Coronavirus (Covid-19) and TCM: Scientific Research and Clinical Evidence

John K. Chen, Ph.D., Pharm.D., O.M.D., L.Ac.
Lori Hsu, MTOM, MS
Michael Norris, L.Ac., C.H.
Debra Nash-Galpern, L.Ac.
Robert Chu, OME
Lorraine Wilcox, L.Ac.
Donna Chow, L.Ac., DiplOM

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Three-Parts Webinars

- **Webinar 1: TCM Treatment of Influenza and Viral Infections.**
  - https://www.elotus.org/free-course/tcm-treatment-influenza-and-viral-infections
  - https://www.youtube.com/watch?v=G7Y86cjf17E
- **Webinar 2: How Coronavirus (Covid-19) is treated with TCM in China.**
  - https://www.elotus.org/free-course/how-coronavirus-covid-19-treated-tcm-china
  - https://www.youtube.com/watch?v=BGcsFzKLdTI&feature=youtu.be
  - https://www.youtube.com/watch?v=DDp6g655LYU
- **Webinar 3: Coronavirus (Covid-19) and TCM: Scientific Research and Clinical Evidence**

- Johns Hopkins University. 4/20/2020.

https://coronavirus.jhu.edu/map.html

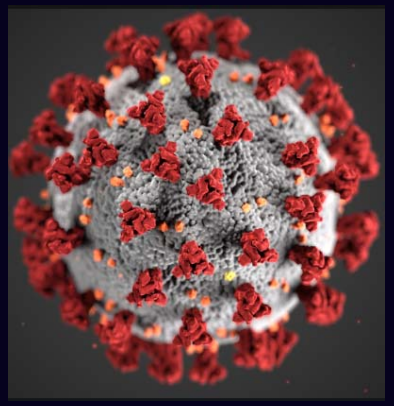
www.eLOTUS.org

- NIH U.S. National Library of Medicine.
- Clinical Trials. 4/20/2020.

https://clinicaltrials.gov/ct2/home

Biology

- Seven known coronaviruses that affect human
- MERS from MERS-CoV (34.3% fatality rate)
- SARS from SARS-CoV (9.6% fatality rate).
- Covid-19 from SARS-CoV-2 (1.38% to 3.4% fatality rate).
- 96% genome identity



- Report of the WHO-China Joint Mission on Coronavirus Disease (COVID-19) 16-24 February 2020.
- https://emcrit.org/ibcc/covid19/?fbclid=IwAR31Xy-vkhL39xSWNAqkx3fECRR2yQLVbyWD2EOOoDG7FYv2WXqdQm7Lu_U#biology
- https://www.medicalnewstoday.com/articles/how-do-sars-and-mers-compare-with-covid-19#SARS

Clinical Manifestation

- Respiratory tract
  - Upper: sneezing, runny nose, nasal congestion, sore throat, lost sense of taste and smell
  - Lower: dry cough, sputum production, shortness of breath
- Gastrointestinal tract
- Systemic

Wang, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* Published online February 7, 2020. doi:10.1001/jama.2020.1585

Clinical Manifestation

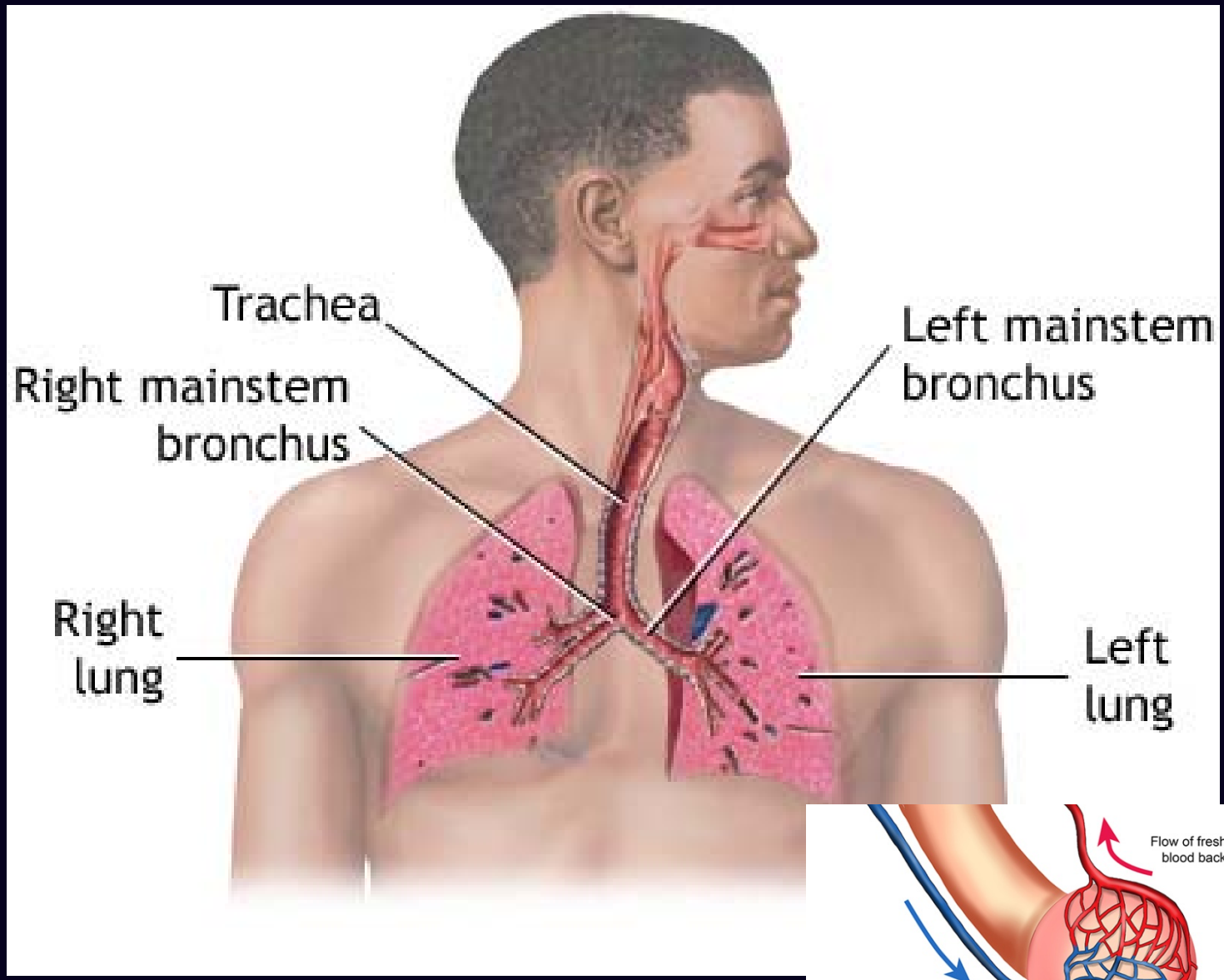
- Respiratory tract
- Gastrointestinal tract
  - 5-10% of patients can present initially with diarrhea or nausea, *before* fever and dyspnea
- Systemic

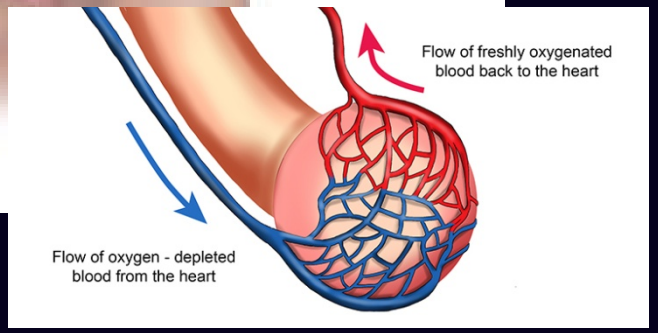
Wang, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* Published online February 7, 2020. doi:10.1001/jama.2020.1585

Clinical Manifestation

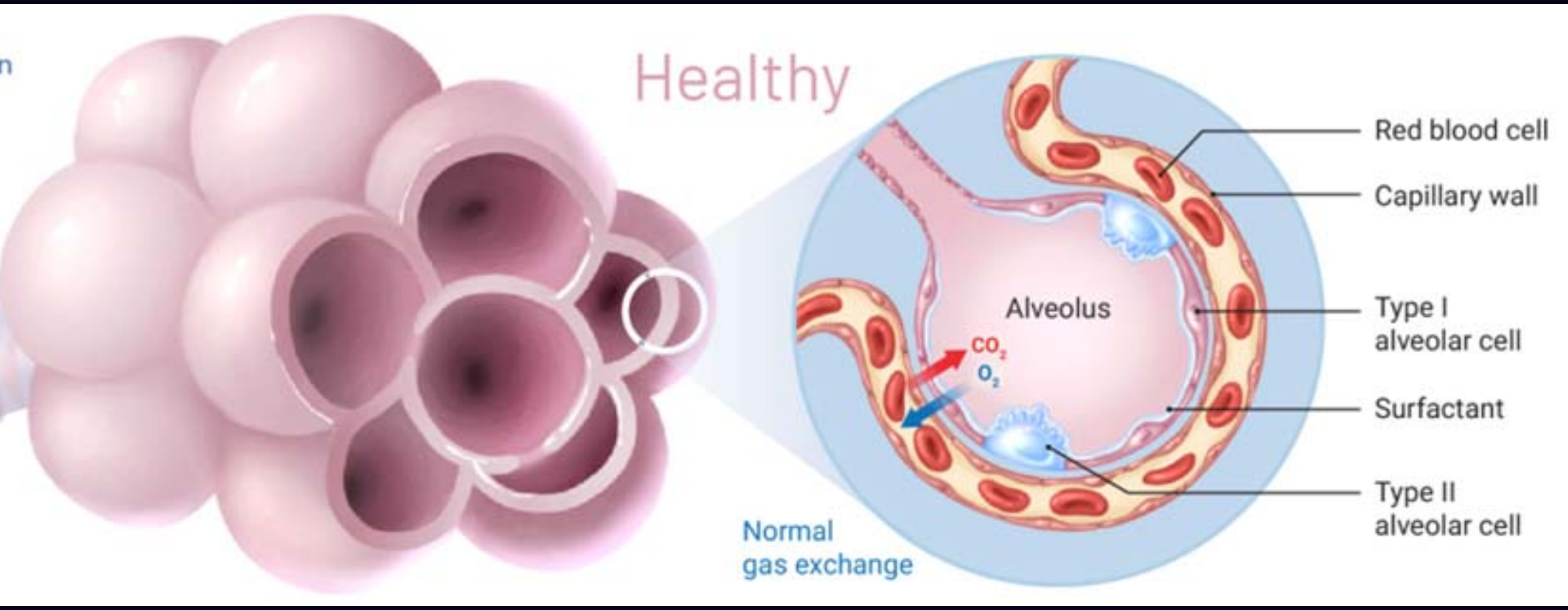
- Respiratory tract
- Gastrointestinal tract
- Systemic
  - fever, lethargy, muscle pain, headache and dehydration.

Wang, et al. Clinical Characteristics of 138 Hospitalized Patients With 2019 Novel Coronavirus–Infected Pneumonia in Wuhan, China. *JAMA.* Published online February 7, 2020. doi:10.1001/jama.2020.1585

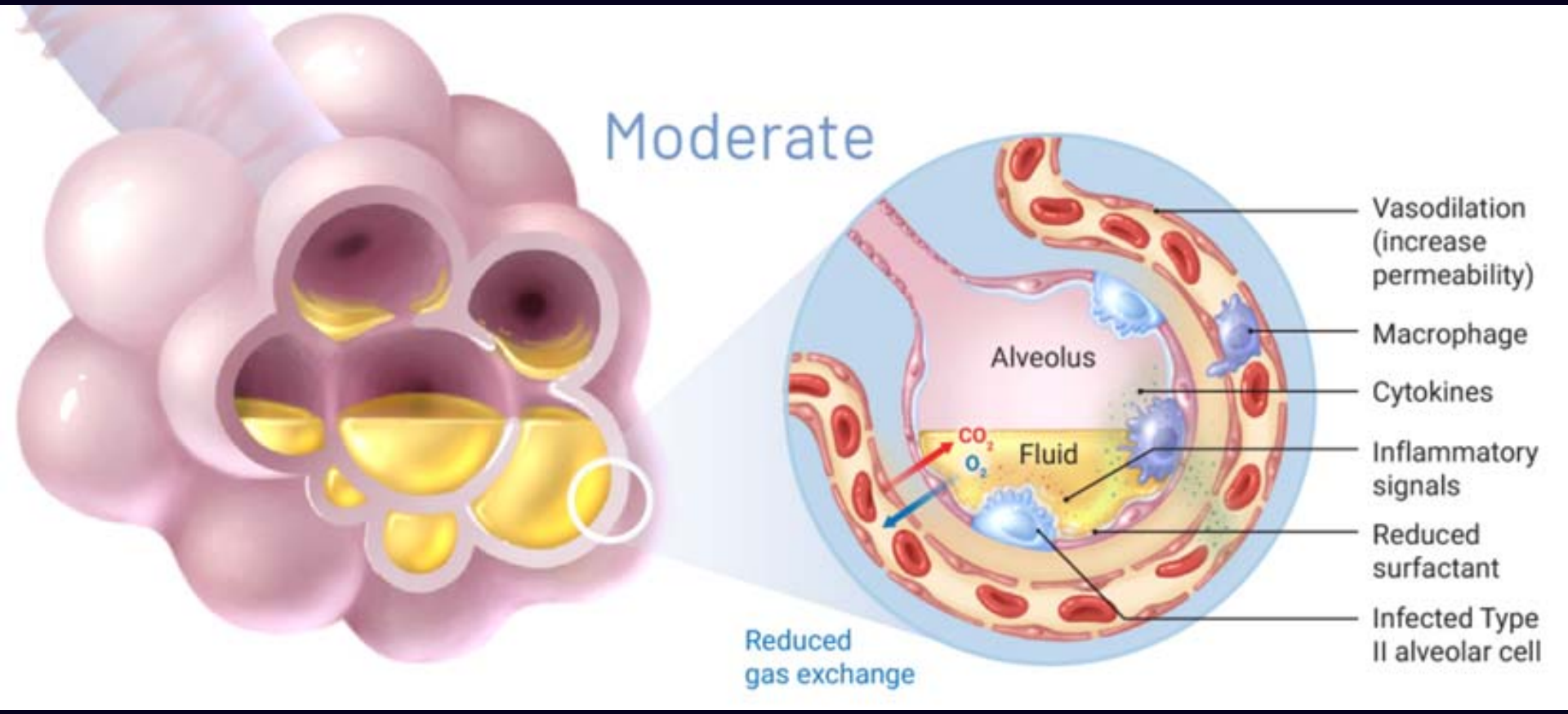




https://medlineplus.gov/ency/imagepages/9248.htm



https://www.visualcapitalist.com/visualizing-what-covid-19-does-to-your-body/



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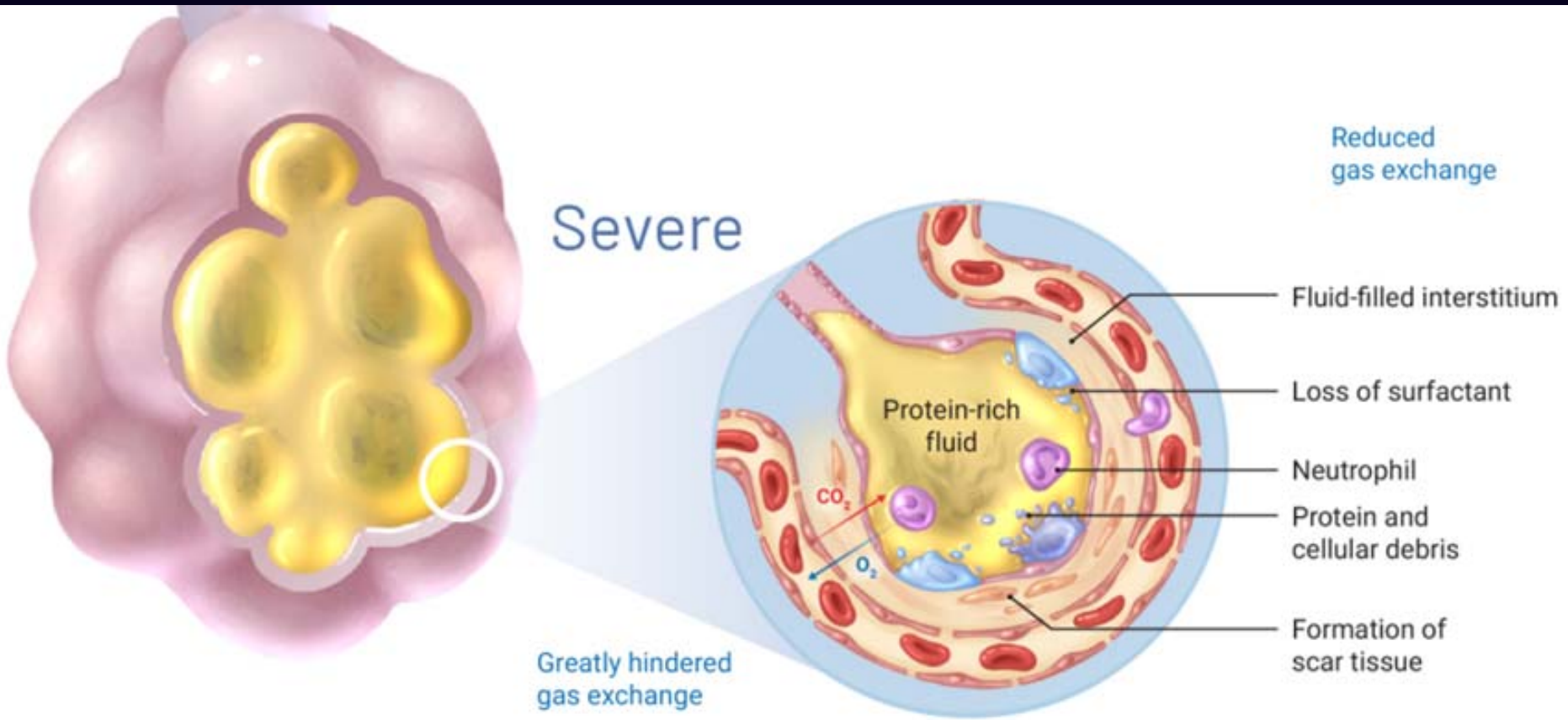

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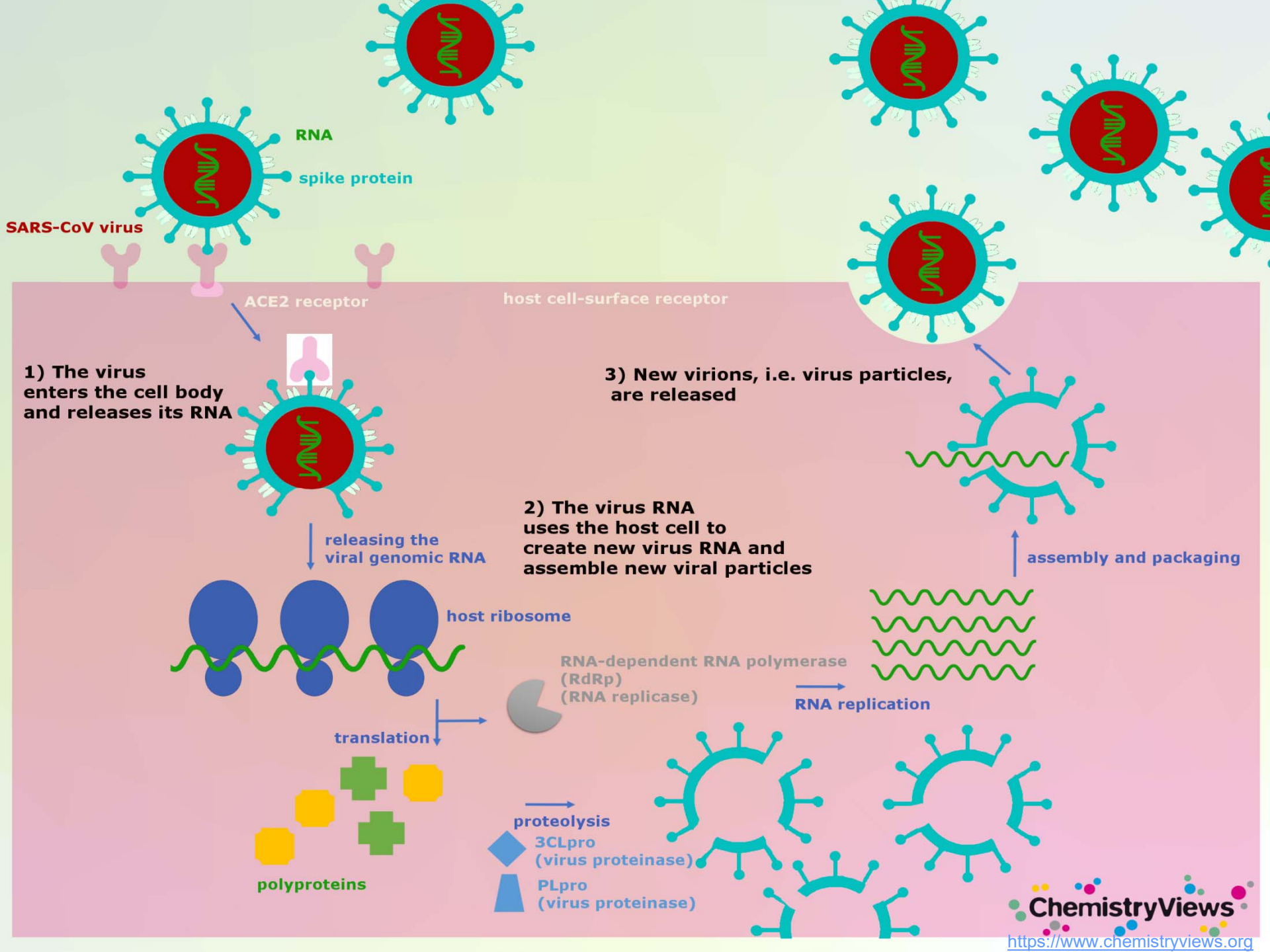

RNA
spike protein
SARS-CoV virus
ACE2 receptor
host cell-surface receptor
1) The virus enters the cell body and releases its RNA
releasing the viral genomic RNA
2) The virus RNA uses the host cell to create new virus RNA and assemble new viral particles
host ribosome
RNA-dependent RNA polymerase (RdRp) (RNA replicase)
translation
RNA replication
assembly and packaging
3) New virions, i.e. virus particles, are released
proteolysis
3CLpro (virus proteinase)
PLpro (virus proteinase)
polyproteins
ChemistryViews
https://www.chemistryviews.org

Diagnosis

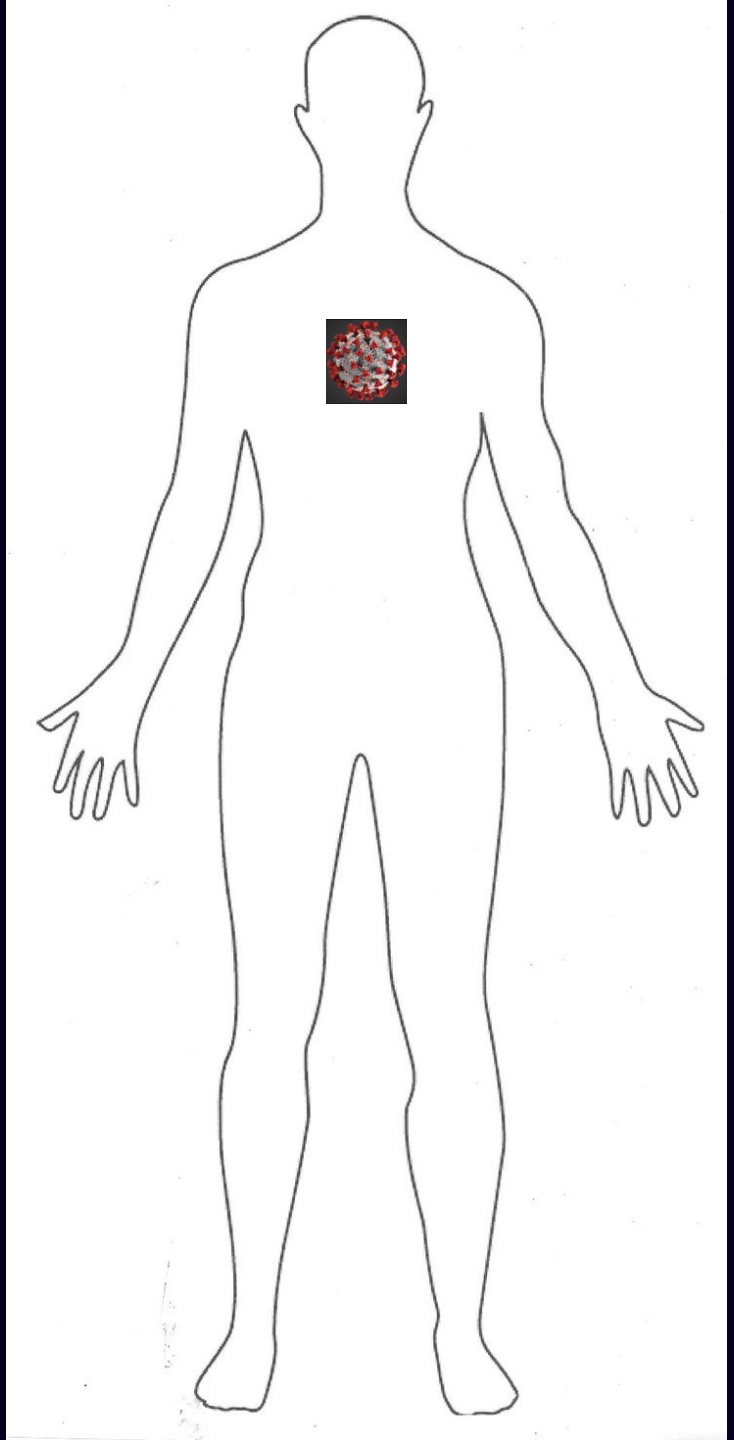
- Covid-19

Wind-Cold at the exterior
Wind-Heat at the exterior
Damp Warmth in Early Phase
Damp Cold in the Lung
Damp Heat Obstructing the Lung
Damp Heat Afflicting the Lung
Toxic Stagnation Obstructing the Lung
Toxic Heat in the Lung
Epidemic Toxins Blocking the Lung
Shaoyang Syndrome with Damp
Closed Interior and Abandoned Exterior

