immunity of patients. It has the application of resistance to H1N1 virus. At present, the mechanism of action of this mushroom has been studied. It is looking forward to funding the research.

Research and development of anti-epidemic products of Malaysia Keding Company: Malaysia Keding International Co., Ltd. Aponte, which is mainly made of *Ganoderma lucidum* in tiger milk, has a good effect on pulmonary infection.

### 5.3. A variety of plants were found to have potential activity with against novel coronavirus pneumonia

From the pathogenesis of novel coronavirus pneumonia, Dr. Wattanathorn Jintanaporn, associate professor at King Kong University of Thailand, focused on the plant varieties with potential resistance to novel coronavirus pneumonia. Metalloproteinase inhibitors in *Clitiera ternatia* were found. Eggplant skin (*Solanum melongena* L.) extract has antiviral, antioxidant and anti-inflammatory effects. White mulberry bark (*Morus alba* Linn) has a therapeutic effect on pulmonary fever, cough and edema, and can inhibit a variety of respiratory viruses, anti-inflammatory

and antioxidant effects, which are considered as mmp-2 and mmp-9 protease inhibitors.

Ginger, garlic and onion (Fig. 5) (*Zingiber officinale* Rosc, *Allium sativum* L. and *Allium cepa* L.) are almost cheap kitchen “medicine” one of the world’s most countries, especially Southeast Asian countries like to eat. They contain antibacterial and antiviral compounds, anti-inflammatory, antioxidant, anti-tumor effects, but also conducive to the human body to improve immunity, to fight against “pathogen invasion”.

Garlic and onions contain 70 phytochemicals that reduce the risk of hypertension. Ginger has a warm and spicy taste, which can enhance blood circulation, stimulate gastric juice secretion, stimulate the intestines and promote digestion. It can play sweating, cooling, and relieve fatigue, fatigue, anorexia, insomnia, abdominal distension, abdominal pain, and so on. The antioxidant, anti-inflammatory and immune-modulation effects are beneficial in improving initial symptoms for COVID-19 patients.

## 6. Discussion and summary

The prevention and control of the COVID-19 epidemic is a top priority for the world. WHO recognizes that traditional, complementary and alternative medicine has many benefits in public health care. We know that the traditional herbal products are very value for treatment and prevention of COVID-19, but note that it needs to research and select traditional medicine products in clinical efficacy and safety for COVID-19 treatment.

WHO welcomes every opportunity to collaborate with countries and researchers to develop new therapies and encourages such collaboration for the development of effective and safe therapies. It concerns not only the safety of the people, but also the stability and development of the world. The members of the China-ASEAN joint laboratory of traditional medicine use the video conference platform to exchange and discuss the advantages of traditional medicine through the form of score exchange and report, and research and develop COVID-19 product amount and issues of concern to research and development.

In summary, this paper mainly contents achievements of the implementation of the epidemic prevention and control plan, advance of scientific basic studies on SARS-CoV-2, analysis and screening of potential targets and pathways of antiviral compounds based on network pharmacology and development of antiviral food dual-use products. The authors believe that the declaration of the (10 + 3) special meeting of national leaders on epidemic prevention and control should raise the issue of medical and pharmaceutical issues of common concern. It is the responsibility of our joint laboratory members to accelerate the development of traditional medicine research and industry. Therefore, we believe that this exchange will certainly promote the development of the cause of cooperation in traditional medicines.

### Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Fig. 5. Onion (*Allium cepa* L.), Ginger (*Zingiber officinale* Rosc) and garlic (*Allium sativum* L.) (from internet).

ond Stage of Construction of China-ASEAN Joint Laboratory for International Cooperation in Traditional Medicine Research (No. GUIKE AD19110155).

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