Treatment

- None

Gě Gēn Tāng 葛根湯 (Kudzu Decoction)
Chái Gě Jiě Jī Tāng 柴葛解肌湯 (Bupleurum and Kudzu Decoction to Release the Muscle Layer)
Má Xìng Gān Shí Tāng 麻杏甘石湯 (Ephedra, Apricot Kernel, Licorice, and Gypsum Decoction)
Má Xìng Yì Gān Tāng 麻杏薏甘湯 (Ephedra, Apricot Kernel, Coicis, and Licorice Decoction)
Xiǎo Xiàn Xiōng Tāng 小陷胸湯 (Minor Sinking into the Chest Decoction)
Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)
Shè Gān Má Huáng Tāng 射干麻黃湯 (Belamcanda and Ephedra Decoction)
Wǔ Líng Sǎn 五苓散 (Five-Ingredient Powder with Poria)
Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Expel Toxin Decoction)
Sì Nì Tāng 四逆湯 (Frigid Extremities Decoction)
Yín Qiào Sǎn 銀翹散 (Honeysuckle and Forsythia Powder)
Sāng Jú Yǐn 桑菊飲 (Mulberry Leaf and Chrysanthemum Decoction)
Sān Rén Tāng 三仁湯 (Three-Nut Decoction)
Qīng Wēn Bài Dú Yǐn 清瘟敗毒飲 (Clear Epidemics and Overcome Toxin Decoction)
Gān Lù Xiāo Dú Dān 甘露消毒丹 (Sweet Dew Special Pill to Eliminate Toxin)
Pǔ Jì Xiāo Dú Yǐn 普濟消毒飲 (Universal Benefit Decoction to Eliminate Toxin)
Dá Yuán Yǐn 達原飲 (Reach the Membrane Source Decoction)
Shā Shēn Mài Dōng Tāng 沙參麥冬湯 (Glehnia and Ophiopogonis Decoction)



Shang Han

伤寒

(Cold Damage)

Wen Bing

温病

(Warm Disease)

Shang Han

伤寒

(Cold Damage)

张仲景 Zhāng Zhòng-Jǐng, 150-219 CE

- 伤寒论 *Shang Han Lun* (Discussion of Cold-Induced Disorders)
  - Taiyang
  - Yangming
  - Shaoyang
  - Taiyin
  - Shaoyin
  - Jueyin

Gě Gēn Tāng 葛根湯 (Kudzu Decoction)

- *Ge Gen* (Radix Puerariae Lobatae) 12g
- *Ma Huang* (Herba Ephedrae) 9g
- *Gui Zhi* (Ramulus Cinnamomi) 6g
- *Bai Shao* (Radix Paeoniae Alba) 6g
- *Zhi Gan Cao* (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle) 6g
- *Sheng Jiang* (Rhizoma Zingiberis Recens), *qie* (sliced) 9g
- *Da Zao* (Fructus Jujubae), *bo* (opened) 12 pieces [3 pieces]

Original Source: *Shang Han Lun* (Discussion of Cold-Induced Disorders) by Zhang Zhong-Jing in the Eastern Han Dynasty

Gě Gēn Tāng 葛根湯 (Kudzu Decoction)

- Releases the exterior and muscle layer
- Promotes generation of body fluids

- *Taiyang* syndrome with wind-cold invasion: severe muscle stiffness of the neck and back, aversion to cold, with or without fever, aversion to wind, absence of perspiration, and diarrhea.

Original Source: *Shang Han Lun* (Discussion of Cold-Induced Disorders) by Zhang Zhong-Jing in the Eastern Han Dynasty

Gě Gēn Tāng 葛根湯 (Kudzu Decoction)

- Antipyretic
- Anti-inflammatory

- Kurokawa M, Kumeda CA, Yamamura J, Kamiyama T, Shiraki K. Antipyretic activity of cinnamyl derivatives and related compounds in influenza virus-infected mice. Eur J Pharmacol 1998 May 1;348(1):45-51.
- Ozaki Y. Studies on antiinflammatory effect of Japanese Oriental medicines (kampo medicines) used to treat inflammatory diseases. Biol Pharm Bull 1995 Apr;18(4):559-62.

Má Xìng Gān Shí Tāng 麻杏甘石湯 (Ephedra, Apricot Kernel, Licorice, and Gypsum Decoction)

- *Ma Huang* (Herba Ephedrae) 12g [5-9g]
- *Ku Xing Ren* (Semen Armeniacae Amarum) 50 kernels [9g]
- *Shi Gao* (Gypsum Fibrosum), *fen sui* pulverized) 24g [18g]
- *Zhi Gan Cao* (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle) 6g

Original Source: *Shang Han Lun* (Discussion of Cold-Induced Disorders) by Zhang Zhong-Jing in the Eastern Han Dynasty

Má Xìng Gān Shí Tāng 麻杏甘石湯 (Ephedra, Apricot Kernel, Licorice, and Gypsum Decoction)

- Ventilates Lung qi
- Clears Lung heat
- Relieves cough and dyspnea

- Cough and dyspnea in Lung heat syndrome caused by exterior pathogenic factors: unremitting fever, thirst with a desire to drink, rhinalgia, coughing, dyspnea, with or without perspiration, a thin, white or thin, yellow tongue coating, and a slippery, rapid pulse.

Original Source: *Shang Han Lun* (Discussion of Cold-Induced Disorders) by Zhang Zhong-Jing in the Eastern Han Dynasty

Má Xìng Gān Shí Tāng 麻杏甘石湯 (Ephedra, Apricot Kernel, Licorice, and Gypsum Decoction)

- *Ma Huang* - Antiasthmatic
- *Ku Xing Ren* - Antitussive
- *Shi Gao* - Antipyretic
- *Zhi Gan Cao* - Anti-inflammatory

- Kao ST, Yeh TJ, Hsieh CC, Shiau HB, Yeh FT, Lin JG. The effects of Ma-Xing-Gan-Shi-Tang on respiratory resistance and airway leukocyte infiltration in asthmatic guinea pigs. Immunopharmacol Immunotoxicol 2001 Aug;23(3):445-58.
- *Zhong Cheng Yao Yan Jiu* (Research of Chinese Patent Medicine) 1987;(4):47.
- *Zhong Cheng Yao Yan Jiu* (Research of Chinese Patent Medicine) 1984;(6):21.
- Ma LQ, et al. Posttreatment with Ma-Xing-Shi-Gan-Tang, a Chinese medicine formula, ameliorates lipopolysaccharide-induced lung microvessel hyperpermeability and inflammatory reaction in rat. Microcirculation. 2014 Oct;21(7):649-63.

Lin et al. BMC Complementary and Alternative Medicine (2016) 16:456
DOI 10.1186/s12906-016-1440-2

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Antitussive, anti-pyretic and toxicological evaluation of Ma-Xing-Gan-Shi-Tang in rodents

Yu-Chin Lin[1], Ching-Wen Chang[2,3] and Chi-Rei Wu[3*]

Abstract

Background: Ma-Xing-Gan-Shi-Tang (abbreviated as MXGST), an important Chinese herbal prescribed for cough, bronchial inflammation and fever from pneumonia, consists of four medicinal herbs, including Ephedrae herb, Semen Pruni Armeniacae, licorice and Gypsum. These components, especially Ephedrae and Semen Pruni Armeniacae, possess antitussive activities, but they have severe adverse effects.

Methods: The pharmacological activities of MXGST extract in clinical use were investigated with citric acid-induced cough, acetylcholine/histamine-induced bronchial contraction and lipopolysaccharide (LPS)-induced fever in rodents. The subacute toxicology of MXGST extract was evaluated after a 28-day repeated oral administration in rats.

Results: Each gram of MXGST extract contained 60 ± 8 μg of ephedrine, 480 ± 40 μg of glycyrrhizic acid and 440 ± 8 μg of amygdalin according to high performance liquid chromatography and a photodiode array detector. MXGST extract produced pronounced, dose-dependent antitussive effects in guinea pigs and reduced hyperthermic syndrome induced by LPS in rats. MXGST extract blocked the bronchial contraction induced by acetylcholine/histamine. Oral administration of MXGST extract for 28 days did not cause any hematological, biochemical or histological changes in rats.

Lin et al. BMC Complementary and Alternative Medicine (2016) 16:456
DOI 10.1186/s12906-016-1440-2

BMC Complementary and Alternative Medicine

RESEARCH ARTICLE Open Access

Antitussive, anti-pyretic and toxicological evaluation of Ma-Xing-Gan-Shi-Tang in rodents

Yu-Chin Lin[1], Ching-Wen Chang[2,3] and Chi-Rei Wu[3*]

- *Ma Huang* stimulates “sympathomimetic α- and β-adrenergic receptors” with ephedra alkaloids”
- *Ku Xing Ren* “inhibits central cough center with amygdalin”
- *Shi Gao* alleviates “hyperthermia via decreasing the hypothalamus prostaglandin E2 levels”
- *Gan Cao* regulates “pituitary adrenal axis”

Immunopharmacology and Immunotoxicology ›

Volume 23, 2001 - Issue 3

THE EFFECTS OF MA-XING-GAN-SHI-TANG ON RESPIRATORY RESISTANCE AND AIRWAY LEUKOCYTE INFILTRATION IN ASTHMATIC GUINEA PIGS

Shung-Te Kao, Tsung-Jen Yeh, Chang-Chi Hsieh, Hung-Bo Shiau, Feng-Tsgh Yeh & Jaung-Geng Lin

Pages 445-458 | Published online: 31 Jul 2001

- MXGST exhibits direct β-adrenoceptor agonist activity.
- MXGST … reduction of neutrophil infiltration into lung tissue and reduce lung inflammation.

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- *Chai Hu* (Radix Bupleuri) 24g [12g]
- *Huang Qin* (Radix Scutellariae) 9g [9g]
- *Ban Xia* (Rhizoma Pinelliae), *xi* (washed) 0.5 cup [9g]
- *Sheng Jiang* (Rhizoma Zingiberis Recens), *qie* (sliced) 9g [9g]
- *Ren Shen* (Radix et Rhizoma Ginseng) 9g [6g]
- *Zhi Gan Cao* (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle) 9g [5g]
- *Da Zao* (Fructus Jujubae), *bo* (opened) 12 pieces [4 pieces]

Original Source: *Shang Han Lun* (Discussion of Cold-Induced Disorders) by Zhang Zhong-Jing in the Eastern Han Dynasty

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- Harmonizes *shaoyang*

- *Shaoyang* syndrome: alternating spells of fever and chills, chest and hypochondriac fullness and discomfort, irritability, a bitter taste in the mouth, lack of appetite, nausea, vomiting, vertigo, a dry throat, a thin, white tongue coating, and a wiry pulse.

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- Hepatitis, viral hepatitis, chronic hepatitis, hepatic fibrosis and carcinoma, hepatocellular carcinomas, jaundice, cholecystitis, cholelithiasis, pancreatitis, fever, fever in cancer, nephritis, chronic renal insufficiency, acute tonsillitis, infectious parotitis, stomatitis, common cold, influenza, measles, bronchitis, pneumonia, pulmonary tuberculosis, cough, allergic rhinitis, bronchial asthma, reflux esophagitis, antral gastritis, gastritis, gastric pain, gastric prolapse, constipation, Meniere's syndrome, dizziness, seizures, migraine, angina, depression, chronic fatigue syndrome, morning sickness, postpartum infection, postpartum fever, dysmenorrhea, premenstrual syndrome, and malaria.

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- Hepatoprotective
- Antihepatic fribrosis
- Cholagogic
- Anti-inflammatory
- Effect on temperature regulation
- Antiulcer
- Antiasthmatic
- Antiallergic
- Antioxidant
- Antitumor
- Antitumor and antimetastatic
- Effect on hypercholesterolemia and hyperlipidemia

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

Complementary medicine: a review of immunomodulatory effects of Chinese herbal medicines[1–3]

Andrea T Borchers, Robert M Hackman, Carl L Keen, Judith S Stern, and M Eric Gershwin

Shosaiko-to (Chinese name: Xiao-Chai-Hu-Tang)

Shosaiko-to, or Xiao-Chai-Hu-Tang, is a hot-water extract from seven species of medicinal plants (*see* Table 1 for the individual constituents and their proportions) (30). It has been used clinically to treat chronic hepatitis B, bronchial asthma, and nephrotic syndrome and has been observed to be a general immunostimulant in mice (30–32). In view of the use of Shosaiko-to in treating hepatitis B, its in vitro effects on peripheral blood mononuclear cells (PBMCs) from eight patients with hepatitis B and four healthy control subjects were examined (36). Of the eight patients with chronic active hepatitis B, four had anti-hepatitis B antibodies to the viral envelope (anti-HBe) and four were positive only for hepatitis B viral envelope antigen (HBeAg). The PBMCs from all three groups of donors were cultured under five conditions: *1*) in the presence of different concentrations of Shosaiko-to, *2*) with purified hepatitis BeAg, *3*) with recombinant antigen to the hepatitis B viral core (rHBcAg), *4*) with purified HBeAg plus Shosaiko-to, or *5*) with rHBcAg plus Shosaiko-to. The supernates were assayed for interferon γ (IFN-γ) with an enzyme-linked immunosorbent assay (ELISA) by using rabbit polyclonal antibody to recombinant IFN-γ. In the control subjects,

Shosaiko-to alone was found to induce IFN-γ production in a dose-dependent manner whereas neither of the hepatitis B antigens alone or in combination elicited a response. In the control group, addition of antigens had no effect on Shosaiko-to–induced production of IFN-γ. By contrast, in the PBMCs from all the infected subjects, Shosaiko-to augmented hepatitis B antigen-induced IFN-γ production significantly and in a dose-dependent manner. Because IFN-γ is known to participate in host-defense mechanisms against viral infections, the authors speculated that the beneficial effects of Shosaiko-to in hepatitis B, a viral infection, are due in part to its ability to increase IFN-γ production.

Natural killer (NK) cells play an important role in overcoming viral infections. The effect of Shosaiko-to on NK cell activity was examined ex vivo in NK cells isolated from peripheral blood, liver, and spleen of female C3H/He mice given oral doses ranging from 500 to 2000 mg/kg (37). In cytotoxicity assays with NK-sensitive and NK-resistant cells,

Andrea T Borchers, Robert M Hackman, Carl L Keen, Judith S Stern, and M Eric Gershwin. Complementary medicine: a review of immunomodulatory effects of Chinese herbal medicines. Am J Clin Nutr l997;66:1303-12. Printed
http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.1001.2594&rep=rep1&type=pdf

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- Immunomodulatory: XCHT significantly significantly inhibits asthmatic over-reaction by reduction of leukocytes, eosinophilic inflammation and downregulation of Th2-type cytokines, chemokines, and decrease of mucus hypersecretion and IgE levels.

Soshiho-tang water extract inhibits ovalbumin-induced airway inflammation via the regulation of heme oxygenase-1
Woo-Young Jeon, Hyeun-Kyoo Shin, In-Sik Shin, Sang Kyum Kim, Mee-Young Lee
BMC Complement Altern Med. 2015; 15: 329. Published online 2015 Sep 18. doi: 10.1186/s12906-015-0857-3

Xiǎo Chái Hú Tāng 小柴胡湯 (Minor Bupleurum Decoction)

- **Interferon-alpha** in patients with pre-existing chronic hepatitis or liver cirrhosis. While the herbs have not been shown to injure the lung tissues, but they may over stimulate the neutrophils to release granulocytes, elastase and oxygen radicals, which subsequently damage lung tissue. The fibroblasts that repair the damaged tissue may increase the risk of pulmonary fibrosis.

- Nakagawa A et al. Five patients of drug-induced pneumonitis due to Sho-saiko-to or interferon-alpha or both. Nihon Kyobu Shikkan Gakkai Zasshi. 1995 Dec; 33(12):1361-1366.
- Murakami K, et al. A possible mechanism of interstitial pneumonia during interferon therapy with sho-saiko-to. Nihon Kyobu Shikkan Gakkai Zasshi 1995 Apr;33(4):389-94
- Ishizaki T, Sasaki F, Ameshima S, Shiozaki K, Takahashi H, Abe Y, Ito S, Kuriyama M, Nakai T, Kitagawa M. Pneumonitis during interferon and/or herbal drug therapy in patients with chronic active hepatitis. European Respiratory Journal 1996 Dec;9(12):2691-6.

Shè Gān Má Huáng Tāng 射干麻黃湯 (Belamcanda and Ephedra Decoction)

- *Ma Huang* (Herba Ephedrae) 12g [9g]
- *She Gan* (Rhizoma Belamcandae) 9g [6-g]
- *Sheng Jiang* (Rhizoma Zingiberis Recens) 12g [9g]
- *Xi Xin* (Radix et Rhizoma Asari) 9g [3g]
- *Zi Wan* (Radix et Rhizoma Asteris) 9g [6g]
- *Kuan Dong Hua* (Flos Farfarae) 9g [6g]
- *Ban Xia* (Rhizoma Pinelliae) 0.5 cup [9g]
- *Wu Wei Zi* (Fructus Schisandrae Chinensis) 0.5 cup [3g]
- *Da Zao* (Fructus Jujubae) 7 pieces [3 pieces]

Original Source: *Jin Gui Yao Lue* (Essentials from the Golden Cabinet) by Zhang Zhong-Jing in the Eastern Han Dynasty

Shè Gān Má Huáng Tāng 射干麻黃湯 (Belamcanda and Ephedra Decoction)

- Ventilates the Lung and dispels phlegm
- Directs Lung qi downward and stops coughing

- *Tan yin* (phlegm retention) with reversed flow of Lung qi: excessive coughing, dyspnea, profuse, clear, watery sputum, rattling sounds in the throat, a feeling of fullness and stifling sensation in the chest and diaphragm, heaviness and pain of the body, swollen face and extremities, and a white, slippery tongue coating.

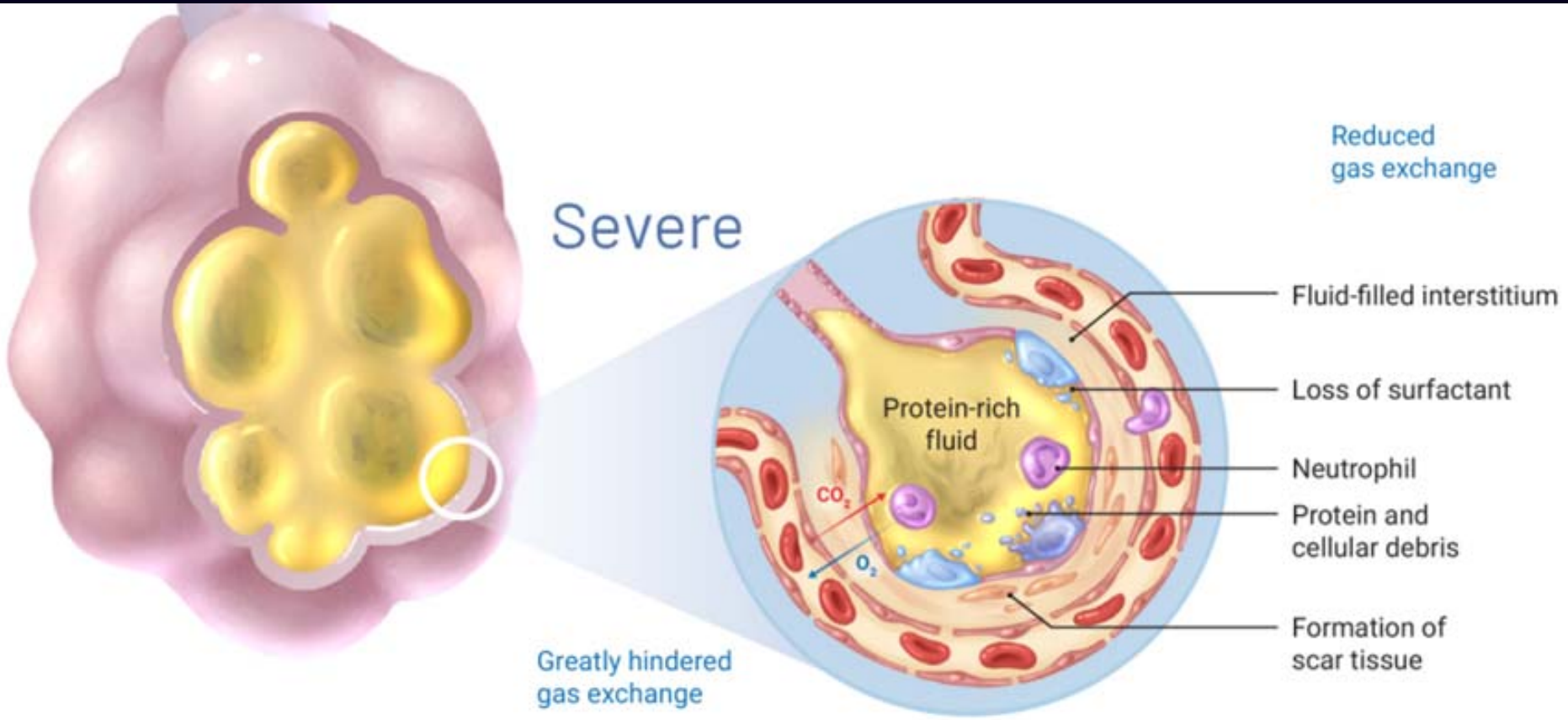
Shè Gān Má Huáng Tāng 射干麻黄湯 (Belamcanda and Ephedra Decoction)

- *Tán Yǐn* 痰饮

- *Tan* 痰 (visible phlegm, tangible phlegm); phlegm
- *Yin* 饮 (invisible phlegm, intangible phlegm); rheum

Original Source: *Jin Gui Yao Lue* (Essentials from the Golden Cabinet) by Zhang Zhong-Jing in the Eastern Han Dynasty

Tán Yǐn 痰饮



https://www.visualcapitalist.com/visualizing-what-covid-19-does-to-your-body/

Shè Gān Má Huáng Tāng 射干麻黃湯 (Belamcanda and Ephedra Decoction)

- Antiasthmatic
- Antitussive
- Expectorant

- *Zhong Yi Yao Xue Bao* (Report of Chinese Medicine and Herbology) 1990;3:36.
- *Zhong Yi Fang Ji Xian Dai Yan Jiu* (Modern Study of Medical Formulae in Traditional Chinese Medicine) 1997;66.
- *Zhong Yi Fang Ji Xian Dai Yan Jiu* (Modern Study of Medical Formulae in Traditional Chinese Medicine) 1997;66-67.

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Shegan-Mahuang Decoction ameliorates asthmatic airway hyperresponsiveness by downregulating Th2/Th17 cells but upregulating CD4+FoxP3+ Tregs

Cheng-Chuang Lin[1], Yuan-Yuan Wang[1], Si-Min Chen[1], Yun-Tao Liu, Ji-Qiang Li, Fang Li, Jie-Chen Dai, Tong Zhang, Feifei Qiu, Huazhen Liu, Zhenhua Dai*, Zhong-De Zhang**

Section of Immunology & Joint Immunology Program, The Second Clinical Medical College of Guangzhou University of Chinese Medicine, Guangdong Provincial Academy of Chinese Medical Sciences, Guangzhou, Guangdong, 510006, China

ARTICLE INFO

Keywords:
Asthma
Shegan-Mahuang decoction
Traditional Chinese medicine
Th2
Th17
Treg

ABSTRACT

Ethnopharmacological relevance: Shegan-Mahuang Decoction (SMD), also named Yakammaoto or Shegan-Mahuang Tang, is a classic formula of traditional Chinese medicine with nine herbs, including Asarum sieboldii Miq., Aster tataricus L.f., Ephedra sinica Stapf, Belamcanda chinensis (L.) Redouté, Pinellia ternata (Thunb.) Breit., Schisandra chinensis (Turcz.) Baill., Tussilago farfara L., Zingiber officinale Roscoe, and Ziziphus jujuba Mill. SMD was originally discovered by Zhang Zhongjing in Eastern Han dynasty. It has been widely used as traditional medicine to treat flu-like symptoms in China and Japan for around twenty centuries. It was also utilized for the treatment of the early stage of acute asthma. However, the immune mechanisms underlying its therapeutic effects remain unknown.

Aim of the study: This study was set to investigate the effects of SMD on asthmatic airway hyperresponsiveness and its impacts on adaptive immunity in a mouse model of asthma.

Materials and methods: The HPLC fingerprint profile of the water extract of SMD recorded 22 peaks, including those equivalent to guanosine, chlorogenic acid, tectoridin, 6-gingerol and wuweizisu B, as described previously (Yen et al., 2014). Airway hyperresponsiveness was assessed by measuring the airway resistance. Cellular infiltration was measured via H&E staining and immunochemistry while gene expression was analyzed using real-time RT-PCR. Treg frequency was determined through flow analysis whereas cytokine production in the supernatant was evaluated using ELISA. Finally, mTOR and NF-kB signalings were analyzed via Western blotting.

Results: We found that SMD largely corrected the imbalance of Th cell subsets in asthmatic mice with a significant inhibition of Th2 and Th17 cytokine production, thereby reducing asthmatic airway hyperresponsiveness. Moreover, lung function tests showed that SMD reduced airway hyperresponsiveness while immunohistochemical analyses demonstrated that SMD attenuated pulmonary infiltration of $CD3^+$ and $CD4^+$ T cells. Further, we observed a significant increase in the proportion of CD4+Foxp3+ Tregs in SMD-treated asthmatic mice. We also found that SMD downregulated gene expression of GATA3 and ROR-γt in murine lung tissue. In addition, both mTOR- and NF-kB-related protein expressions were reduced in the lung tissue of SMD-treated mice. SMD inhibited Th2/Th17 cytokine production by $CD4^+$ T cells and also their mTOR activity in vitro.

Conclusions: Our findings demonstrate that SMD attenuates asthmatic airway hyperresponsiveness by hindering Th2/Th17 differentiation, promoting CD4+FoxP3+ Treg generation and suppressing mTOR and NF-kB activities.

Shegan-Mahuang Decoction ameliorates asthmatic airway hyperresponsiveness by downregulating Th2/Th17 cells but upregulating CD4+FoxP3+ Tregs

- **Immunomodulatory**: *She Gan Ma Huang Tang* has been shown to effectively regulate the immune system and treat asthmatic airway hyper-responsiveness. *She Gan Ma Huang Tang* downregulates the Th_2 and Th_{17} differentiation, upregulates T_{reg} generation, and inhibits the excessive cytokine prodution to alleviate asthmatic airway hyperresponsiveness.

- Lin CC, et al. Shegan-Mahuang Decoction ameliorates asthmatic airway hyperresponsiveness by downregulating Th2/Th17 cells but upregulating CD4+FoxP3+ Tregs. J Ethnopharmacol. 2020 May 10;253:112656.

Wǔ Líng Sǎn 五苓散 (Five-Ingredient Powder with Poria)

- *Ze Xie* (Rhizoma Alismatis) 3.75g [15g]
- *Zhu Ling* (Polyporus) 2.25g [9g]
- *Fu Ling* (Poria) 2.25g [9g]
- *Bai Zhu* (Rhizoma Atractylodis Macrocephalae) 2.25g [9g]
- *Gui Zhi* (Ramulus Cinnamomi) 1.5g [6g]

Wǔ Líng Sǎn 五苓散 (Five-Ingredient Powder with Poria)

- Regulates water circulation and dispels dampness
- Warms yang and disperses water accumulation

- Exterior syndrome with accumulation of water and dampness in the interior: headache, fever, irritability, thirst with a strong desire to drink but vomiting immediately after drinking, urinary difficulty, white tongue coating, and a superficial pulse.
- Accumulation of water and dampness in the interior: edema, loose stools, urinary difficulty, vomiting, and diarrhea due to sudden turmoil disorder.
- *Tan yin* (phlegm retention): abdominal pulsation below the umbilicus, vomiting of foamy saliva, vertigo, shortness of breath, and possibly coughing.

Wǔ Líng Sǎn 五苓散 (Five-Ingredient Powder with Poria)

- Diuretic
- Nephroprotective

- *Zhong Yi Fang Ji Xian Dai Yan Jiu* (Modern Study of Medical Formulae in Traditional Chinese Medicine) 1997;1407.
- *Guo Wai Yi Xue Zhong Yi Zhong Yao Fen Ce* (Monograph of Chinese Herbology from Foreign Medicine) 1981;2:121.
- *Zhong Hua Yi Xue Za Zhi* (Chinese Journal of Medicine) 1961;17(1):7.
- *Guo Wai Yi Xue Zhong Yi Zhong Yao Fen Ce* (Monograph of Chinese Herbology from Foreign Medicine) 1983;3:43.

Journal of Ethnopharmacology
Volume 124, Issue 2, 15 July 2009, Pages 211-218

The amelioration of streptozotocin diabetes-induced renal damage by Wu-Ling-San (Hoelen Five Herb Formula), a traditional Chinese prescription

I-Min Liu [a], Thing-Fong Tzeng [b], Shorong-Shii Liou [a], Chia Ju Chang [a]

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https://doi.org/10.1016/j.jep.2009.04.021

Abstract

Ethnopharmacological relevance

Wu-Ling-San (Hoelen Five Herb Formula) is a Chinese prescription used to promote water metabolism.

Aim of the study

The present study was undertaken to characterize the effects of Wu-Ling-San on diabetic nephropathy.

Journal of Ethnopharmacology
Volume 112, Issue 2, 13 June 2007, Pages 333-340

Wen-pi-tang-Hab-Wu-ling-san attenuates kidney ischemia/reperfusion injury in mice: A role for antioxidant enzymes and heat-shock proteins

Young Mi Seok [a, c], Jinu Kim [a, c], Ki Choon Choi [a], Cheol Ho Yoon [d], Yong Chool Boo [b, c], Yongki Park [e], Kwon Moo Park [a, c]

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https://doi.org/10.1016/j.jep.2007.03.015 Get rights and content

Abstract

The purpose of this study was to investigate the effects of Wen-pi-tang-Hab-Wu-ling-san (WHW) extract, which has been used for treatment of renal diseases, on kidney ischemia/reperfusion (I/R) injury. Thirty minutes of bilateral renal ischemia resulted in disruption of kidney tubular epithelial cells and increased plasma creatinine levels in mice, however these effects were significantly attenuated when WHW was administered prior to I/R. WHW-administration also inhibited post-ischemic decreases of catalase, copper–zinc superoxide dismutase (CuZnSOD), and manganese superoxide dismutase (MnSOD) activity in kidney tissue, leading to decreased tissue hydrogen peroxide levels and lipid peroxidation. Post-ischemic increases of heat-shock protein (HSP)-27 and -72 expressions were greater in mouse

Phytotherapy Research

Research Article

Wen-pi-tang-Hab-Wu-ling-san attenuates kidney fibrosis induced by ischemia/reperfusion in mice

Young Mi Seok, Jinu Kim, Mae Ja Park, Yong Chool Boo, Yong-Ki Park, Kwon Moo Park

First published:29 July 2008 | https://doi.org/10.1002/ptr.2440 | Citations: 15

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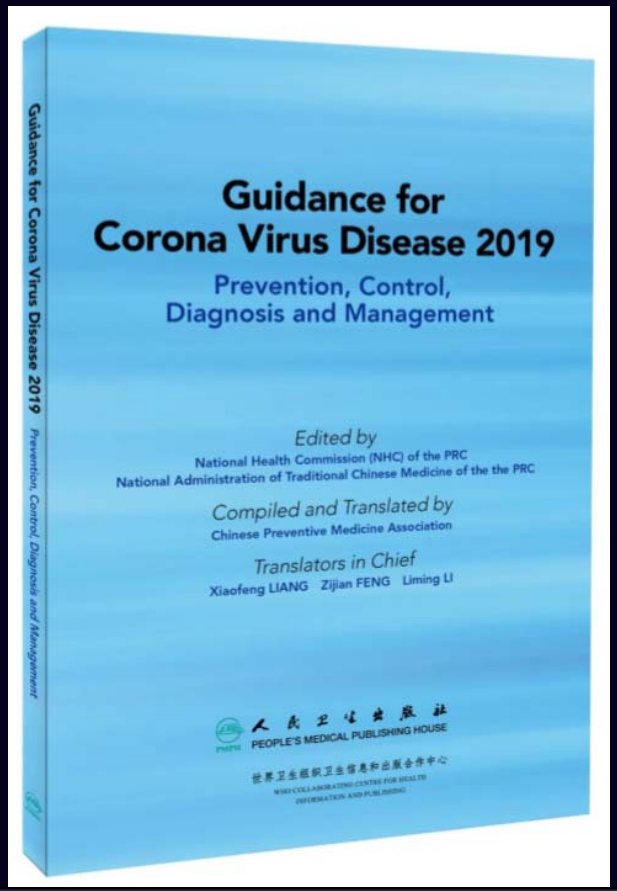
Abstract

Renal fibrosis is highly implicated as a cause of chronic renal failure, for which suitable therapeutics have not yet been developed. Recently, it was reported that Wen-pi-tang-Hab-Wu-ling-san (WHW) extract attenuates epithelial cells undergoing mesenchymal transition in cultured Madin-Darby canine kidney cells. This study investigated whether WHW extract prevents renal fibrosis induced by ischemia/reperfusion (I/R) in mice. Ischemia/reperfusion resulted in kidney fibrosis at 14 days after the procedure. When WHW was administered orally to mice beginning from 2 days after the onset of ischemia

Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Eliminate Toxins Decoction)



- Taiyang
- Yangming
- Shaoyang
- Taiyin
- Shaoyin
- Jueyin

- 英文版全文_新型冠状病毒肺炎防控和诊疗指南
  https://mp.weixin.qq.com/s/nOAmosQ4YqkXHKdJbBE9GA

Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Eliminate Toxins Decoction)

- *Ma Huang Xing Ren Gan Cao Shi Gao Tang* 麻杏甘石湯 (Ephedra, Apricot Kernel, Licorice, Gypsum Decoction)
- *Xiao Chai Hu Tang* 小柴胡湯 (Minor Bupleurum Decoction)
- *She Gan Ma Huang Tang* 射干麻黃湯 (Belamcanda and Ephedra Decoction)
- *Wu Ling San* 五苓散 (Five-Ingredient Powder with Poria)

国家中医药管理局; https://mp.weixin.qq.com/s/0U9tAMdfQfrWZz_43Bc0bg

Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Eliminate Toxins Decoction)

- *Ma Huang* (Herba Ephedrae), 9g
- *Zhi Gan Cao* (Radix et Rhizoma Glycyrrhizae Praeparata cum Melle), 6g
- *Ku Xing Ren* (Semen Armeniacae Amarum), 9g
- *Shi Gao* (Gypsum Fibrosum), 15-30g (pre-decoct)
- *Gui Zhi* (Ramulus Cinnamomi), 9g
- *Ze Xie* (Rhizoma Alismatis), 9g
- *Zhu Ling* (Polyporus), 9g
- *Bai Zhu* (Rhizoma Atractylodis Macrocephalae), 9g
- *Fu Ling* (Poria), 15g
- *Chai Hu* (Radix Bupleuri), 16g
- *Huang Qin* (Radix Scutellariae), 6g
- *Jiang Ban Xia* (Rhizoma Pinelliae Praeparatum cum Zingibere et Alumine), 9g
- *Sheng Jiang* (Rhizoma Zingiberis Recens), 9g
- *Zi Wan* (Radix et Rhizoma Asteris), 9g
- *Kuan Dong Hua* (Flos Farfarae), 9g
- *She Gan* (Rhizoma Belamcandae), 9g
- *Xi Xin* (Radix et Rhizoma Asari), 6g
- *Shan Yao* (Rhizoma Dioscoreae), 12g
- *Zhi Shi* (Fructus Aurantii Immaturus), 6g
- *Chen Pi* (Pericarpium Citri Reticulatae), 6g
- *Guang Huo Xiang* (Herba Pogostemonis), 9g

国家中医药管理局; https://mp.weixin.qq.com/s/0U9tAMdfQfrWZz_43Bc0bg

Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Eliminate Toxins Decoction)

- 701 patients in 10 provinces with Covid-19:
  - 130 recovered and discharged
  - 51 resolution of s/sx
  - 268 improvement of s/sx
  - 212 stabilization of s/sx
  - 94.3% rate of effectiveness

国家中医药管理局; https://mp.weixin.qq.com/s/0U9tAMdfQfrWZz_43Bc0bg

Qing Fei Pai Du Tang 清肺排毒汤 (Clear the Lung and Eliminate Toxins Decoction)

- 1,262 patients with Covid-19
  - 1,253 recovered and discharged (99.28%)
  - None deteriorated from mild/moderate to severe
  - Symptoms and signs resolved within 3-6 days
  - Negative test for Covid-19 within ~10 days
  - Dated April 17, 2020

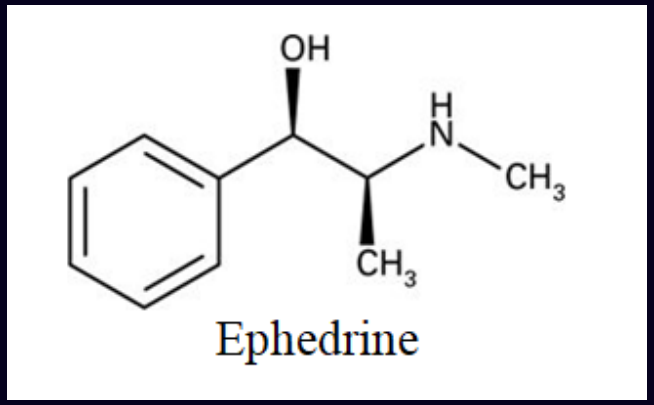
国家中医药管理局; https://mp.weixin.qq.com/s/pNBLQqSoAceAB0WU4DGCIg

Ma Huang (Herba Ephedrae)

- Releases the exterior through diaphoresis
- Relieves wheezing and dyspnea, stops cough
- Regulates water circulation and relieves edema
- Warms and disperses cold

Ma Huang (Herba Ephedrae)

- *Ephedra sinica, Ephedra intermedia, Ephedra equisetina*
  - Ephedrine alkaloids 0.481-2.47% (l-ephedrine, d-pseudoephedrine, l-norephedrine, d-norpseudoephedrine, l-methylephedrine, d-methylpseudoephedrine)



Ephedrine

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Ma Huang (Herba Ephedrae)

- Caution (TCM): *Ma Hua*ng is extremely acrid and warm, and, if used incorrectly, may induce profuse perspiration and damage the qi and yin of the body. Therefore, it should only be used in conditions having all of the following characteristics: wind, cold, exterior, and excess.
- Caution (WM): anorexia, bulimia, glaucoma, hypertension, seizure, epilepsy, convulsion, hyperthyroidism, prostatic enlargement and diabetes mellitus.

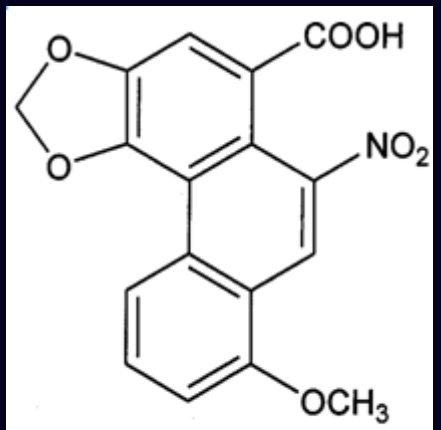
Xi Xin (Radix et Rhizoma Asari)

- Dispels exterior wind-cold
- Warms the lung and resolves phlegm

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Xi Xin (Radix et Rhizoma Asari)

- *Asarum heterotropoides* f. *mandshuricum* (Maxim.) Kitag.
  (北细辛 *Běi Xì Xīn*; 辽细辛 *Liáo Xì Xīn*);
- *Asarum sieboldii* Miq. var. *seoulense* Nakai.
  (汉城细辛 *Hàn Chéng Xì Xīn*);
- *Asarum sieboldii* Miq.
  (华细辛 *Huá Xì Xīn*)



Aristolochic Acid

Xi Xin (Radix et Rhizoma Asari)

- Caution (TCM):
  - *Xi Xin* is contraindicated in patients with febrile disorders, cough due to yin deficiency and Lung heat, headache due to yin deficiency and yang excess, and perspiration from qi deficiency.
  - *Xi Xin* is contraindicated in pregnant women, children, elderly persons, and individuals with underlying weakness and deficiencies.
- Caution (WM):
  - *Xi Xin* is contraindicated in individuals with pre-existing kidney disorders, as it contains a trace amount of aristolochic acids, which is nephrotoxic and carcinogenic.

•Jong, TT et al. Analysis of aristolochic acid in nine sources of Xixin, a traditional Chinese medicine, by liquid chromatography/atmospheric pressure chemical ionization/tandem mass spectrometry. Journal of Pharmaceutical and Biomedical Analysis. Volume 33, Issue 4, 24 November 2003, Pages 831-837.
•*Zhong Yao Du Xing Li Lun Yu An Quan Xing Ping Jia* (Chinese Medicine Toxicity Theory and Safety Evaluation), 2012; 470-474.

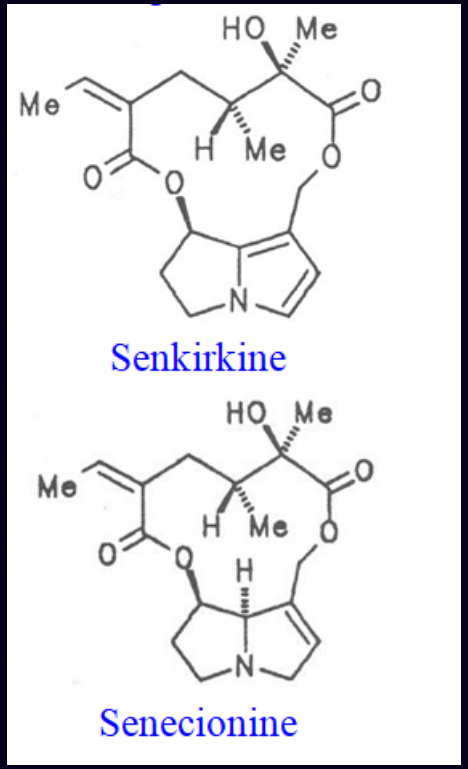
Kuan Dong Hua (Flos Farfarae)

- Moistens the Lung, descends qi, dissolves phlegm, stops cough

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Kuan Dong Hua (Flos Farfarae)

- Pyrrolizidine alkaloids:
  - senkirkine
  - senecionine



Kuan Dong Hua (Flos Farfarae)

- Caution (TCM): Acrid and warm, *Kuan Dong Hua* should be used with caution for patients who have coughing caused by yin deficiency, dryness or heat. *Kuan Dong Hua* should also be used with caution for patients with lung abscesses with pus and blood in the sputum.
- Caution (WM): Pyrrolizidine alkaloids (senkirkine and senecionine) are potentially hepatotoxic and carcinogenic. Therefore, *Kuan Dong Hua* must be used with extreme caution, if at all, in individuals with pre-existing liver disorders.

Zhang Boli *

- *Ma Huang* (Herba Ephedrae) – *Xiang Ru* (Herba Moslae) [3-10g]*
- *Xi Xin* (Radix et Rhizoma Asari) – *Gan Jiang* (Rhizoma Zingiberis) 6g*
- *Kuan Dong Hua* (Flos Farfarae) – *Pi Pa Ye* (Folium Eriobotryae) [6-10]#

* Suggested substitutes by Zhang Boli.
# Suggested substitute by John Chen.

Shang Han

伤寒

(Cold Damage)

Wen Bing

温病

(Warm Disease)


Barnaul
Abakan
RUSSIA
Kyzyl
Irkutsk
Chita
Khabarovsk
SIBERIA
Ulan-Ude
KAZAKHSTAN
Ulaanbaatar
Ulan Bator
Qiqihar
Harbin
MONGOLIA
Almaty
Changchun
Shenyang
Ürümqi
GOBI
Dandong
Ch'ŏng
XINJIANG UYGUR
AUTONOMOUS REGION
Baotou
Beijing
P'yŏngyang
Seoul
SOUTH
KOREA
Xinchuan
Shijiazhuang
Taiyuan
QINGHAI
Xining
Jinan
Mokp'o
Cheju
Lanzhou
Zhengzhou
Yangtze
GANSU
Xi'an
Nanjing
Shanghai
Yushu
CHINA
Chandigarh
Lahore
TIBET
Wuhan
ANHUI
Hangzhou
Delhi
Chengdu
Lhasa
Chongqing
East China Sea
SICHUAN
Changsha
Fuzhou
Taipei
Kathmandu
Patna
Guiyang
T'aichung
Tropic of Cancer
Kunming
Guangzhou
Canton
Bhopāl
Imphāl
YUNNAN
Kaohsiung
Dhaka
Aizawl
INDIA
Chittagong
Hanoi
South
China
Sea
Hyderābād
Bay of
Bengal
MYANMAR
LAOS
Vinh
Haikou
Aparri
95°
100°
105°
110°
115°
120°

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- 温疫论 *Wen Yi Lun* (Discussion of Epidemic Warm Disease), 1642

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- Wu You-Xing lived during the transition from the Ming dynasty to the Qing dynasty, a period dominated by war and characterized by extreme poverty and poor sanitary conditions. As a result, countless epidemics ravaged the country and killed millions of people.

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- At the time, most physicians strictly followed the guidelines of 伤寒 *shang han* (cold damage), and achieved little or no success in treating 温疫 *wen yi* (warm epidemic).

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- Wu observed that *wen yi* (warm epidemic) plagued everyone, starting "from one person to the entire household, from one household to the entire street, and from one street to the entire village."

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- To better understand the patterns of this kind of disease, Wu risked his life by entering affected households and neighborhoods to personally observe and directly treat those who became ill.

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- After years of clinical observation, Wu stated that epidemics such as *wen yi* (warm epidemic) are "***not*** caused by wind, cold, summer-heat, nor dampness, but rather by 戾气 *li qi* (perverse/pestilence qi)."

吴有性 Wū Yǒu-Xìng, 1580's-1660's

- He elaborated that *li qi* existed in the universe, but have "no sound nor smell, and no shape nor shadow." Furthermore, he observed that *li qi* may be transmitted from one person to another via "heaven [air borne]" or "earth [direct contact]," and affect weak, deficient individuals (i.e., those with low immunity).

叶桂 Yè Guì, 1666-1745

- 温热论 *Wen Re Lun* (Discussion of Warm and Hot Disorders)
  - *wei* (defensive) level
  - *qi* (energy) level
  - *ying* (nutritive) level
  - *xue* (blood) level

Yín Qiào Sǎn 銀翹散 (Honeysuckle and Forsythia Powder)

- *Jin Yin Hua* (Flos Lonicerae Japonicae) 30g [15g]
- *Lian Qiao* (Fructus Forsythiae) 30g [15g]
- *Jing Jie Sui* (Spica Schizonepetae) 12g [4g]
- *Dan Dou Chi* (Semen Sojae Praeparatum) 15g [5g]
- *Jie Geng* (Radix Platycodonis) 18g [6g]
- *Niu Bang Zi* (Fructus Arctii) 18g [6g]
- *Bo He* (Herba Menthae) 18g [6g]
- *Zhu Ye* (Herba Phyllostachys) 12g [4g]
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 15g [5g]

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Yín Qiào Sǎn 銀翹散 (Honeysuckle and Forsythia Powder)

- Releases the exterior with acrid and cold herbs
- Clears heat and eliminates toxins

- Onset of *wen bing* (warm disease): fever, aversion to cold, slight aversion to wind, slight or absence of perspiration, headache, thirst, a sore throat, cough, a red tongue tip with a thin, white or thin, yellow tongue coating, and a superficial, rapid pulse.

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Yín Qiào Sǎn 銀翹散 (Honeysuckle and Forsythia Powder)

- Caution: Wind-heat conditions can change rapidly. Optimal treatment requires close monitoring of clinical presentations and immediate adjustment of the herbal treatment.

Jin Yin Hua (Flos Lonicerae Japonicae)
Lian Qiao (Fructus Forsythiae)

Jin Yin Hua (Flos Lonicerae Japonicae)
Lian Qiao (Fructus Forsythiae)

- Clears heat
- Clears heat and eliminates toxins
- Treats diarrhea or dysentery caused by toxic heat
- Clears heat
- Clears heat and eliminates toxins
- Promotes urination

Jin Yin Hua (Flos Lonicerae Japonicae) *Lian Qiao* (Fructus Forsythiae)

- *Jin Yin Hua* has an antiviral effect against various viruses, including influenza virus, echo virus, herpes simplex virus, pseudorabies virus, cytomegalovirus, avian influenza virus, adenovirus, Newcastle virus, human immunodeficiency virus and SARS coronavirus.[1,2] Specifically, one cyclic peroxide from *Jin Yin Hua* shows significant antiviral activities against influenza virus and respiratory syncytial. The homosecoiridoid alkaloids of *Jin Yin Hua* have antiviral activity against the influenza virus H3N2 (A/Hanfang/359/95) and coxsackie virus B_3. The glucosylated caffeoylquinic acid isomers from *Jin Yin Hua* exhibits inhibitory activity against coxsackie virus B_3.

- *Lian Qiao* shows antiviral effect against and influenza virus, coxsackie B virus, echovirus, respiratory syncytial virus, Asian influenza A virus, rhinovirus and others.[1]

- Lu Y, et al. *Zhong Yao Yao Li Xue* (Pharmacology of Chinese Materia Medica). People's Medical Publishing House. 2016; 91-93.
- Chen C, et al. Zhongyao Yaolixue, 2nd Edition. Shanghai Science and Technology Publishing, 2015; 85-87.
- Shen Y, et al. Zhong Yao Yao Li Xue (Pharmacology of Chinese Materia Medica), 2nd Edition. People's Medical Publishing House Co., LTD. 2017; 217-220.
- Li Y, Ooi LS, Wang H, But PP, Ooi VE. Antiviral activities of medicinal herbs traditionally used in southern mainland China. Phytother Res 2004; 18: 718-722.
- Yu DQ, et al. The structure and absolute configuration of Shuangkangsu: a novel natural cyclic peroxide from Lonicera japonica (Thunb.). J Asian Nat Prod Res. 2008 Sep-Oct;10(9-10):851-6.
- Yu Y, et al. Homosecoiridoid alkaloids with amino acid units from the flower buds of Lonicera japonica. J Nat Prod. 2013 Dec 27;76(12):2226-33.
- Yu Y, et al. Glucosylated caffeoylquinic acid derivatives from the flower buds of Lonicera japonica. Acta Pharm Sin B. 2015 May;5(3):210-4.
- Shen Y, et al. Zhong Yao Yao Li Xue (Pharmacology of Chinese Materia Medica), 2nd Edition. People's Medical Publishing House Co., LTD. 2017; 220-223.
- Chen C, et al. Zhongyao Yaolixue, 2nd Edition. Shanghai Science and Technology Publishing, 2015; 87-88.

Jin Yin Hua (Flos Lonicerae Japonicae) *Lian Qiao* (Fructus Forsythiae)

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Science Press

Methodology

In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus

Deng-hai Zhang[a,*], Kun-lun Wu[b], Xue Zhang[a], Sheng-qiong Deng[c], Bin Peng[a]

[a] *Shanghai Health Commission Key Lab of Artificial Intelligence (AI)-Based Management of Inflammation and Chronic Diseases, Sino-French Cooperative Central Lab, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*
[b] *Department of Traditional Chinese Medicine, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*
[c] *Department of Research Affair Management, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*

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Chinese herbal
Pneumonia
Natural compounds
Molecular docking
Network pharmacology

ABSTRACT

Objective: In this study we execute a rational screen to identify Chinese medical herbs that are commonly used in treating viral respiratory infections and also contain compounds that might directly inhibit 2019 novel coronavirus (2019-nCoV), an ongoing novel coronavirus that causes pneumonia.
Methods: There were two main steps in the screening process. In the first step we conducted a literature search for natural compounds that had been biologically confirmed as against sever acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus. Resulting compounds were cross-checked for listing in the Traditional Chinese Medicine Systems Pharmacology Database. Compounds meeting both requirements were subjected to absorption, distribution, metabolism and excretion (ADME) evaluation to verify that oral administration would be effective. Next, a docking analysis was used to test whether the compound had the potential for direct 2019-nCoV protein interaction. In the second step we searched Chinese herbal databases to identify plants containing the selected compounds. Plants containing 2 or more of the compounds identified in our screen were then checked against the catalogue for classic herbal usage. Finally, network pharmacology analysis was used to predict the general *in vivo* effects of each selected herb.
Results: Of the natural compounds screened, 13 that exist in traditional Chinese medicines were also found to have potential anti-2019-nCoV activity. Further, 125 Chinese herbs were found to contain 2 or more of these 13 compounds. Of these 125 herbs, 26 are classically catalogued as treating viral respiratory infections. Network pharmacology analysis predicted that the general *in vivo* roles of these 26 herbal plants were related to regulating viral infection, immune/inflammation reactions and hypoxia response.
Conclusion: Chinese herbal treatments classically used for treating viral respiratory infection might contain direct anti-2019-nCoV compounds.

Please cite this article as: Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. *In silico* screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *J Integr Med*. 2020; 18(2): 152–158.

- *Jin Yin Hua* contains two and *Lian Qiao* contains three compounds that have potential to directly inhibit 2019 novel coronavirus.

Jin Yin Hua (Flos Lonicerae Japonicae) *Lian Qiao* (Fructus Forsythiae)

- *Jin Yin Hua* and *Lian Qiao* interfere with spike protein binding to ACE2 receptor to block viral entry of SARS-CoV.

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Institute for Advanced Research in Asian Science and Medicine
DOI: 10.1142/S0192415X20500378

COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease

Kam Wa Chan,* Vivian Taam Wong† and Sydney Chi Wai Tang*

*Department of Medicine

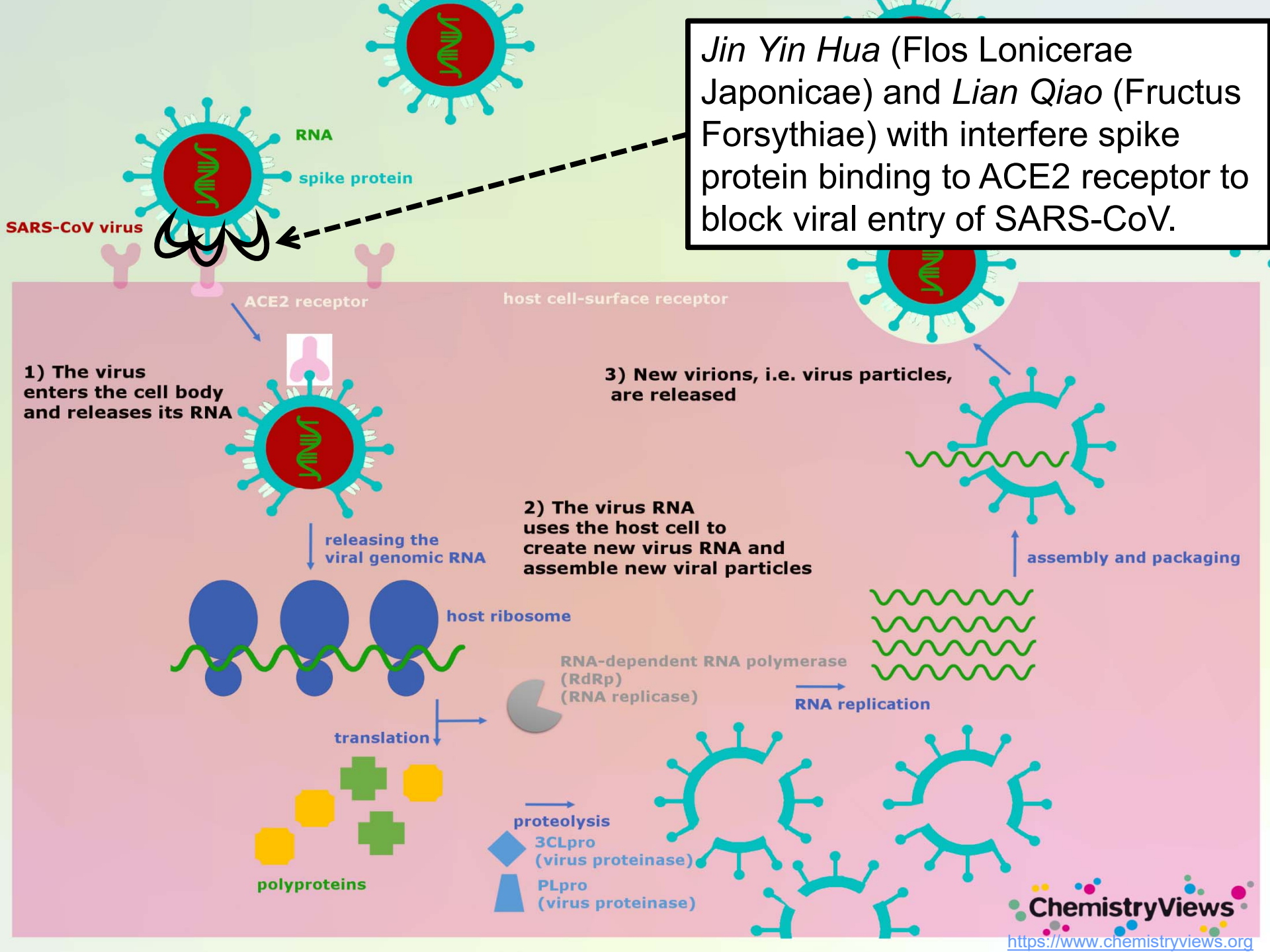
†School of Chinese Medicine

The University of Hong Kong, Hong Kong

Published 13 March 2020

Chan KW, et al. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease. The American Journal of Chinese Medicine, Vol. 48, No. 3, 1–26.

Jin Yin Hua (Flos Lonicerae Japonicae) and *Lian Qiao* (Fructus Forsythiae) with interfere spike protein binding to ACE2 receptor to block viral entry of SARS-CoV.



Small molecules targeting severe acute respiratory syndrome human coronavirus

Chung-Yi Wu*, Jia-Tsrong Jan†‡, Shiou-Hwa Ma†, Chih-Jung Kuo*, Hsueh-Fen Juan§, Yih-Shyun E. Cheng*, Hsien-Hua Hsu*, Hsuan-Cheng Huang*, Douglass Wu¶, Ashraf Brik¶, Fu-Sen Liang¶, Rai-Shung Liu‖, Jim-Min Fang*,**, Shui-Tein Chen*, Po-Huang Liang*, and Chi-Huey Wong*¶††

*Genomics Research Center and Institute of Biological Chemistry, Academia Sinica, Taipei 115, Taiwan; †Institute of Preventive Medicine, National Defense Medical Center, National Defense University, Taipei 114, Taiwan; §Department of Chemical Engineering, National Taipei University of Technology, Taipei 106, Taiwan; **Department of Chemistry, National Taiwan University, Taipei 106, Taiwan; ¶Department of Chemistry and The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, CA 92037; and ‖Department of Chemistry, National Tsing Hua University, Hsinchu 300, Taiwan

Contributed by Chi-Huey Wong, May 26, 2004

Severe acute respiratory syndrome (SARS) is an infectious disease caused by a novel human coronavirus. Currently, no effective antiviral agents exist against this type of virus. A cell-based assay, with SARS virus and Vero E6 cells, was developed to screen existing drugs, natural products, and synthetic compounds to identify effective anti-SARS agents. Of >10,000 agents tested, 50 compounds were found active at 10 μ[illegible] are existing drugs (Reserpine 13[illegible] in clinical development. These 5[illegible] again, and compounds 2–6, 10, ar[illegible] 50% inhibitory concentrations for[illegible] (EC_{50}) and host growth (CC_{50}) we[illegible] tivity index ($SI = CC_{50}/EC_{50}$) was[illegible] ELISA, and SI for Reserpine, Aesc[illegible] (SI = 7.3), 6.0 μM (SI = 2.5), and[illegible] Additional studies were carried[illegible] mode of action of some active co[illegible] ern blot analysis, immunofluorescence and flow cytometry assays, and inhibition against the 3CL protease and viral entry. Of particular interest are the two anti-HIV agents, one as an entry blocker and the other as a 3CL protease inhibitor ($K_i = 0.6$ μM).

Severe acute respiratory syndrome (SARS) is an acute respiratory illness caused by infection with a novel human coro-

Materials and Methods

The agents tested in this study include ≈200 drugs approved by the Food and Drug Administration, >8,000 synthetic compounds, ≈1,000 traditional Chinese herbs, and ≈500 protease inhibitors.

[illegible] in DMSO to 10 mM and trans-[illegible]ates to assay for antiviral activity [illegible] SARS-virus-mediated cytopathic [illegible]e studies were done by cytotoxic-[illegible]ISA, Western blot analysis, flow [illegible]xpression with SARS-CoV-spike [illegible]tibodies, and protease inhibition.

[illegible]S-CoV Compounds. Vero E6 cells [illegible]red in a 96-well plate in DMEM [illegible]The culture medium was removed after a 1-day incubation when the cells reached 80–90% confluence. A solution of 100 μl of DMEM, with 2% FBS containing the compound to be tested, was placed in three wells. Cells were incubated in a CO_2 incubator at 37°C for 2 h and inoculated with SARS-CoV (H.K. strain) at a dose of 100 $TCID_{50}$ per well; the cytopathic morphology of the cells was examined by using an inverted microscope 72 h after infection.

- *Jin Yin Hua* (Flos Lonicerae Japonicae) inhibits SARS-CoV replication.

Sāng Jú Yĭn 桑菊飲 (Mulberry Leaf and Chrysanthemum Decoction)

- *Sang Ye* (Folium Mori) 7.5g
- *Ju Hua* (Flos Chrysanthemi) 3g
- *Bo He* (Herba Menthae) 2.4g
- *Lian Qiao* (Fructus Forsythiae) 4.5g
- *Jie Geng* (Radix Platycodonis) 6g
- *Ku Xing Ren* (Semen Armeniacae Amarum) 6g
- *Lu Gen* (Rhizoma Phragmitis) 6g
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 2.4g

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Sāng Jú Yǐn 桑菊飲 (Mulberry Leaf and Chrysanthemum Decoction)

- Dispels wind and clears heat
- Ventilates the Lung and arrests coughing

- Early stage of wind-warmth syndrome: cough, mild fever, and slight thirst.

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Sāng Jú Yǐn 桑菊飲 (Mulberry Leaf and Chrysanthemum Decoction)

- Antipyretic
- Anti-inflammatory

- *Zhong Yao Tong Bao* (Journal of Chinese Herbology) 1986;11(1):51.
- *Zhong Yao Yao Li Yu Ying Yong* (Pharmacology and Applications of Chinese Herbs) 1993;(1):1.

Sang Ye (Folium Mori)
Ju Hua (Flos Chrysanthemi)

Sang Ye (Folium Mori)
Ju Hua (Flos Chrysanthemi)

- Dispels wind-heat
- Clears Lung heat and moistens dryness
- Calms the Liver and brightens the eyes
- Cools the blood and stops bleeding

- Dispels wind-heat
- Clears the Liver and benefits the eyes
- Calms Liver yang
- Clears heat and eliminates toxins

Sang Ye (Folium Mori)
Ju Hua (Flos Chrysanthemi)

- Antibacterial
- Anti-inflammatory

- Antibacterial
- Antiviral
- Antipyretic

Sang Ye (Folium Mori) *Ju Hua* (Flos Chrysanthemi)

Journal of Integrative Medicine 18 (2020) 152–158

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Science Press

Methodology

In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus

Deng-hai Zhang [a,*], Kun-lun Wu [b], Xue Zhang [a], Sheng-qiong Deng [c], Bin Peng [a]

[a] *Shanghai Health Commission Key Lab of Artificial Intelligence (AI)-Based Management of Inflammation and Chronic Diseases, Sino-French Cooperative Central Lab, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*
[b] *Department of Traditional Chinese Medicine, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*
[c] *Department of Research Affair Management, Shanghai Pudong Gongli Hospital, Secondary Military Medical University, Shanghai 200135, China*

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ABSTRACT

Objective: In this study we execute a rational screen to identify Chinese medical herbs that are commonly used in treating viral respiratory infections and also contain compounds that might directly inhibit 2019 novel coronavirus (2019-nCoV), an ongoing novel coronavirus that causes pneumonia.
Methods: There were two main steps in the screening process. In the first step we conducted a literature search for natural compounds that had been biologically confirmed as against sever acute respiratory syndrome coronavirus or Middle East respiratory syndrome coronavirus. Resulting compounds were cross-checked for listing in the Traditional Chinese Medicine Systems Pharmacology Database. Compounds meeting both requirements were subjected to absorption, distribution, metabolism and excretion (ADME) evaluation to verify that oral administration would be effective. Next, a docking analysis was used to test whether the compound had the potential for direct 2019-nCoV protein interaction. In the second step we searched Chinese herbal databases to identify plants containing the selected compounds. Plants containing 2 or more of the compounds identified in our screen were then checked against the catalogue for classic herbal usage. Finally, network pharmacology analysis was used to predict the general *in vivo* effects of each selected herb.
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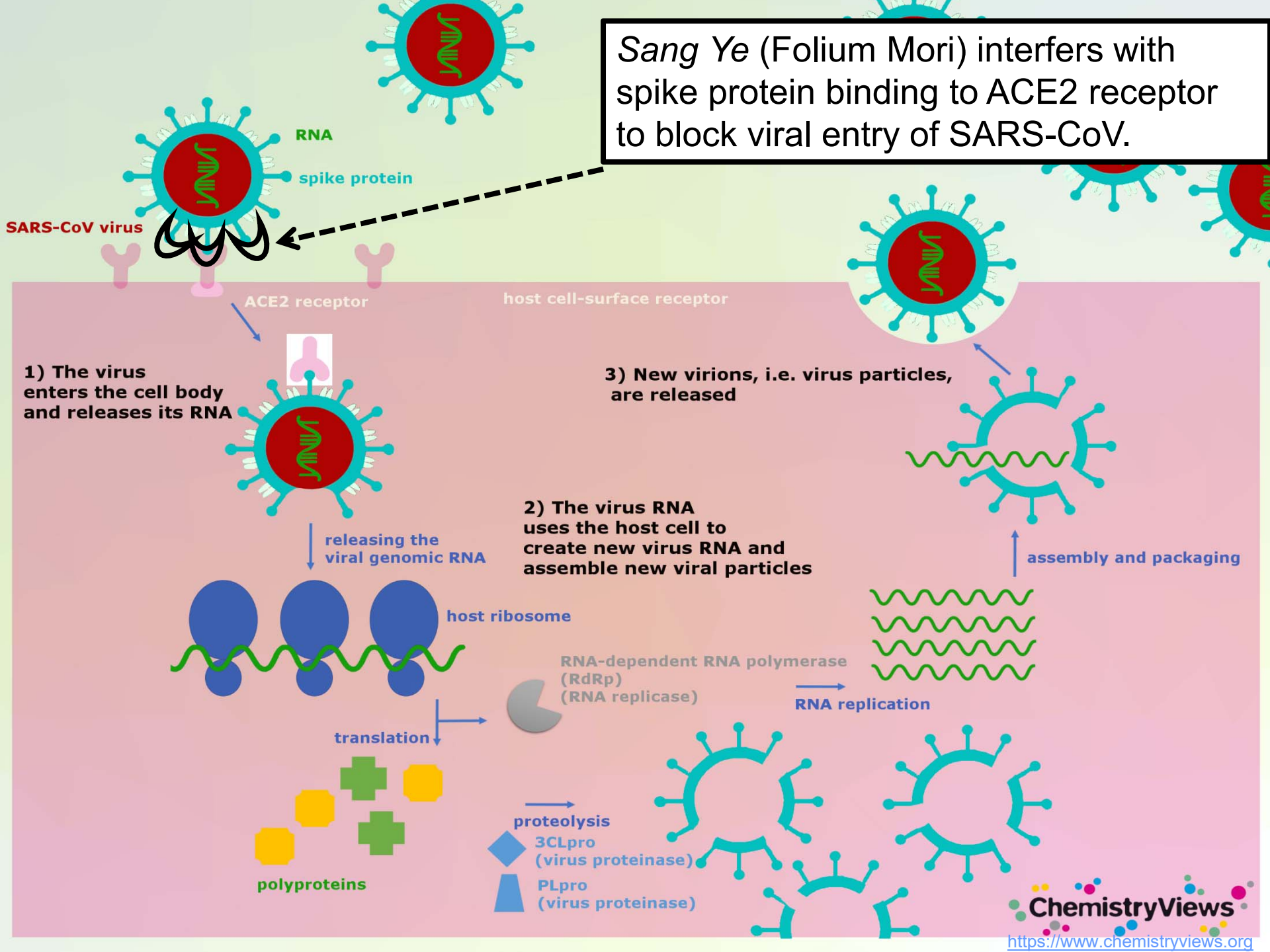
Conclusion: Chinese herbal treatments classically used for treating viral respiratory infection might contain direct anti-2019-nCoV compounds.

Please cite this article as: Zhang DH, Wu KL, Zhang X, Deng SQ, Peng B. *In silico* screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. *J Integr Med.* 2020; 18(2): 152–158.

- *Sang Ye* and *Ju Hua* each contains two compounds that have potential to directly inhibit 2019 novel coronavirus.

Sang Ye (Folium Mori) interfers with spike protein binding to ACE2 receptor to block viral entry of SARS-CoV.



Qīng Wēn Bài Dú Yǐn 清瘟敗毒飲 (Clear Epidemics and Overcome Toxin Decoction)

- *Huang Lian* (Rhizoma Coptidis)
- *Huang Qin* (Radix Scutellariae)
- *Zhi Zi* (Fructus Gardeniae)
- *Shi Gao* (Gypsum Fibrosum)
- *Zhi Mu* (Rhizoma Anemarrhenae)
- *Shui Niu Jiao* (Cornu Bubali)
- *Di Huang* (Radix Rehmanniae)
- *Chi Shao* (Radix Paeoniae Rubra)
- *Mu Dan Pi* (Cortex Moutan)
- *Lian Qiao* (Fructus Forsythiae)
- *Xuan Shen* (Radix Scrophulariae)
- *Zhu Ye* (Herba Phyllostachys), fresh
- *Jie Geng* (Radix Platycodonis)
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae)

Original Source: *Yi Zhen Yi De* (Achievements Regarding Epidemic Rashes) by Yu Shi-Yu in 1794

Qīng Wēn Bài Dú Yǐn 清瘟敗毒飲 (Clear Epidemics and Overcome Toxin Decoction)

- Clears heat and eliminates toxins
- Purges fire and cools the blood
- *Wen yi* (warm epidemics) characterized by excess heat and toxins in the *qi* (energy) and *xue* (blood) levels: high fever, extreme thirst, splitting headaches, dry heaves, mania, delirium, blurred vision, maculae, hematemesis, epistaxis, extreme coldness or convulsions of the four extremities, scorched lips, a dark red tongue body with dry or prickly tongue coating. The pulse may be any of the following: deep and rapid; deep, fine and rapid; or superficial, big and rapid.

Huang Lian (Rhizoma Coptidis)
Huang Qin (Radix Scutellariae)

Huang Lian (Rhizoma Coptidis)
Huang Qin (Radix Scutellariae)

- Clears Heat and Dries Dampness
- Sedates Fire, Eliminates Toxins

- Clears heat and dries dampness
- Clears heat and sedates fire
- Clears heat and eliminates toxins
- Calms and stabilizes the fetus

Huang Lian (Rhizoma Coptidis)
Huang Qin (Radix Scutellariae)

- Antibacterial
- Antitoxin
- Antiviral
- Antifungal and antiparasitic
- Anti-inflammatory
- Antidiarrheal

- Antibacterial
- Antitoxin
- Antiviral
- Antifungal
- Antiparasitic
- Anti-inflammatory

ELSEVIER

Journal of Clinical Virology 31 (2004) 69–75

JOURNAL OF CLINICAL VIROLOGY

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Short communication

In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds

F. Chen [a], K.H. Chan [b], Y. Jiang [c], R.Y.T. Kao [b], H.T. Lu [a], K.W. Fan [a], V.C.C. Cheng [b], W.H.W. Tsui [b], I.F.N. Hung [b], T.S.W. Lee [b], Y. Guan [b], J.S.M. Peiris [b], K.Y. Yuen [b,*]

[a] *Centre for Research in Plant Drugs Development, Department of Botany, The University of Hong Kong, Pokfulam Road, Hong Kong*
[b] *Division of Infectious Diseases, Department of Microbiology, The University of Hong Kong, University Pathology Building, Queen Mary Hospital, Hong Kong*
[c] *Department of Biology, Hong Kong Baptist University, Kowloon Tong, Hong Kong*

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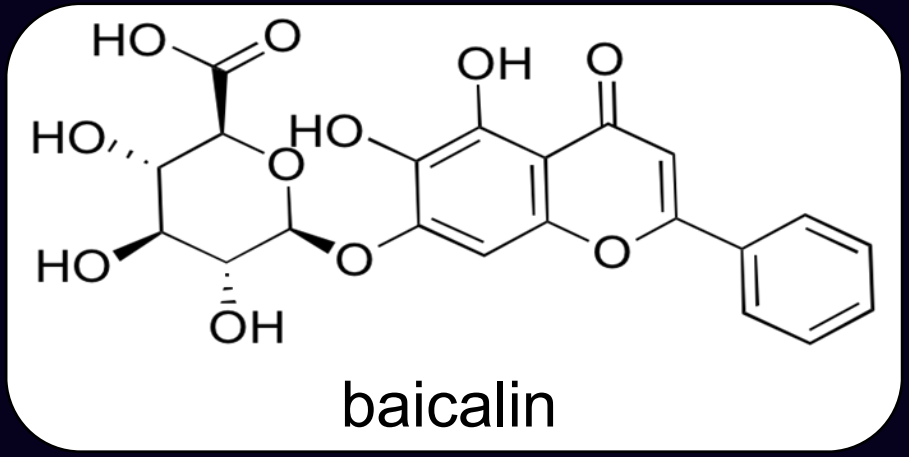
Abstract

Effective antiviral agents are urgently needed to combat the possible return of severe acute respiratory syndrome (SARS). Commercial antiviral agents and pure chemical compounds extracted from traditional Chinese medicinal herbs were screened against 10 clinical isolates of SARS coronavirus by neutralisation tests with confirmation by plaque reduction assays. Interferon-beta-1a, leukocytic interferon-alpha, ribavirin, lopinavir, rimantadine, baicalin and glycyrrhizin showed antiviral activity. The two interferons were only active if the cell lines were pre-incubated with the drugs 16 h before viral inoculation. Results were confirmed by plaque reduction assays. Antiviral activity varied with the use of different cell lines. Checkerboard assays for synergy were performed showing combinations of interferon beta-1a or leukocytic interferon-alpha with ribavirin are synergistic. Since the clinical and toxicity profiles of these agents are well known, they should be considered either singly or in combination for prophylaxis or treatment of SARS in randomised placebo controlled trials in future epidemics.

Huang Qin (Radix Scutellariae)

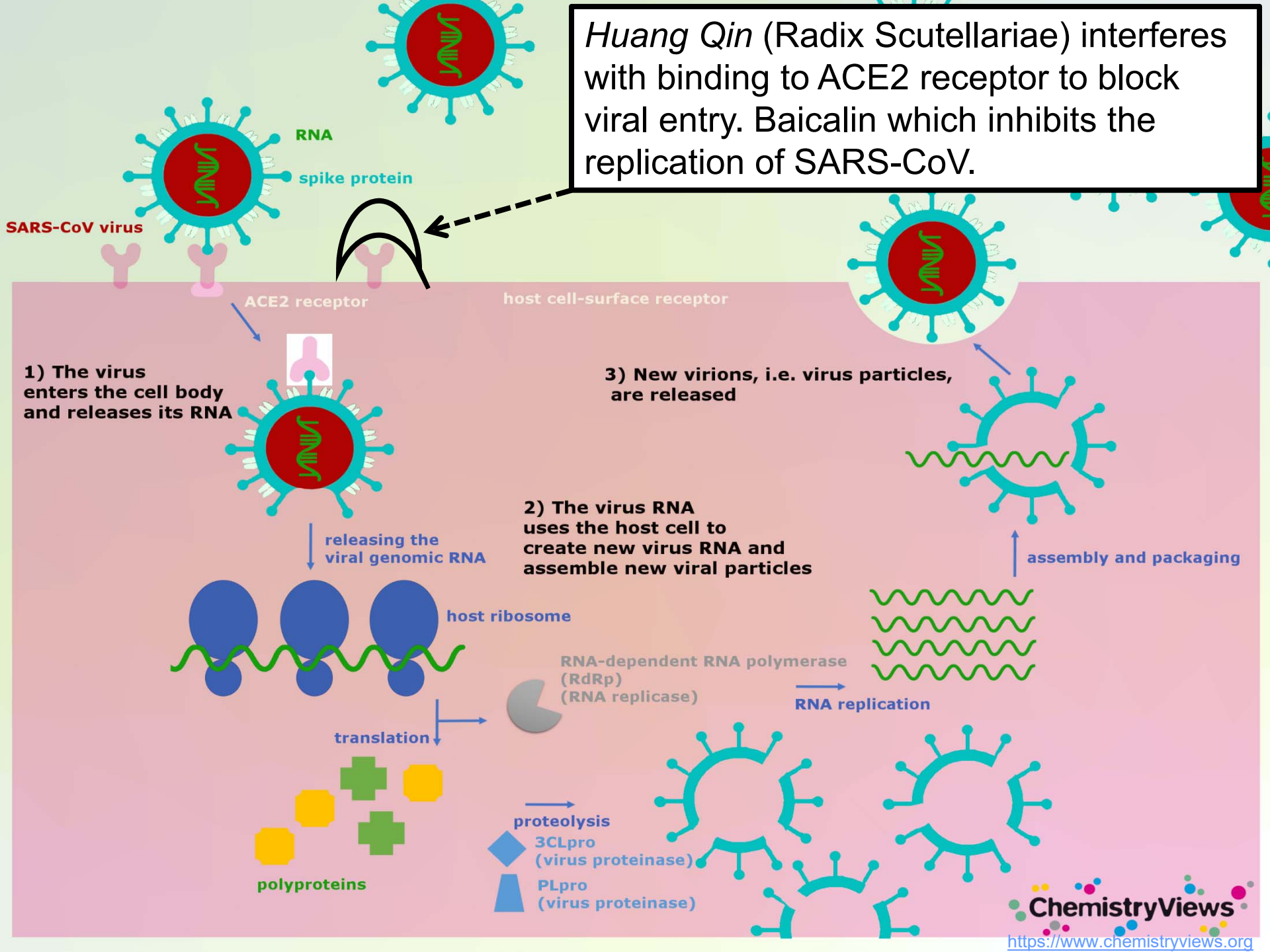
- *Huang Qin* contains baicalin which inhibits the replication of SARS-CoV.



baicalin

F. Chen, et al. Short communication In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. Journal of Clinical Virology 31 (2004) 69–75.

Huang Qin (Radix Scutellariae) interferes with binding to ACE2 receptor to block viral entry. Baicalin which inhibits the replication of SARS-CoV.



Gān Lù Xiāo Dú Dān 甘露消毒丹 (Sweet Dew Special Pill to Eliminate Toxin)

- *Hua Shi* (Talcum), *shui fei* (refined with water) 450g [15g]
- *Yin Chen* (Herba Artemisiae Scopariae) 330g [11g]
- *Huang Qin* (Radix Scutellariae) 300g [10g]
- *Shi Chang Pu* (Rhizoma Acori Tatarinowii) 180g [6g]
- *Dou Kou* (Fructus Amomi Rotundus) 120g [4g]
- *Guang Huo Xiang* (Herba Pogostemon) 120g [4g]
- *She Gan* (Rhizoma Belamcandae) 120g [4g]
- *Bo He* (Herba Menthae) 120g [4g]
- *Chuan Bei Mu* (Bulbus Fritillariae Cirrhosae) 150g [5g]
- *Mu Tong* (Caulis Akebiae) 150g [5g]
- *Lian Qiao* (Fructus Forsythiae) 120g [4g]

Original Source: *Xu Ming Yi Lei An* (Continuation of Famous Physicians' Cases Organized by Categories) by Wei Zhi-Xiu in 1770

Gān Lù Xiāo Dú Dān 甘露消毒丹 (Sweet Dew Special Pill to Eliminate Toxin)

- Resolves dampness and dissolves turbidity
- Clears heat and eliminates toxins
-
- Damp-warmth febrile disorder or epidemic diseases affecting the *qi* (energy) level: fever, lethargy, chest oppression, abdominal fullness, soreness of the extremities, sore throat, swelling of the lower cheeks, yellow discoloration of the skin, vomiting, diarrhea, thirst, scanty, dark, turbid urine, and a pale and white, a thick and greasy, or a dry and yellow tongue coating.

Guang Huo Xiang (Herba Pogostemon)

- Dispels damp, releases the exterior and relieves summer-damp
- Relieves nausea and vomiting
- Treats fungal infection

Guang Huo Xiang (Herba Pogostemon)

- Antibacterial
- Antiviral
- Antifungal
- Analgesic and anti-inflammatory
- Antipyretic
- Gastrointestinal

药学学报 Acta Pharmaceutica Sinica 2020, 55(3): 374 −383

基于网络药理学和分子对接技术初步探索“清肺排毒汤”抗新型冠状病毒肺炎作用机制

吴 昊[1#], 王佳琪[1#], 杨雨薇[1], 李天怡[1], 曹一佳[1], 曲玉霞[1], 靳玉洁[2], 张晨宁[1,2*], 孙毅坤[1*]

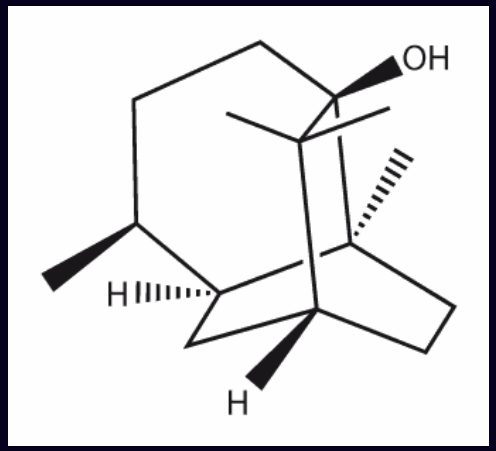
(1. 北京中医药大学中药学院, 北京 102488; 2. 十堰市太和医院, 湖北医药学院附属医院, 湖北 十堰 442000)

摘要: 利用中药网络药理学和分子对接技术初步探索“清肺排毒汤”抗新型冠状病毒肺炎 (coronavirus disease 2019, COVID-19) 作用机制。结合中国药典 (2015 版) 以及中药系统药理学数据库及分析平台 (Traditional Chinese Medicine Systems Pharmacology, TCMSP)、OMIM (Online Mendelian Inheritance in Man)、GeneCard、STRING 等在线数据库, 进行一系列网络构建、核心靶点筛选以及信号通路富集分析, 最后对重要化合物进行分子对接预测。结果发现, 清肺排毒汤化合物−肺炎靶点网络包含 292 个化合物和相应靶点 214 个, 核心靶点涉及 AKT1 (AKT serine/threonine kinase 1)、IL6 (interleukin 6)、MAPK8 (mitogen-activated protein kinase 8)、MAPK1 (mitogen-activated protein kinase 1) 和 JUN (jun proto-oncogene) 等。应用 GO (Gene Ontology) 数据库功能富集分析得到 858 个 GO 条目, 应用 KEGG (Kyoto Encyclopedia of Genes and Genomes) 数据库富集筛选得到 122 条有关通路, 其中包含低氧诱导因子-1 (hypoxia inducible factor-1, HIF-1) 通路、Toll 样受体 (Toll-like receptors, TLRs) 通路等已报道与肺炎相关的通路, 也包括 T 细胞受体 (T-cell receptor, TCR) 通路等与肺损伤保护相关的通路。分子对接结果显示, 清肺排毒汤中药材部分核心化合物对新型冠状病毒 (2019-nCoV) 的 3C 类似蛋白酶 (3C-like protease, 3CLpro) 和血管紧张素转换酶 2 (angiotensin-converting enzyme 2, ACE2) 蛋白具有一定的亲和力。本文初步探索了清肺排毒汤抗 COVID-19 的作用机制, 且预测了其药效物质基础, 期待本结果能为进一步确证清肺排毒汤抗 COVID-19 有效成分和作用机制提供帮助。

Wu H et al. Preliminary exploration of the mechanism of Qingfei Paidu decoction against novel coronavirus pneumonia based on network pharmacology and molecular docking technology. Acta Pharmaceutica Sinica 2020, 55(3): 374 −383

Guang Huo Xiang (Herba Pogostemon)

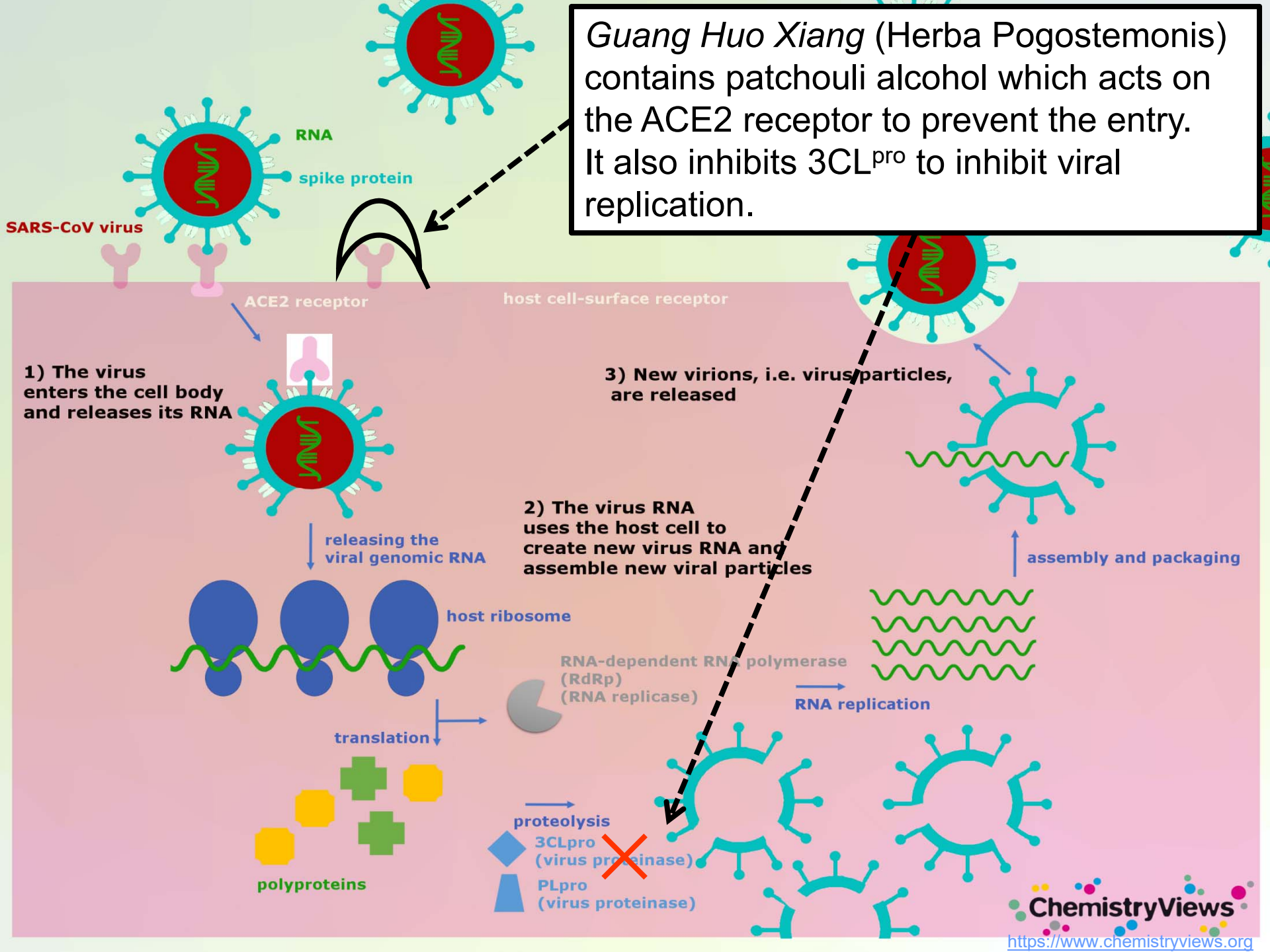
- Patchouli alcohol acts on the ACE2 receptor to prevent the entry, and inhibits the $3CL^{pro}$ enzyme activities to suppress the replication, of 2019-nCoV.



Patchouli Alcohol

Wu H et al. Preliminary exploration of the mechanism of Qingfei Paidu decoction against novel coronavirus pneumonia based on network pharmacology and molecular docking technology. Acta Pharmaceutica Sinica 2020, 55(3): 374 −383

Guang Huo Xiang (Herba Pogostemonis) contains patchouli alcohol which acts on the ACE2 receptor to prevent the entry. It also inhibits $3CL^{pro}$ to inhibit viral replication.



Pǔ Jì Xiāo Dú Yǐn 普濟消毒飲 (Universal Benefit Decoction to Eliminate Toxin)

- *Huang Qin* (Radix Scutellariae), *chao* (dry-fried) with liquor 15g
- *Huang Lian* (Rhizoma Coptidis), *chao* (dry-fried) with liquor 15g
- *Niu Bang Zi* (Fructus Arctii) 3g
- *Lian Qiao* (Fructus Forsythiae) 3g
- *Bo He* (Herba Menthae) 3g
- *Jiang Can* (Bombyx Batryticatus) 2.1g
- *Xuan Shen* (Radix Scrophulariae) 6g
- *Ma Bo* (Lasiosphaera seu Calvatia) 3g
- *Ban Lan Gen* (Radix Isatidis) 3g
- *Jie Geng* (Radix Platycodonis) 6g
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 6g
- *Chen Pi* (Pericarpium Citri Reticulatae) 6g
- *Sheng Ma* (Rhizoma Cimicifugae) 2.1g
- *Chai Hu* (Radix Bupleuri) 6g
- *Ren Shen* (Radix et Rhizoma Ginseng) 9g [3g]

Original Source: *Dong Heng Shi Xiao Fang* (Tested and Effective Formulas by Dong Heng) by Li Gao (also known as Li Dong-Heng) in 1266

Pǔ Jì Xiāo Dú Yǐn 普濟消毒飲 (Universal Benefit Decoction to Eliminate Toxin)

- Clears heat and eliminates toxin
- Dispels wind and disperses pathogenic factors
-
- *Da tou wen* (swollen head epidemic) with the presence of wind, heat, and toxin in the upper *jiao* and head: redness, swelling and pain of the face and head; red and swollen eyes, difficulty in opening the eyes; fever, aversion to cold, a sore throat, thirst, a dry, red tongue with a yellow tongue coating, and a rapid, forceful pulse.

Ban Lan Gen (Radix Isatidis)
Da Qing Ye (Folium Isatidis)

Ban Lan Gen (Radix Isatidis)
Da Qing Ye (Folium Isatidis)

- Clears heat, eliminates toxins, cools blood and benefits the throat
- Clears heat and eliminates toxins
- Cools blood and eliminates maculae

Ban Lan Gen (Radix Isatidis)
Da Qing Ye (Folium Isatidis)

- Antibacterial
- Antitoxin
- Antiviral
- Anti-inflammatory

- Antibacterial
- Antitoxin
- Antiviral
- Antifungal
- Anti-inflammatory

Ban Lan Gen (Radix Isatidis)

- **Antiviral**: *Ban Lan Gen* exerts antiviral effect against influenza A virus, seasonal influenza virus, human or avian influenza virus, novel swine-originating influenza virus, Japanese encephalitis virus, adenovirus, herpes simplex virus, mumps virus, hepatitis B virus, human cytomegalovirus, coxsackie virus, and SARS coronavirus.[,] The hot water extract of *Ban Lan Gen* exerts antiviral activities against influenza A and B viruses by inhibiting the hemagglutination to prevent infection. In addition, *Ban Lan Gen* affects the attachment of influenza virus by interfering with the viral particles, thereby preventing the binding of the virus to the host cell surface. Specifically, indirubin has significant cytotoxicity on swine pseudorabies virus, and an inhibitory effect against influenza virus infection in the human bronchial epithelial cells. Isatindigotindolosides shows antiviral activity against influenza virus. Isoformononetein exhibits antiviral activity against the influenza virus, the herpes simplex virus and coxsackie virus B_3. Isatindigobisindolosides exhibit antiviral activity against both the influenza virus and coxsackie virus B_3. Clemastanin B inhibits different subtypes of human and avian influenza viruses. Lastly, sinigrin, indigo and beta-sitosterol exhibit direct effect to inhibit 3C-like protease ($3CL^{Pro}$) to inhibit replication of SARS coronavirus.

- Chen C, et al. Zhongyao Yaolixue, 2nd Edition. Shanghai Science and Technology Publishing, 2015; 88-90.
- Mei Q, et al. *Xian Dai Zhong Yao Yao Yu Li Lin Chuan Ying Yong Shou Ce* (Handbook of Pharmacology and Clinical Application of Modern Chinese Medicine), 3rd edition. 2016; 144-146.
- Yang ZF, et al. The effects of a hot water soluble extract (S-03) isolated from Isatis indigotica root on influenza A and B viruses in vitro. Bing Du Xue Bao. 2011 May;27(3):218-23.
- Yang Z, et al. In vitro inhibition of influenza virus infection by a crude extract from Isatis indigotica root resulting in the prevention of viral attachment. Mol Med Report. 2012 Mar;5(3):793-9.
- Hsuan SL, et al. The cytotoxicity to leukemia cells and antiviral effects of Isatis indigotica extracts on pseudorabies virus. J Ethnopharmacol. 2009 May 4;123(1):61-7. Epub 2009 Mar 4.
- Mak NK, et al. Inhibition of RANTES expression by indirubin in influenza virus-infected human bronchial epithelial cells. Biochem Pharmacol. 2004 Jan 1;67(1):167-74.
- Liu YF, et al. Indole alkaloid glucosides from the roots of Isatis indigotica. J Asian Nat Prod Res. 2016;18(1):1-12.
- Wang XL, et al. Chemical consitituents from root of Isatis indigotica. Zhongguo Zhong Yao Za Zhi. 2013 Apr;38(8):1172-82.
- Liu YF, et al. Antiviral glycosidic bisindole alkaloids from the roots of Isatis indigotica. J Asian Nat Prod Res. 2015;17(7):689-704.
- Yang Z, et al. Antiviral activity of Isatis indigotica root-derived clemastanin B against human and avian influenza A and B viruses in vitro. Int J Mol Med. 2013 Apr;31(4):867-73.
- Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, et al. AntiSARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res 2005; 68: 36-42.

Da Qing Ye (Folium Isatidis)

- **Antiviral**: *Da Qing Ye* has antiviral effect against influenza A virus, Japanese encephalitis virus, adenovirus, herpes simplex virus 1 and 2, hepatitis B virus and coxsackie virus. In addition, *Da Qing Ye* extract exhibits antiviral effect against SARS-CoV and SARS-CoV-2 by inhibiting 3-chymotrypsin-like protease (3CLpro) to stop the replication of the virus. ,

- Chen C, et al. Zhongyao Yaolixue, 2nd Edition. Shanghai Science and Technology Publishing, 2015; 88-90.
- Yang Y et al.Review Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective. International Journal of Biological Sciences 2020; 16(10): 1708-1717.
- Lin CW, et al. Anti-SARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res. 2005; 68: 36-42.

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Antiviral Research 68 (2005) 36–42
Antiviral Research
www.elsevier.com/locate/antiviral

Anti-SARS coronavirus 3C-like protease effects of *Isatis indigotica* root and plant-derived phenolic compounds

Cheng-Wen Lin [a,b,*], Fuu-Jen Tsai [c,*], Chang-Hai Tsai [c], Chien-Chen Lai [c], Lei Wan [c], Tin-Yun Ho [d], Chang-Chi Hsieh [e], Pei-Dawn Lee Chao [f]

[a] *Department of Medical Laboratory Science and Biotechnology, China Medical University, No. 91, Hsueh-Shih Road, Taichung 404, Taiwan, ROC*
[b] *Clinical Virology Laboratory, Department of Laboratory Medicine, China Medical University Hospital, Taichung 404, Taiwan, ROC*
[c] *Department of Medical Genetics and Medical Research, China Medical University Hospital, Taichung 404, Taiwan, ROC*
[d] *Institute of Chinese Medical Science, China Medical University, Taichung 404, Taiwan, ROC*
[e] *Institute of Integration Chinese and Western Medicine, China Medical University, Taichung 404, Taiwan, ROC*
[f] *Department of Pharmacy, China Medical University, Taichung 404, Taiwan, ROC*

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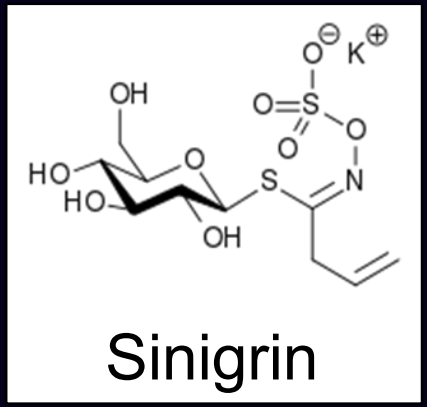
Abstract

The 3C-like protease ($3CL^{pro}$) of SARS-coronavirus mediates the proteolytic processing of replicase polypeptides 1a and 1ab into functional proteins, becoming an important target for the drug development. In this study, *Isatis indigotica* root extract, five major compounds of *I. indigotica* root, and seven plant-derived phenolic compounds were tested for anti-SARS-CoV $3CL^{pro}$ effects using cell-free and cell-based cleavage assays. Cleavage assays with the $3CL^{pro}$ demonstrated that IC_{50} values were in micromolar ranges for *I. indigotica* root extract, indigo, sinigrin, aloe emodin and hesperetin. Sinigrin (IC_{50}: 217 μM) was more efficient in blocking the cleavage processing of the $3CL^{pro}$ than indigo (IC_{50}: 752 μM) and beta-sitosterol (IC_{50}: 1210 μM) in the cell-based assay. Only two phenolic compounds aloe emodin and hesperetin dose-dependently inhibited cleavage activity of the $3CL^{pro}$, in which the IC_{50} was 366 μM for aloe emodin and 8.3 μM for hesperetin in the cell-based assay.

Ban Lan Gen (Radix Isatidis)

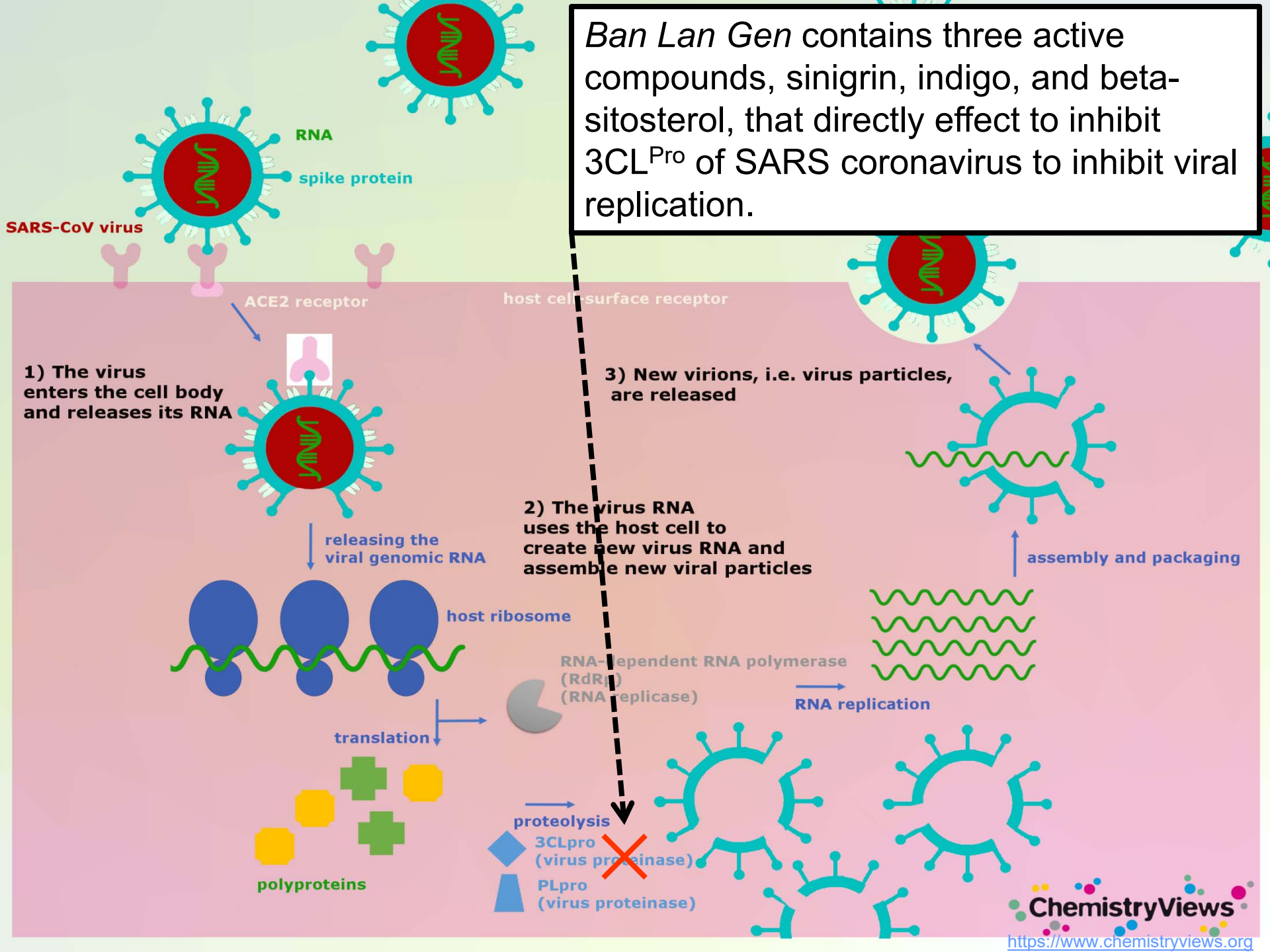
- *Ban Lan Gen* contains three active compounds, sinigrin, indigo, and beta-sitosterol, that directly effect to inhibit 3C-like protease ($3CL^{Pro}$) of SARS coronavirus.



Sinigrin

- Lin CW, Tsai FJ, Tsai CH, Lai CC, Wan L, Ho TY, et al. AntiSARS coronavirus 3C-like protease effects of Isatis indigotica root and plant-derived phenolic compounds. Antiviral Res 2005; 68: 36-42.

Ban Lan Gen contains three active compounds, sinigrin, indigo, and beta-sitosterol, that directly effect to inhibit $3CL^{Pro}$ of SARS coronavirus to inhibit viral replication.



Dá Yuán Yǐn 達原飲 (Reach the Membrane Source Decoction)

- *Bing Lang* (Semen Arecae) 6g
- *Hou Po* (Cortex Magnoliae Officinalis) 3g
- *Cao Guo* (Fructus Tsaoko) 1.5g
- *Zhi Mu* (Rhizoma Anemarrhenae) 3g
- *Bai Shao* (Radix Paeoniae Alba) 3g
- *Huang Qin* (Radix Scutellariae) 3g
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 1.5g

Original Source: *Wen Yi Lun* (Discussion of Epidemic Warm Disease) by Wu You-Xing in 1642

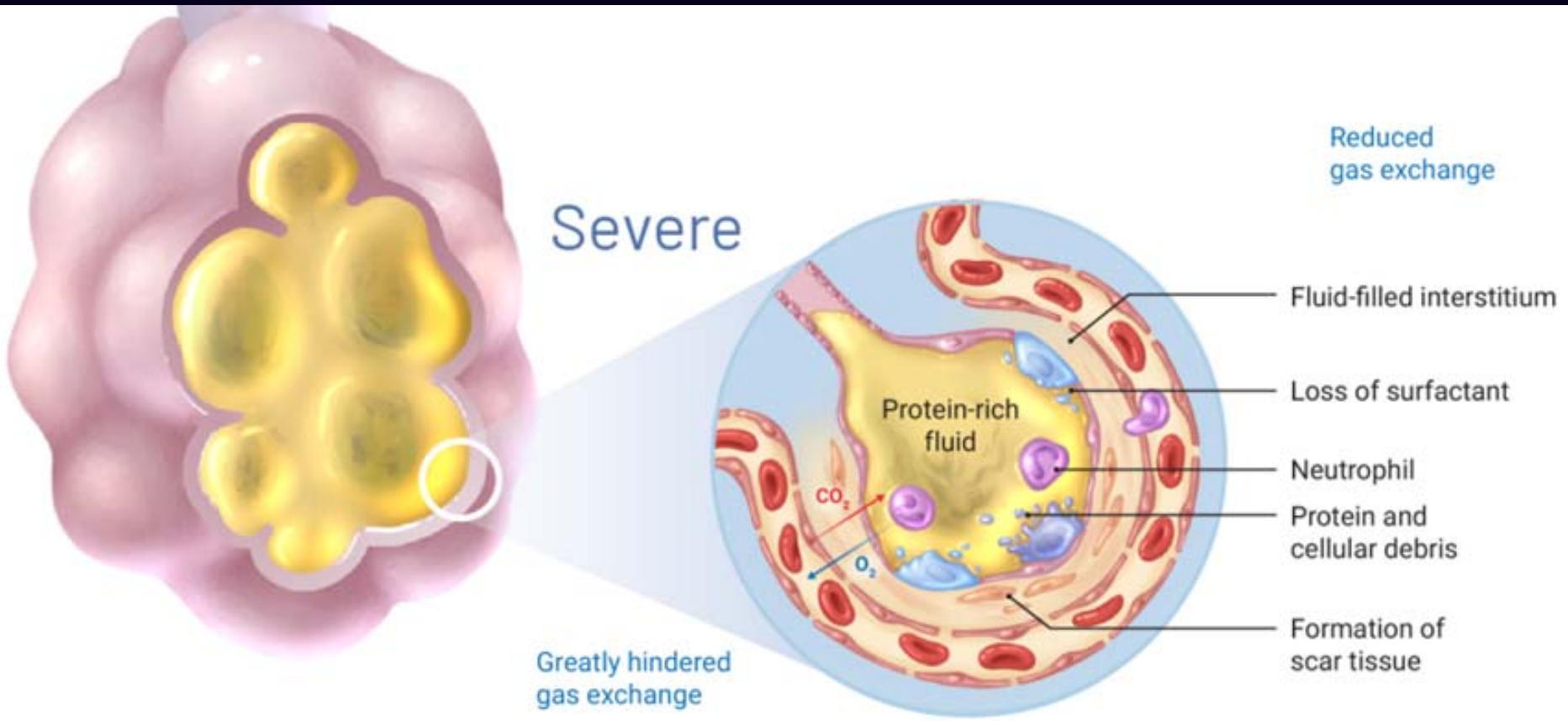
Dá Yuán Yǐn 達原飲 (Reach the Membrane Source Decoction)

- Vents the *mo yuan* (membrane source) and eliminates dampness and turbidity.

- Febrile disorders with pathogenic factors affecting the *mo yuan,* causing such symptoms as unpredictable patterns of alternating fever and chills (once every one to three days), chest oppression, nausea, vomiting, headache, irritability, restlessness, a wiry, rapid pulse, and a greasy tongue coating.

Original Source: *Wen Yi Lun* (Discussion of Epidemic Warm Disease) by Wu You-Xing in 1642

Mo Yuan (Membrane Source)



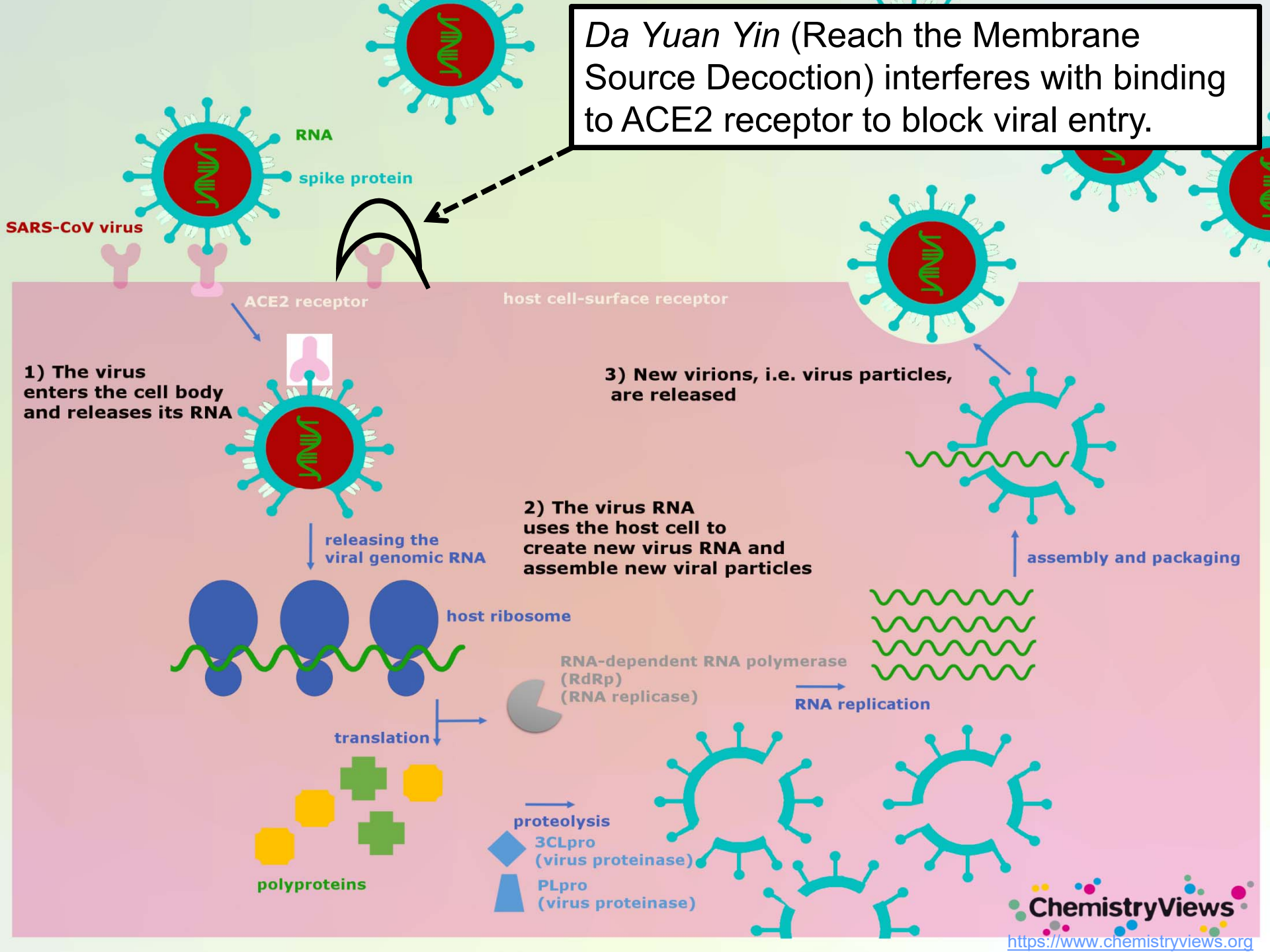
https://www.visualcapitalist.com/visualizing-what-covid-19-does-to-your-body/

Dá Yuán Yǐn 達原飲 (Reach the Membrane Source Decoction)

- *Da Yuan Yin* has been shown to regulate T cells and bind with ACE2 receptors and may be beneficial for management of 2019 novel coronavirus disease.

- Chan KW, et al. COVID-19: An Update on the Epidemiological, Clinical, Preventive and Therapeutic Evidence and Guidelines of Integrative Chinese–Western Medicine for the Management of 2019 Novel Coronavirus Disease. The American Journal of Chinese Medicine, Vol. 48, No. 3, 1–26.

Da Yuan Yin (Reach the Membrane Source Decoction) interferes with binding to ACE2 receptor to block viral entry.



Mian Ma Guan Zhong (Rhizoma Dryopteridis Crassirhizomatis)

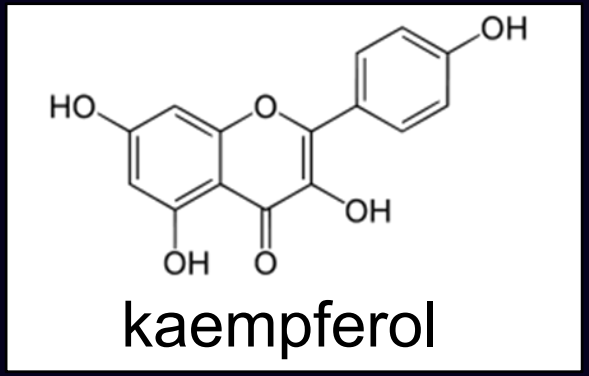
- Kills parasites
- Clears heat, eliminates toxins
- Stops bleeding

Mian Ma Guan Zhong (Rhizoma Dryopteridis Crassirhizomatis)

- Antiparasitic
- Nematicidal
- Antibacterial
- Antiviral

Mian Ma Guan Zhong (Rhizoma Dryopteridis Crassirhizomatis)

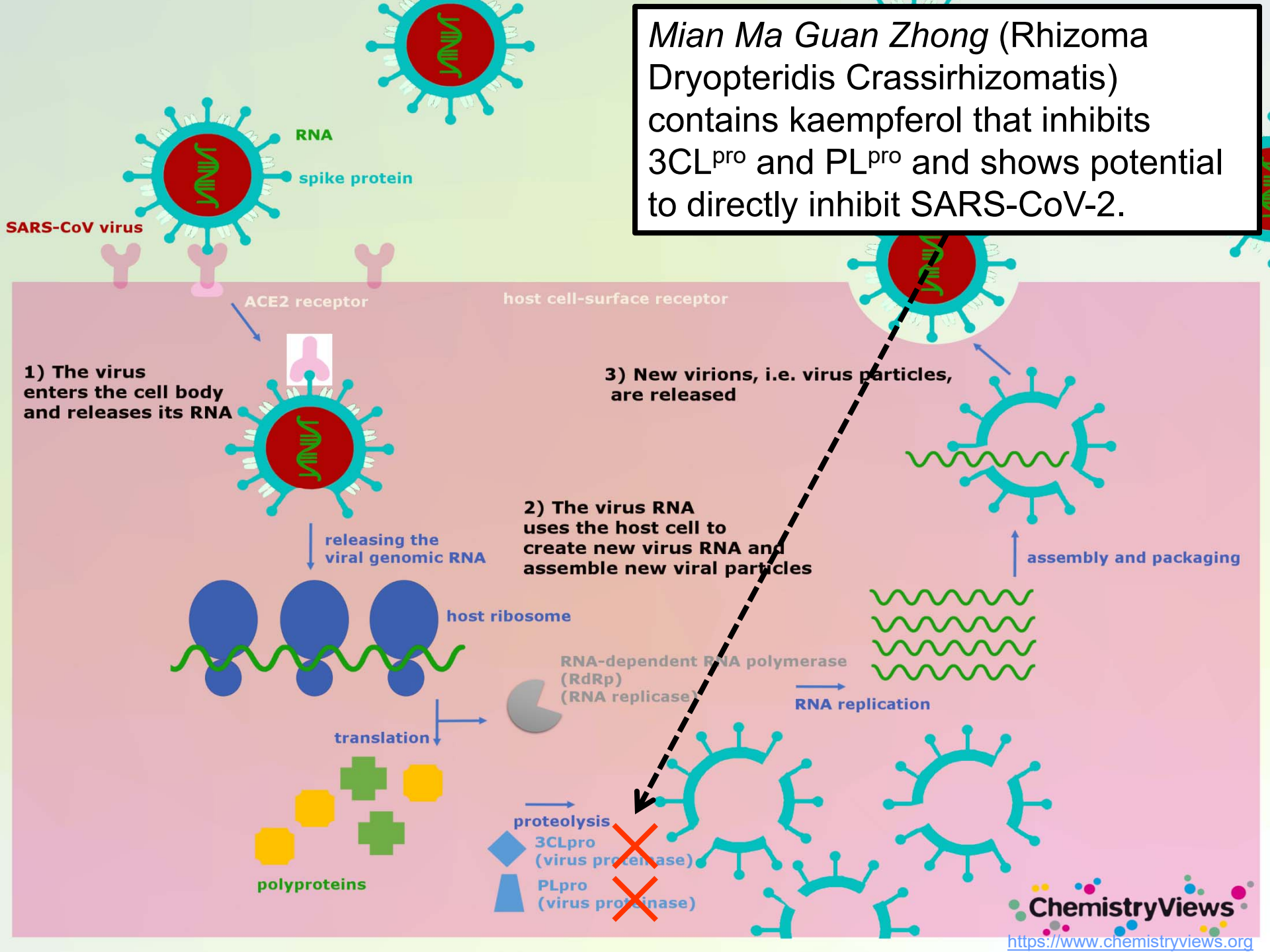
- *Mian Ma Guan Zhong* contains kaempferol that inhibits $3CL^{pro}$ and PL^{pro} and shows potential to directly inhibit SARS-CoV-2.



kaempferol

- Zhang DH, et al. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. Journal of Integrative Medicine 18 (2020) 152–158.

Mian Ma Guan Zhong (Rhizoma Dryopteridis Crassirhizomatis) contains kaempferol that inhibits $3CL^{pro}$ and PL^{pro} and shows potential to directly inhibit SARS-CoV-2.



Xiang Chun Ye (Folium Toonae Sinensis)

- *Xiang Chun Ye* clears heat and eliminates toxins to treat Lung heat with cough.
- It also clears heat and eliminates toxins from the skin to treat sores and abscesses.

香椿葉

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Journal of Ethnopharmacology 120 (2008) 108–111

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Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication

Chung-Jen Chen[a,b,*], Martin Michaelis[c], Hseng-Kuang Hsu[d], Chin-Chuan Tsai[e], Kunder D. Yang[f,g], Yang-Chang Wu[h], Jindrich Cinatl Jr.[c], Hans Wilhelm Doerr[c]

[a] *Division of Rheumatology, Allergy and Immunology, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[b] *School of Chinese Medicine, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[c] *Institute of Medical Virology, Frankfurt University, Frankfurt Am Mein, Germany*
[d] *Department of Physiology, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan*
[e] *Department of Chinese Medicine, E-DA Hospital, I-Shou University, Kaohsiung County, Taiwan*
[f] *Division of Pediatric Immunology and Allergy, Chang Gung Memorial Hospital-Kaohsiung Medical Center, Chang Gung University College of Medicine, Kaohsiung, Taiwan*
[g] *School of Medicine, Chang Gung University College of Medicine, Taoyuan, Taiwan*
[h] *Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung, Taiwan*

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Traditional Chinese medicine (TCM)
Toona sinensis Roem

ABSTRACT

Aim of the study: Severe acute respiratory syndrome (SARS) is a life-threatening disease caused by the SARS coronavirus (SARS-CoV). The development of new antiviral agents for SARS-CoV is an important issue. We tried to find potential resource from Traditional Chinese medicine (TCM) for development of new drugs against SARS-CoV.

Materials and Methods: Our team recruited the potential TCM formulae (also known as Kampo) from two TCM books, Shang-Han Lun (Discussion of Cold-Induced Disorders) and Wen-Bing Tiau-Bein (Differential Management of Febrile Diseases). Several herbs, which were believed to be beneficial for SARS by experienced TCM doctors were also recruited. In addition, a vegetable polular in Taiwan, China and Malaysia, the tender leaf of *Toona stnensts* Roem (also known as Cedrela sinensis, belongs to the family Meliacceae) was also recruited under the suggestion of botanic experts. These TCM products and plant extrats were then tested for the effectiveness against SARS-CoV in vitro.

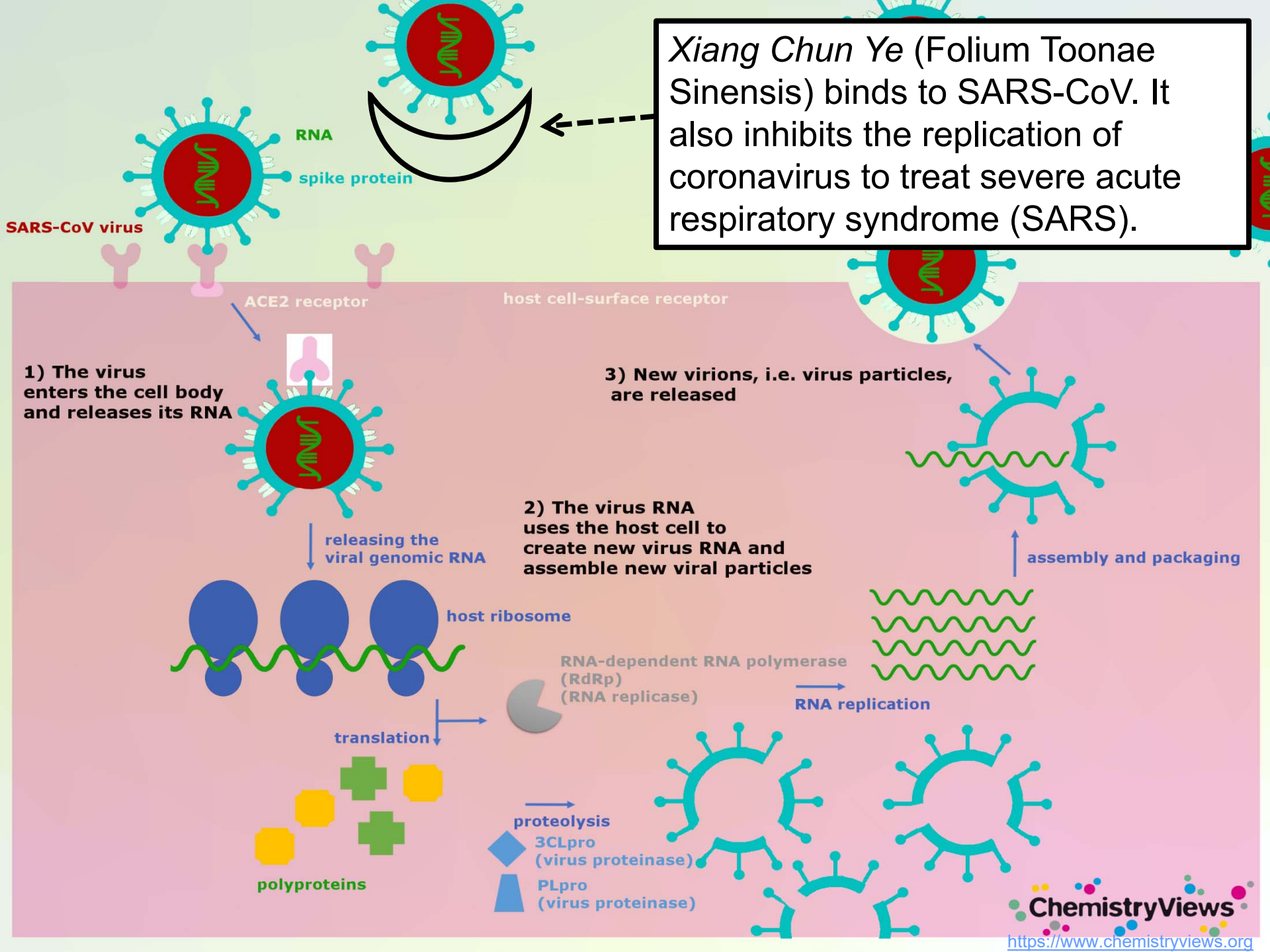
Results: Only TSL-1, the extract from tender leaf of *Toona stnensts* Roem was found to have an evident effect against SARS-CoV with selectivity index 12~17.

Conclusion: This paper reports for the first time that extract from a vegetable, the tender leaf of *Toona stnensts* Roem, can inhibit SARS-CoV in vitro. Thererfore, the tender leaf of *Toona stnensts* Roem may be an important resource agninst SARS-CoV.

Xiang Chun Ye (Folium Toonae Sinensis)

- *Xiang Chun Ye* (Folium Toonae Sinensis) contains a compound (TSL-1) that selectively bind to SARS-CoV virus to inhibit the cellular entry of the virus into the host cells.
- *Xiang Chun Ye* inhibits the replication of coronavirus to treat severe acute respiratory syndrome (SARS).

- Chen CJ, Michaelis M, Hsu HK, Tsai CC, Yang KD, Wu YC, et al. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. J Ethnopharmacol 2008; 120: 108-111.


Xiang Chun Ye (Folium Toonae Sinensis) binds to SARS-CoV. It also inhibits the replication of coronavirus to treat severe acute respiratory syndrome (SARS).
RNA
spike protein
SARS-CoV virus
ACE2 receptor
host cell-surface receptor
1) The virus enters the cell body and releases its RNA
releasing the viral genomic RNA
host ribosome
translation
polyproteins
2) The virus RNA uses the host cell to create new virus RNA and assemble new viral particles
RNA-dependent RNA polymerase (RdRp) (RNA replicase)
RNA replication
proteolysis
3CLpro (virus proteinase)
PLpro (virus proteinase)
assembly and packaging
3) New virions, i.e. virus particles, are released
ChemistryViews
https://www.chemistryviews.org

Xiang Chun Ye (Folium Toonae Sinensis)

- *Xiang Chun Ye* is the most effective herb of all tested from *Shang Han Lun* (Discussion of Cold-Induced Disorders) and *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease).

• Chen CJ, et al. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. J Ethnopharmacol. 2008 Oct 30;120(1):108-11.

Wu Bei Zi (Galla Chinensis)

- Contains leakage of lung qi, clears deficiency fire
- Binds the intestines
- Consolidates kidney *jing* (essence)
- Restrains sweating
- Stops bleeding
- Eliminates toxins and reduces swelling

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

JOURNAL OF VIROLOGY, Oct. 2004, p. 11334–11339 Vol. 78, No. 20
0022-538X/04/$08.00+0 DOI: 10.1128/JVI.78.20.11334–11339.2004

Small Molecules Blocking the Entry of Severe Acute Respiratory Syndrome Coronavirus into Host Cells

Ling Yi,[1]† Zhengquan Li,[2]† Kehu Yuan,[1]† Xiuxia Qu,[1] Jian Chen,[1] Guangwen Wang,[1] Hong Zhang,[1] Hongpeng Luo,[2] Lili Zhu,[2] Pengfei Jiang,[1] Lirong Chen,[2] Yan Shen,[1] Min Luo,[1] Guoying Zuo,[2] Jianhe Hu,[1] Deliang Duan,[2] Yuchun Nie,[1] Xuanling Shi,[1] Wei Wang,[1] Yang Han,[3] Taisheng Li,[3] Yuqing Liu,[4] Mingxiao Ding,[1] Hongkui Deng,[1]* and Xiaojie Xu[2]*

Department of Cell Biology and Genetics, College of Life Sciences,[1] and College of Chemistry and Molecular Engineering,[2] Peking University, and Department of Infectious Disease, PUMC Hospital, CAMS and PUMC,[3] Beijing, and Centre for the Study of Liver Disease and Department of Surgery, The University of Hong Kong, Pokfulam, Hong Kong,[4] Peoples Republic of China

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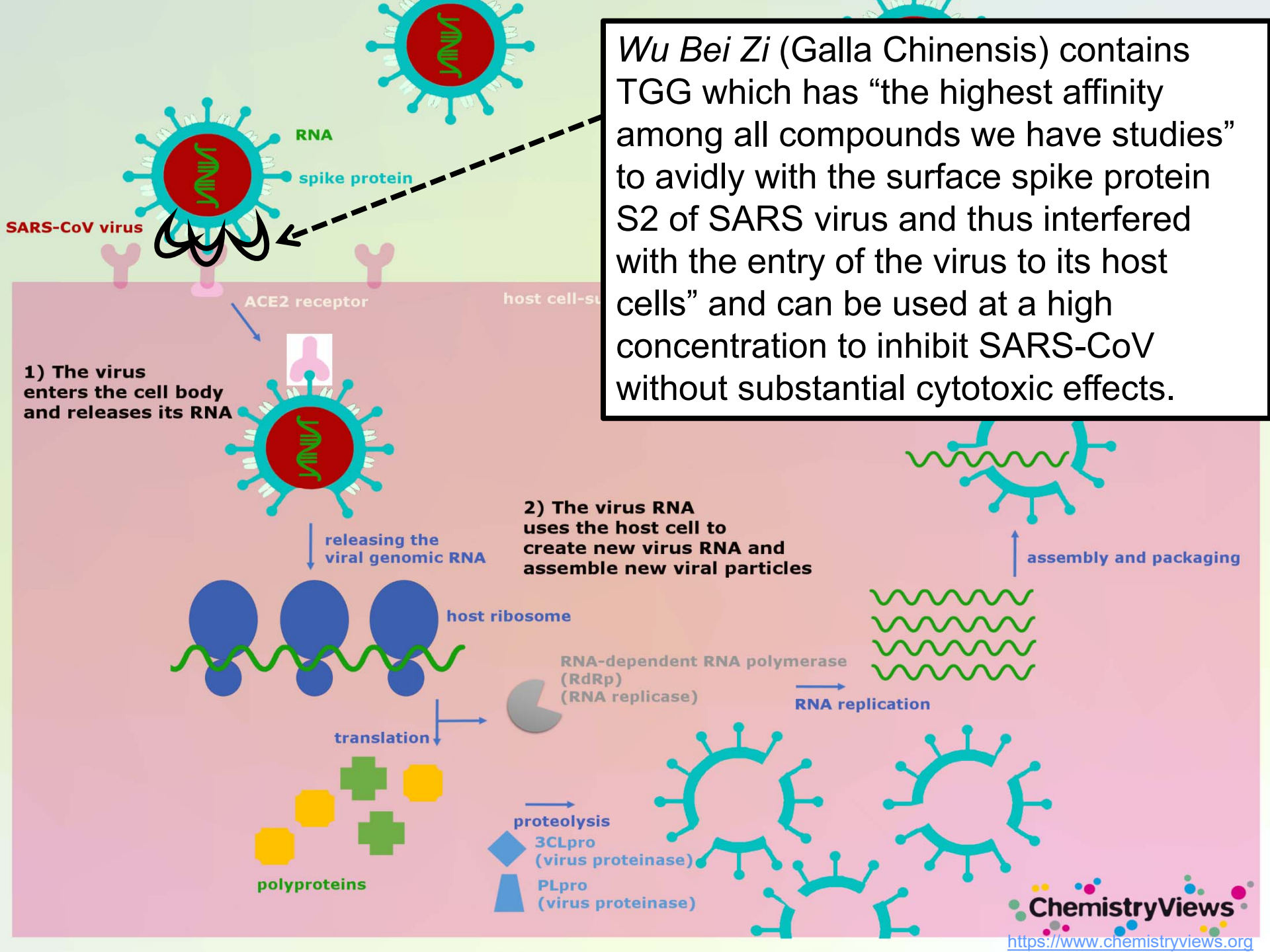
Severe acute respiratory syndrome coronavirus (SARS-CoV) is the pathogen of SARS, which caused a global panic in 2003. We describe here the screening of Chinese herbal medicine-based, novel small molecules that bind avidly with the surface spike protein of SARS-CoV and thus can interfere with the entry of the virus to its host cells. We achieved this by using a two-step screening method consisting of frontal affinity chromatography-mass spectrometry coupled with a viral infection assay based on a human immunodeficiency virus (HIV)-luc/SARS pseudotyped virus. Two small molecules, tetra-*O*-galloyl-β-D-glucose (TGG) and luteolin, were identified, whose anti-SARS-CoV activities were confirmed by using a wild-type SARS-CoV infection system. TGG exhibits prominent anti-SARS-CoV activity with a 50% effective concentration of 4.5 μM and a selective index of 240.0. The two-step screening method described here yielded several small molecules that can be used for developing new classes of anti-SARS-CoV drugs and is potentially useful for the high-throughput screening of drugs inhibiting the entry of HIV, hepatitis C virus, and other insidious viruses into their host cells.

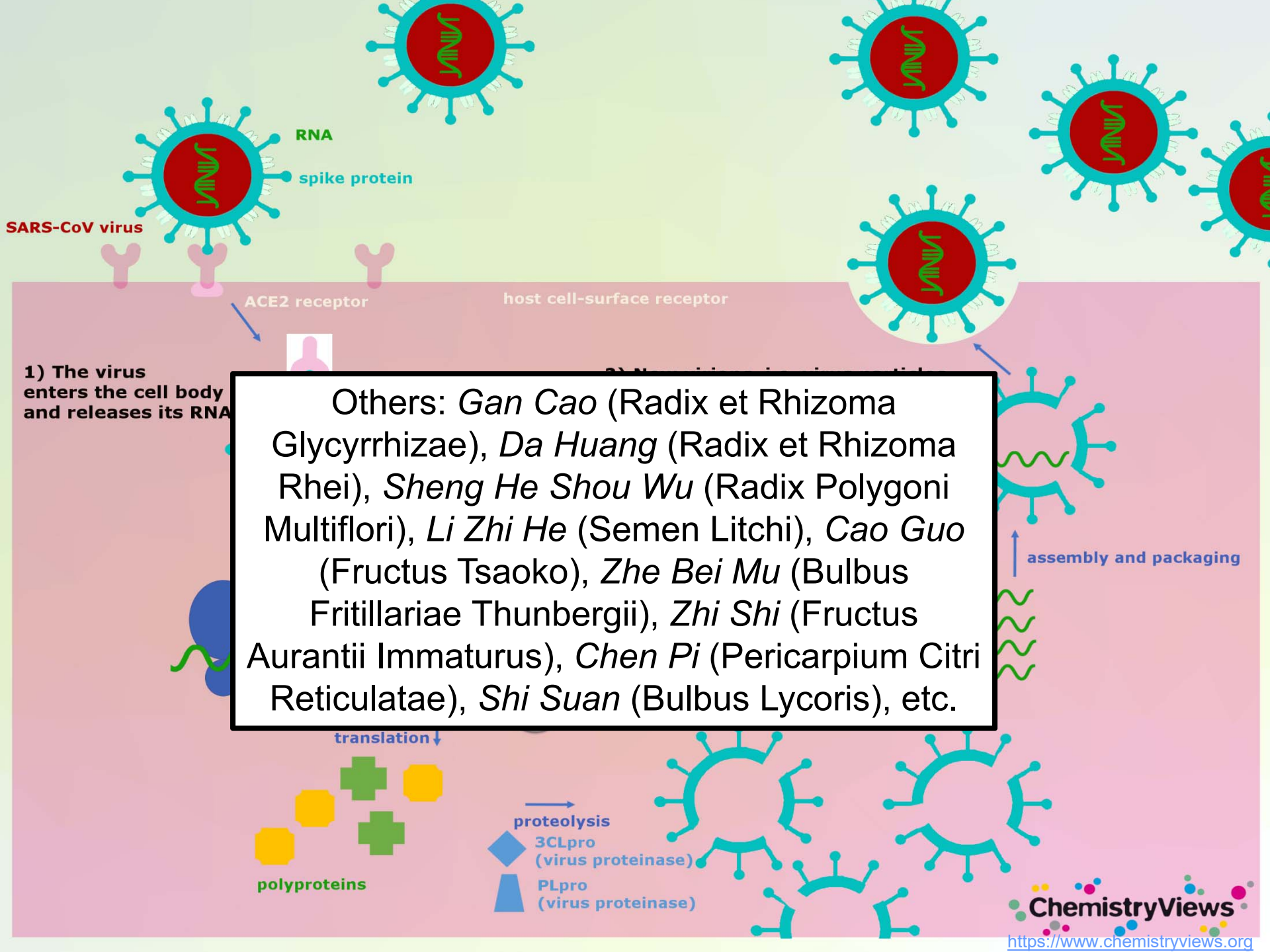
Wu Bei Zi (Galla Chinensis)

- *Wu Bei Zi* (Galla Chinensis) contains tetra-O-galloyl-β-D-glucose (TGG) that exhibits prominent anti-SARS virus activity.
- TGG has “the highest affinity among all compounds we have studies” to avidly with the surface spike protein S2 of SARS virus and thus interfered with the entry of the virus to its host cells.
- TGG can be used at a high concentration to inhibit SARS-CoV without substantial cytotoxic effects.

- Yi L, Li Z, Yuan K, Qu X, Chen J, Wang G, et al. Small molecules blocking the entry of severe acute respiratory syndrome coronavirus into host cells. J Virol 2004; 78: 1133411339.

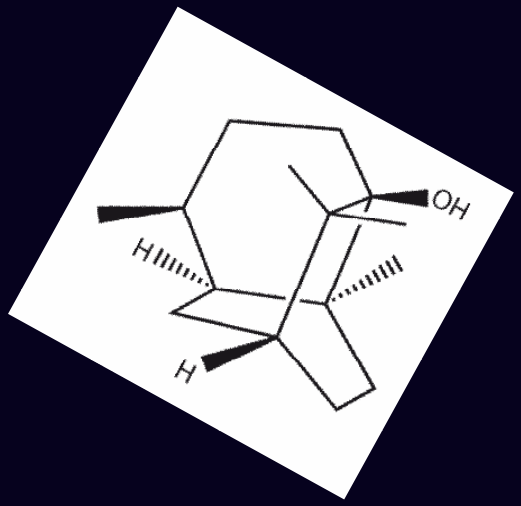


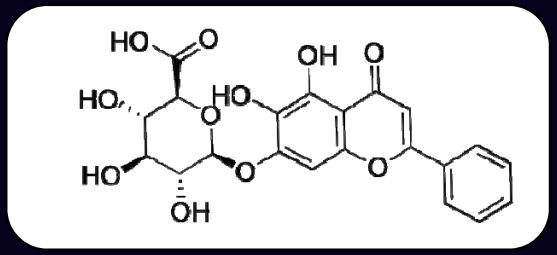
Wu Bei Zi (Galla Chinensis) contains TGG which has "the highest affinity among all compounds we have studies" to avidly with the surface spike protein S2 of SARS virus and thus interfered with the entry of the virus to its host cells" and can be used at a high concentration to inhibit SARS-CoV without substantial cytotoxic effects.

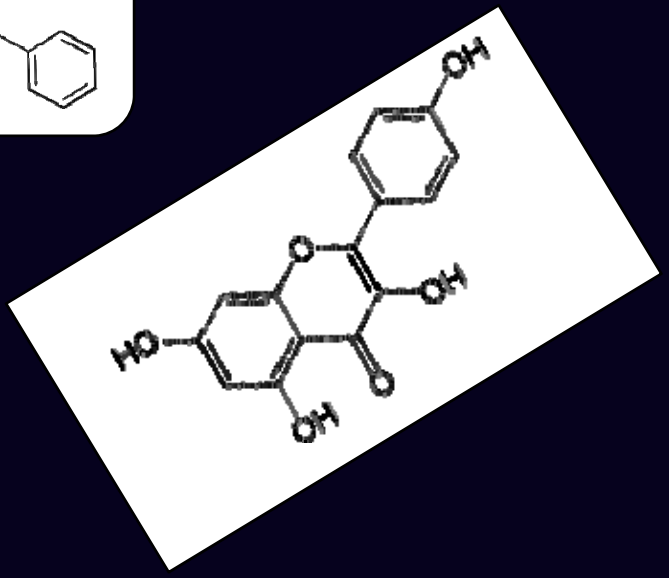


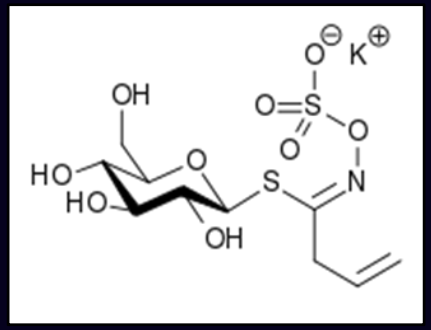
Others: *Gan Cao* (Radix et Rhizoma Glycyrrhizae), *Da Huang* (Radix et Rhizoma Rhei), *Sheng He Shou Wu* (Radix Polygoni Multiflori), *Li Zhi He* (Semen Litchi), *Cao Guo* (Fructus Tsaoko), *Zhe Bei Mu* (Bulbus Fritillariae Thunbergii), *Zhi Shi* (Fructus Aurantii Immaturus), *Chen Pi* (Pericarpium Citri Reticulatae), *Shi Suan* (Bulbus Lycoris), etc.

Structure-Activity-Relationship (SAR)









Shang Han

伤寒

(Cold Damage)

Wen Bing

温病

(Warm Disease)

Yu Fang

預防

Prevention

Shang Han

伤寒

(Cold Damage)

Wen Bing

温病

(Warm Disease)

Cell Death & Differentiation
https://doi.org/10.1038/s41418-020-0530-3

Cell Death & Differentiation

EDITORIAL

COVID-19 infection: the perspectives on immune responses

Yufang Shi[1,2] · Ying Wang[2] · Changshun Shao[1] · Jianan Huang[1] · Jianhe Gan[1] · Xiaoping Huang[1] · Enrico Bucci[3,4] · Mauro Piacentini[5] · Giuseppe Ippolito[5] · Gerry Melino[6,7]

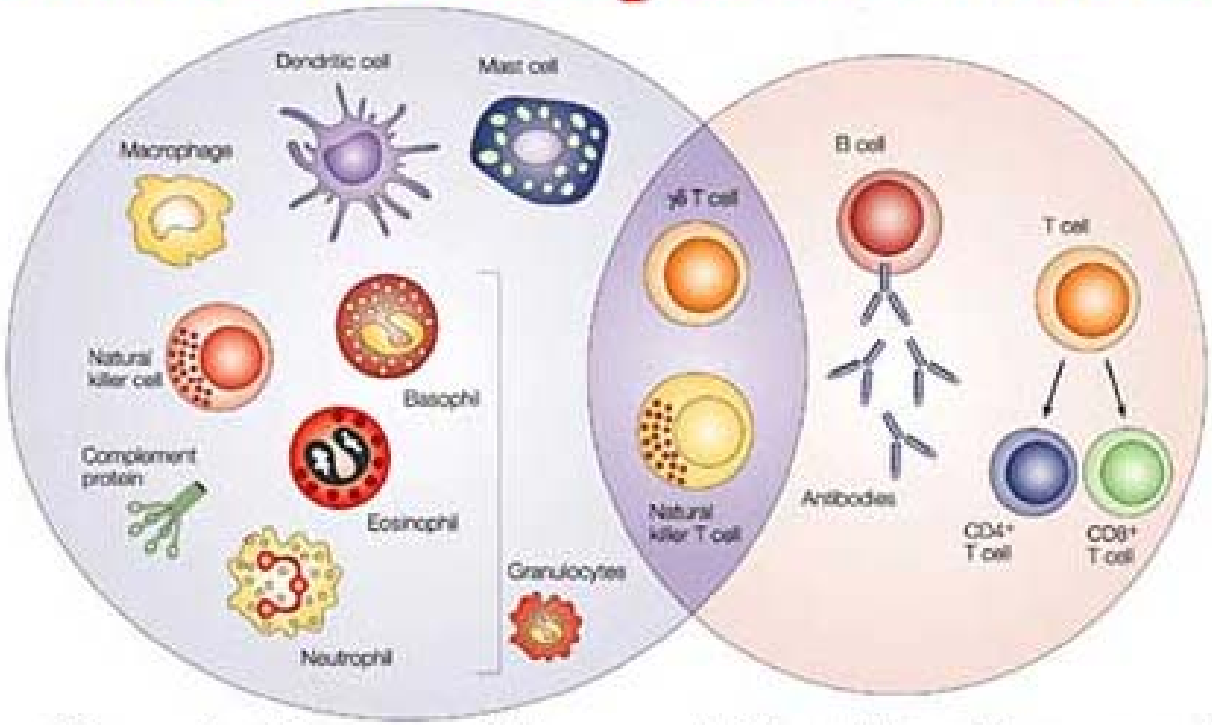
Received: 1 March 2020 / Revised: 10 March 2020 / Accepted: 10 March 2020

We believe that the two-phase division is very important: the first immune defense-based protective phase and the second inflammation-driven damaging phase. Doctors should try to boost immune responses during the first, while suppressing it in the second phase.

More than 100 ye…on remains to be enza pandemic, v… The outbreak of…n Wuhan, except infection is spread…, it infects all the with this virus f…he confirmed cases clinicians have le…e is a higher chance COVID-19, and it…vere phase [1]. One to SARS-CoV-2 …why some develop develop severe r…y, the conventional CoV-2 infection …e infected patients stage I, an asympt…ease presentation. detectable virus; stage II, non-severe symptomatic period with the presence of virus; stage III, severe respiratory symptomatic stage with high viral load [2]. From the point of view of prevention, individuals at stage I, the stealth

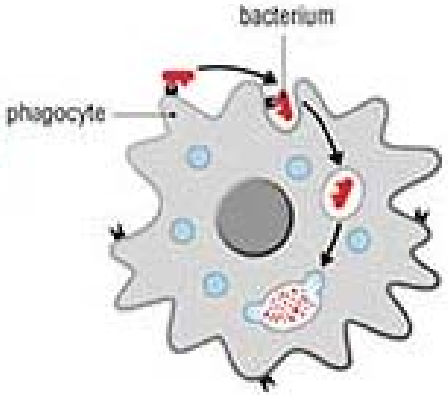
Two-phase immune responses induced by COVID-19 infection

Innate and Adaptive Immunity



Innate Immunity **Adaptive Immunity**

Nature Reviews | Cancer



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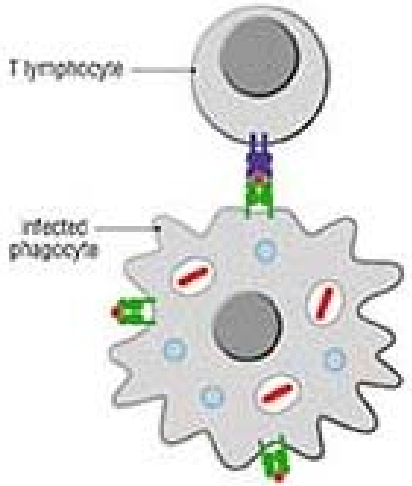


BMJ. 2003 Sep 13; 327(7415): 620.
doi: 10.1136/bmj.327.7415.620-b

PMCID: PMC194123
PMID: 12969939

SARS: understanding the coronavirus

Apoptosis may explain lymphopenia of SARS

Roddy O'Donnell, associate lecturer, paediatrics

Email: roddy.odonnell@addenbrookes.nhs.uk

Robert C Tasker, university lecturer, paediatrics and Michael F E Roe, clinical research fellow

Clinical School, University of Cambridge, Cambridge CB2 2QQ

EDITOR—In their review of the severe acute respiratory syndrome (SARS) Wong et al emphasise lymphopenia as a hallmark feature.[1] Panesar suggested that glucocorticoids or stimulation of the hypothalamic-pituitary-adrenal axis leads to lymphocyte margination and that patients without lymphopenia may have adrenal insufficiency.[2]

In their review of the severe acute respiratory syndrome (SARS) Wong et al emphasise lymphopenia as a hallmark feature.

Ap…ans such as r…with Car… resp…

Chi…y lower absolute lymphocyte counts than those with mild disease. Bronchiolitis is ubiquitous and, in the developed world, the commonest reason a child under 1 year of age is admitted to hospital. Studies in mice show that not only is the lymphocyte immune response to virus essential in controlling the virus but it also causes disease.[4] The fact the immune response is both saint and sinner is believed to be why the use of ribavirin has proved less effective in bronchiolitis than was first hoped.

Cellular & Molecular Immunology www.nature.com/cmi

CORRESPONDENCE OPEN

SARS-CoV-2 infects T lymphocytes through its spike protein-mediated membrane fusion

Xinling Wang[1], Wei Xu[1], Gaowei Hu[1], Shuai Xia[1], Zhiping Sun[1], Zezhong Liu[1], Youhua Xie[1], Rong Zhang[1], Shibo Jiang[1,2] and Lu Lu[1]

Cellular & Molecular Immunology _####################_; https://doi.org/10.1038/s41423-020-0424-9

COVID-19, the novel coronavirus disease caused by SARS-CoV-2 and outbroken at the end of 2019 in Wuhan, China,[1] becomes a worldwide pandemic. SARS-CoV-2 belongs to the betacoronavirus genus and has 79.5% identity to SARS-CoV. SARS-CoV-2 uses angiotensin-converting enzyme 2 (ACE2) as its host entry receptor.[2] The clinical manifestations of COVID-19 include pneumonia, diarrhea, dyspnea, and multiple organ failure. Interestingly, lymphocytopenia, as a diagnostic indicator is common in COVID-19 patients. Xiong
and p53 pathi
reported that
especially in p
lymphocytes.[4,
respiratory syn
human primar
extrinsic and i
T lymphocytes
infect T cells, resulting in lymphocytopenia.

SARS-CoV-2 infects and kills T lymphocytes, but the virus cannot replicate inside the T lymphocytes.

To address this question, we evaluated the susceptibility of T lymphocytes to SARS-CoV-2 infection. To accomplish this, pseudotyped SARS-CoV and SARS-CoV-2 were packaged based on methods described previously.[7] The pseudoviruses could infect permissive cells (293T/ACE2 and Huh7 cells) expressing the ACE2 receptor, but could not infect nonpermissive cells (HeLa cells) (Fig. 1a). We used pseudovirus with equal infectivity to 293T/ACE2 cells (Fig. 1c) to infect two T lymphocyte cell lines, MT-2 and A3.01, with very low, or close to negative, expression level of hACE2 mRNA (Fig. 1b). Surprisingly, over several replicates, we saw that

inhibits receptor-mediated infection by interacting with HR1 to block the formation of the six-helix bundle (6-HB), further inhibiting fusion between viral and target cell membranes. We found that the EK1 peptide had significant inhibitory activity against SARS-CoV-2 pseudoviruses on MT-2 cells (Fig. 1d), suggesting that virus entry depends on receptor-mediated fusion. However, only a high concentration (40 μM) of EK1 had inhibitory activity on MT-2 cells. Meanwhile, the IC50 value of EK1 was 2.38
t SARS-CoV-2
tor-mediated
ARS-CoV-2 S-
us studies.[7,10]
V-2 S protein
he fused cells
n fluorescent
he SARS-CoV
t SARS-CoV-2
might infect T cells through S protein-mediated membrane fusion.

To further determine the susceptibility of MT-2 cells to live virus, we used SARS-CoV-2 to infect MT-2 cells and detected the SARS-CoV-2 nucleoprotein (NP) in the cells as reported previously.[6] Notably, several MT-2 cells were infected with SARS-CoV-2 (Fig. 1f). Quantitatively, the percentage of SARS-CoV-2 NP-positive MT-2 cells was 23.11% higher than that of uninfected cells at 24 h post infection, which is about 4.6-fold of the portion at 1 h (Fig. 1f). This result means that the virus penetrated MT-2 cells at 24 h and infected them.

Given that MERS-CoV can efficiently infect, but not replicate, in

Yù Píng Fēng Sǎn 玉屏風散 (Jade Windscreen Powder)

- *Huang Qi* (Radix Astragali) 30g [6g]
- *Bai Zhu* (Rhizoma Atractylodis Macrocephalae) 60g [12g]
- *Fang Feng* (Radix Saposhnikoviae) 30g [6g]

- The source text states to grind the ingredients into powder. Cook 9g of the powdered herbs and 3 slices of *Sheng Jiang* (Rhizoma Zingiberis Recens) in 1.5 large bowls of water for decoction. Today, this formula may be prepared as a decoction with the doses suggested in brackets, with addition of 3 slices of *Sheng Jiang* (Rhizoma Zingiberis Recens) and 1 piece of *Da Zao* (Fructus Jujubae).

Original Source: *Dan Xi Xin Fa* (Teachings of [Zhu] Dan-Xi) by Zhu Zhen-Heng in 1481

Yù Píng Fēng Sǎn 玉屏風散 (Jade Windscreen Powder)

- Tonifies *wei* (defensive) *qi*
- Consolidates the exterior

- *Wei* (defensive) *qi* deficiency: spontaneous sweating, aversion to wind and cold, increased susceptibility to invasion of exterior pathogens, pale face, pale tongue, white tongue coating, and a floating, deficient pulse.

Huang Qi (Radix Astragali)

- **Immunostimulant**:
  - Administration of *Huang Qi* (Radix Astragali) is associated with promotion of T cells.
  - The polysaccharides from *Huang Qi* (Radix Astragali) have been shown to activate B cells.

- Qu LL, et al. Astragalus membranaceus injection delayed allograft survival related with CD4+ CD25+ regulatory T cells. Transplant Proc. 2010 Nov;42(9):3793-7.
- Shao BM, et al. A study on the immune receptors for polysaccharides from the roots of Astragalus membranaceus, a Chinese medicinal herb. Biochem Biophys Res Commun. 2004 Aug 6;320(4):1103-11.

Yù Píng Fēng Sǎn 玉屏風散 (Jade Windscreen Powder)

JOURNAL ARTICLE

Analysis of immunostimulatory activity of polysaccharide extracted from Yu-Ping-Feng in vitro and in vivo

Wentao Fan, Pimiao Zheng, Yang Wang, Pan Hao, Jianzhu Liu, Xiaona Zhao

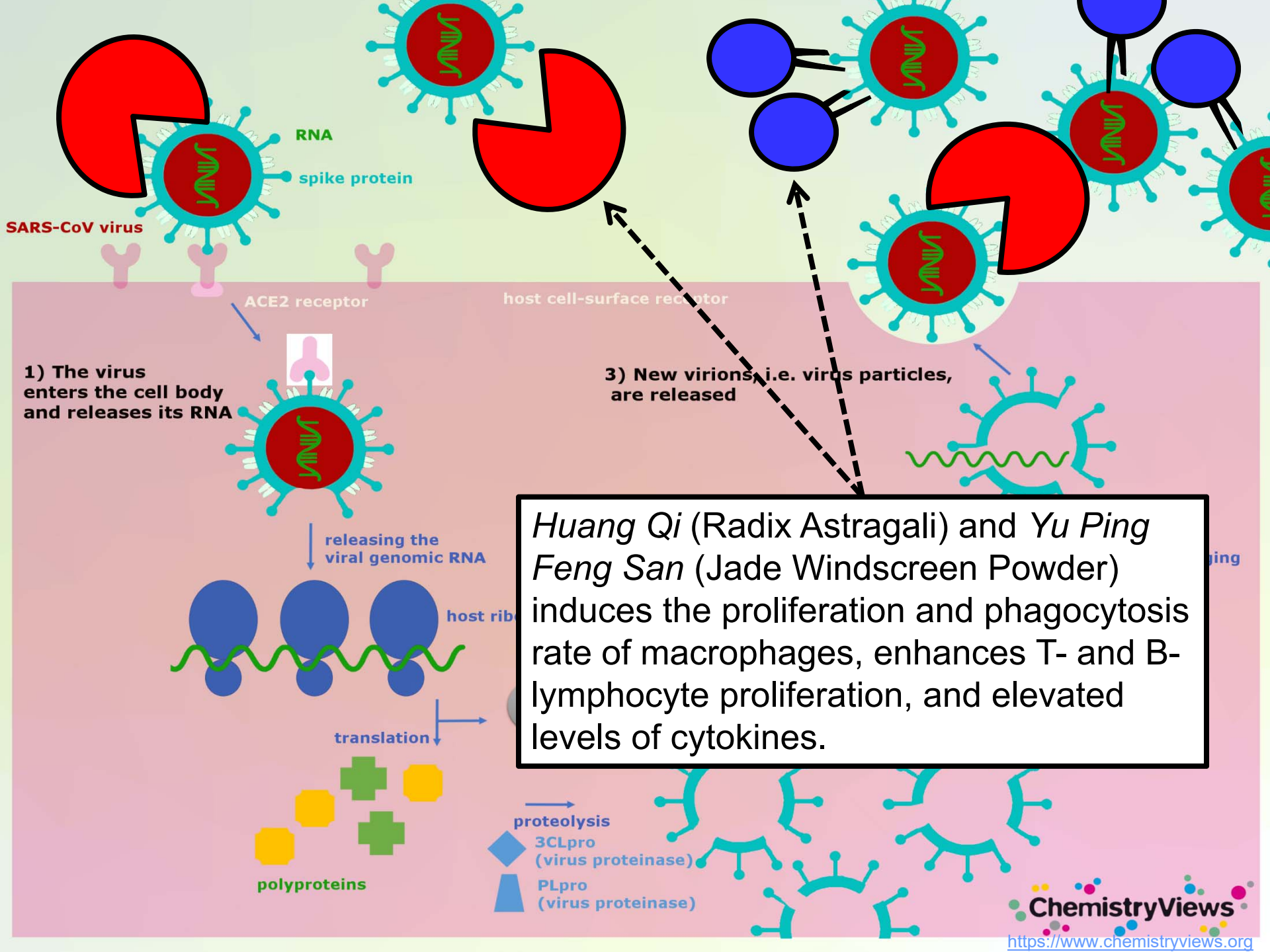
Biomedicine & Pharmacotherapy 2017, 93: 146-155

As a traditional Chinese multiherbal formula, Yu-Ping-Feng (YPF) is frequently used to treat cold, flu and inflammation-associated diseases. We aimed to evaluate the immunostimulatory effects of polysaccharide isolated from YPF (YPF-PS) in vitro and in vivo. In in vitro experiment, macrophage cell proliferation, phagocytosis rate, cytokine and costimulatory molecule release, T lymphocyte proliferation, cell cycle distribution, CD4+ and CD8+ T cell percentages were determined. To investigate the in vivo effects of YPF-PS treatment, different doses YPF-PS were administered to chicken vaccinated against Newcastle disease. The immune organ index, lymphocyte proliferation, antibody titer, cell cycle distribution, and the cell percentage of CD4+ and CD8+ were assessed. In vitro results indicated that YPF-PS at 15.62μgmL-1 could increase the LPS-induced macrophage cell proliferation and phagocytosis rate significantly. The levels of cytokine (nitric oxide, tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, and interferon beta) and costimulatory molecules (CD80 and CD86) were also considerably enhanced. Moreover, YPF-PS could significantly enhance T lymphocyte proliferation individually or synergistically with phytohemagglutinin. It promoted lymphocyte entry into S and G2/M phases and increased the percentages of CD4+ and CD8+ T cells effectively. In addition, in vivo experiments showed that YPF-PS could enhance serum HI antibody titer. The results about T lymphocyte proliferation, cell cycle distribution, CD4+ and CD8+ cell percentages in chickens were also confirmed. YPF-PS has efficacious immunomodulatory properties and could be used as a new potential immune stimulator for food and medical purposes.

Yù Píng Fēng Sǎn 玉屏風散 (Jade Windscreen Powder)

- **Immunostimulatory**: The polysaccharides isolated from YPFS exhibits significant immunostimulatory effects:
  - induces the proliferation and phagocytosis rate of macrophages
  - enhances T- and B- lymphocyte proliferation
  - elevates levels of cytokine (nitric oxide, tumor necrosis factor-alpha, interleukin-1 beta, interleukin-6, and interferon beta).

Fan W, et al. Analysis of immunostimulatory activity of polysaccharide extracted from Yu-Ping-Feng in vitro and in vivo. Biomed Pharmacother. 2017 Sep;93:146-155.



Huang Qi (Radix Astragali) and *Yu Ping Feng San* (Jade Windscreen Powder) induces the proliferation and phagocytosis rate of macrophages, enhances T- and B-lymphocyte proliferation, and elevated levels of cytokines.

Phytotherapy Research

Research Article

Yu Ping Feng San, an Ancient Chinese Herbal Decoction, Induces Gene Expression of Anti-viral Proteins and Inhibits Neuraminidase Activity

Crystal Y.Q. Du, Ken Y.Z. Zheng, Cathy WC Bi, Tina T.X. Dong, Huangquan Lin, Karl W.K. Tsim

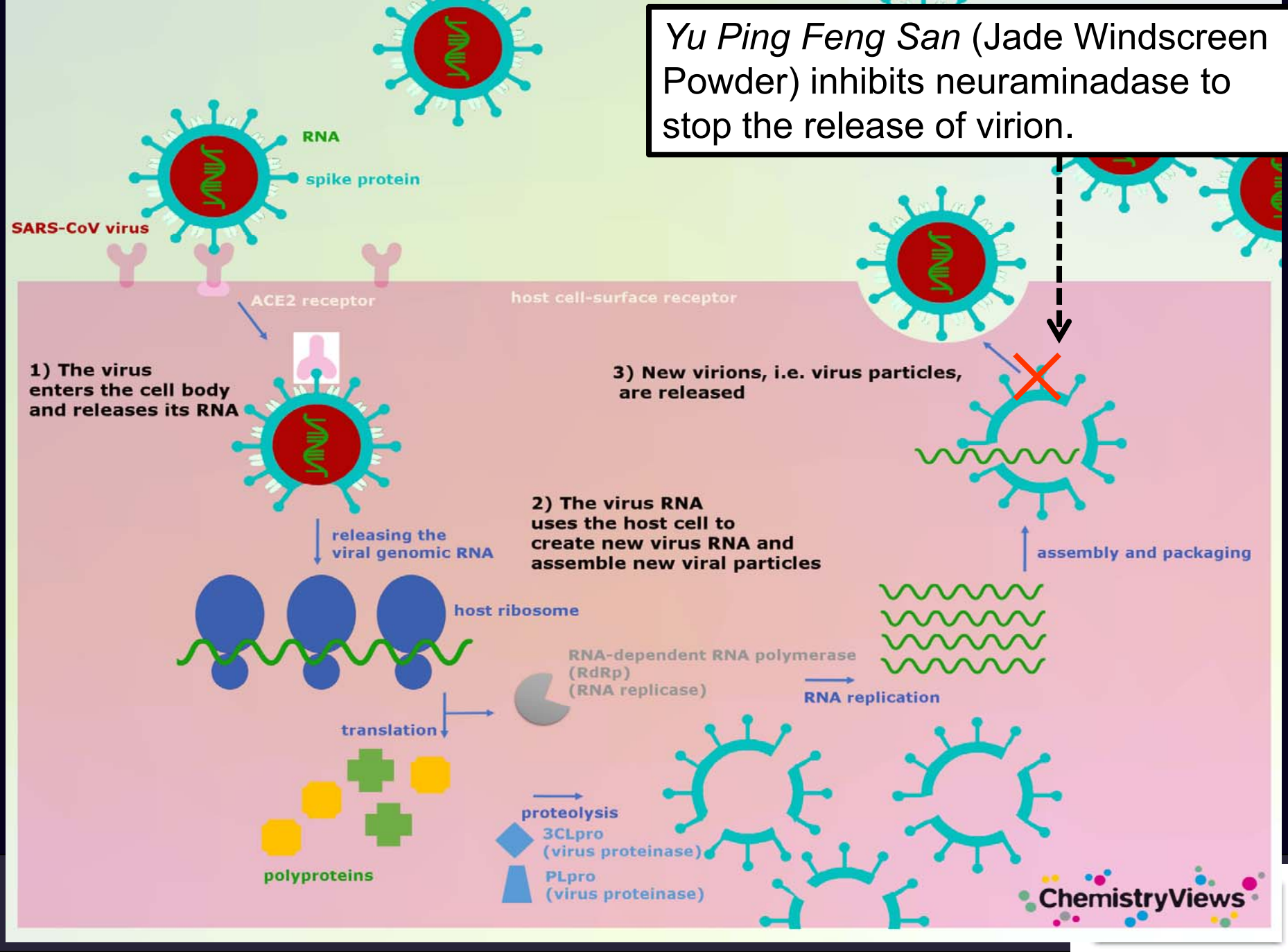
First published:14 January 2015 | https://doi.org/10.1002/ptr.5290 | Citations: 11

Abstract

Yu Ping Feng San (YPFS), a Chinese herbal decoction comprised of Astragali Radix (Huangqi), Atractylodis Macrocephalae Rhizoma (Baizhu) and Saposhnikoviae Radix (Fangfeng), has been used clinically for colds and flus; however, the action mechanism of which is not known. Previously, we had demonstrated that YPFS could modulate inflammatory response and phagocytosis in exerting anti-viral and anti-bacterial effects. Here, we further evaluated the bioactivities of YPFS in gene expression regulated by interferon (IFN) signaling and neuraminidase activity of influenza virus A. Application of YPFS onto cultured murine macrophages, the expressions of mRNAs encoding

Du CY, et al. Yu Ping Feng San, an Ancient Chinese Herbal Decoction, Induces Gene Expression of Anti-viral Proteins and Inhibits Neuraminidase Activity. Phytother Res. 2015 May;29(5):656-61.

Yu Ping Feng San (Jade Windscreen Powder) inhibits neuraminadase to stop the release of virion.



Du CY, et al. Yu Ping Feng San, an Ancient Chinese Herbal Decoction, Induces Gene Expression of Anti-viral Proteins and Inhibits Neuraminidase Activity. Phytother Res. 2015 May;29(5):656-61.

https://www.chemistryviews.org

Yù Píng Fēng Sǎn 玉屏風散 (Jade Windscreen Powder)

- Caution / Contraindication:
  - pre-existing autoimmune diseases;
  - individuals taking immunosuppressants for organ transplant
  - Covid-19 patients with cytokine storm

THE JOURNAL OF ALTERNATIVE AND COMPLEMENTARY MEDICINE
Volume 11, Number 1, 2005, pp. 49–55

The Use of an Herbal Formula by Hospital Care Workers During the Severe Acute Respiratory Syndrome Epidemic in Hong Kong to Prevent Severe Acute Respiratory Syndrome Transmission, Relieve Influenza-Related Symptoms, and Improve Quality of Life: A Prospective Cohort Study

JOSEPH T.F. LAU, Ph.D.,[1] P.C. LEUNG, D.Sc., D.Soc.Sc., M.S.,[2] E.L.Y. WONG, M.P.H.,[2] C. FONG, R.N.,[2] K.F. CHENG, M.D.,[2] S.C. ZHANG, M.D.,[3] C.W.K. LAM, Ph.D.,[4] V. WONG, M.B.B.S., M.R.C.O.G., M.R.C.P.,[5] K.M. CHOY, B.M.B.C.H. (Oxon),[5] and W.M. KO, M.B.B.S, FRCS[5]

• Lau J, Leung P, Wong E, Fong C, Cheng K, Zhang S, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory. J Alternat Complement Med 2005;11:49-55.

Prevention of SARS

- Study: 16,437 hospital care workers, including doctors, nurses and others in Hong Kong
  - 1,063 herb group
  - 15,374 in non-herb group

- Lau J, Leung P, Wong E, Fong C, Cheng K, Zhang S, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory. J Alternat Complement Med 2005;11:49-55.

Kwan Du Bu Fei Dang 抗毒補肺湯 (Fight Toxins and Tonify Lung Decoction)

- *Huang Qi* 黃耆(Radix Astragali) 7.5g
- *Fang Feng* 防風 (Radix Saposhnikoviae) 5g
- *Sang Ye* 桑葉 (Folium Mori) 3.75g
- *Ju Hua* 菊花 (Flos Chrysanthemi) 1.5g
- *Bo He* 薄荷 (Herba Menthae) 1.25g
- *Lian Qiao* 連翹 (Fructus Forsythiae) 2.5g
- *Jie Geng* 桔梗 (Radix Platycodonis) 3g
- *Ku Xing Ren* 苦杏仁 (Semen Armeniacae Amarum) 3g
- *Lu Gen* 蘆根 (Rhizoma Phragmitis) 3g
- *Gan Cao* 甘草 (Radix et Rhizoma Glycyrrhizae) 1.25g
- *Da Qing Ye* 大青葉 (Folium Isatidis) 8g
- *Huang Qin* 黃芩 (Radix Scutellariae) 6g

- Lau J, Leung P, Wong E, Fong C, Cheng K, Zhang S, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory. J Alternat Complement Med 2005;11:49-55.

Kwan Du Bu Fei Dang 抗毒補肺湯 (Fight Toxins and Tonify Lung Decoction)

- *Yu Ping Feng San* (Jade Windscreen Powder)
- *Sang Ju Yin* (Mulberry Leaf and Chrysanthemum Decoction)
- *Da Qing Ye* (Folium Isatidis)
- *Huang Qin* (Radix Scutellariae)

- Take one sachet (4g) the herbal supplement daily for 2 weeks.

- Lau J, Leung P, Wong E, Fong C, Cheng K, Zhang S, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory. J Alternat Complement Med 2005;11:49-55.

Prevention of SARS

- Results:
  - 1,063 herb group; 0 infected (0%)
  - 15,374 in non-herb group; 64 infected (0.4%)
  - *P* = 0.035

- Note: Among 1,063 who took herbs, 19 (1.8%) with minor side effects such as diarrhea, sore throat, dizziness and nausea

- Lau J, Leung P, Wong E, Fong C, Cheng K, Zhang S, et al. The use of an herbal formula by hospital care workers during the severe acute respiratory syndrome epidemic in Hong Kong to prevent severe acute respiratory. J Alternat Complement Med 2005;11:49-55.

Chan B, et al., J Emerg Med Trauma Surg Care 2020, 2: 007

Henry

Review Article

Journal of Emergency Medicine, Trauma & Surgical Care

What can we do for the Personal Protection against the CoVID-19 infection? Immuno-boostering Specific Supplement could be the Answer

Ben Chan[1], CK Wong[2], Ping Chung Leung[1]*

[1]*Institute of Chinese Medicine, The Chinese University of Hong Kong, Hong Kong*

[2]*Department of Chemical Pathology, The Chinese University of Hong Kong, Hong Kong*

(As a matter of fact, a single arm, self-control, cross-over pilot study focusing on prevention using only KDBFD already started in March 2020).

Subjects will be required to take one sachet of KDBFD (4 g) or placebo once per day for 14 days,

KP Fung 馮國培
PC Leung 梁秉中
KWS Tsui 徐國榮
CCD Wan 溫志昌
KB Wong 黃錦波
MYM Waye 韋妙宜
WNS Au 區詠娥
CK Wong 黃振國
WKC Lam 林偉基
BSC Lau 劉碧珊

Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study

Key Messages

1. The herbal formula Kwan Du Bu Fei Dang transiently modulated the human immune system.
2. *Coriolus versicolor* had an immunostimulatory effect in mouse splenic lymphocytes.
3. *Ganoderma lucidum* inhibited SARS-CoV RNA-dependent RNA polymerase.
4. *Houttuynia cordata* possessed both immunostimulatory and anti-viral activities.
5. Kwan Du Bu Fei Dang, *Houttuynia cordata* and *Coriolus versicolor* were essentially non-toxic to laboratory animals after oral

Introduction

Severe acute respiratory syndrome (SARS) was a life-threatening form of pneumonia caused by SARS-coronavirus (SARS-CoV). Symptoms included cough, high fever and headache that could progress to interstitial infiltrates in the lung. From late 2002 to mid-2003, SARS affected more than 8000 persons worldwide, mostly in China. Due to the absence of definitive therapeutic western medicines, agents active against this disease are still needed.

The herbal formula Kwan Du Bu Fei Dang (抗毒補肺湯) [KDBFD] was an innovative product packaged in the form of sachets. It was based on two classical, popularly used formulae for treating influenza-like diseases known as Wan Bin (溫病). The formula was a combination of Sang Ju Yin (桑菊飲) and Yu Ping Feng San (玉屏風散) plus two other herbs with well-known antiviral properties. The herbs in the formula were Folium Mori (3.75 g), Flos Chrysanthemi (1.5 g), Semen Armeniacae Amarum (3.0 g), Fructus Forsythiae (2.5 g), Herba Menthae (1.25 g), Radix Platycodonis (3.0 g), Radix Glycyrrhizae (1.25 g), Rhizoma Phragmitis (3.0 g), Radix Scutellariae (6.0 g), Folium Isatidis (8.0 g), Radix Astragali (7.5 g) and Radix Saposhnikovia (5.0 g). These raw herbs were boiled to form a decoction and then freeze-dried into granules and packaged (4.0 g per sachet), ready for reconstitution as a tea-like drink. The granules were prepared according to standard Good Manufacturing Practice.

Fung KP, et al. Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study. Hong Kong Med J Vol 17 No 1 Supplement 2 February 2011

Kwan Du Bu Fei Dang 抗毒補肺湯
(Fight Toxins and Tonify Lung Decoction), modified*

- *Huang Qi* 黃耆(Radix Astragali) 7.5g
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- *Da Qing Ye* 大青葉 (Folium Isatidis) 8g
- *Huang Qin* 黃芩 (Radix Scutellariae) 6g
- *Yu Xing Cao* 魚腥草(Herba Houttuyniae) [15 to 25 g]*
- *Qing Feng Teng* 青風藤 (Caulis Sinomenii) [6 to 12 g]*
- *Ling Zhi* 靈芝(Ganoderma) [6 to 12 g]*
- *Yun Zhi* 雲芝 (Trametes) [9 to 27 g]*

Kwan Du Bu Fei Dang 抗毒補肺湯
(Fight Toxins and Tonify Lung Decoction), modified*

- 80 subjects
- Take one sachet of KDBFD (4g) or placebo once per day for 7 days.
- On day 7: herb group showed increased T-lymphocytes, cytotoxic T-lymphocytes, helper T-lymphocytes, and NK cells
- On day 21: no significant elevation in both groups

Fung KP, et al. Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study. Hong Kong Med J Vol 17 No 1 Supplement 2 February 2011

Líng Zhī (Ganoderma)

- Nourishes the heart and calms the *shen* (spirit)
- Stops coughing and arrests wheezing
- Tonifies qi and nourishes blood

Yu Xing Cao (Herba Houttuyniae)

- Clears heat, eliminates toxins and drains pus
- Promotes normal urination

Chen J and Chen T. Chinese Medical Herbology and Pharmacology. Art of Medicine Press. 2004.

Immunomodulatory activities of the herbal formula Kwan Du Bu Fei Dang in healthy subjects: a randomised, double-blind, placebo-controlled study

KP Fung 馮國培
PC Leung 梁秉中
KWS Tsui 徐國榮
CCD Wan 溫志昌
KB Wong 黃錦波
MYM Waye 韋妙宜
WNS Au 區詠娥
CK Wong 黃振國
WKC Lam 林偉基
BSC Lau 劉碧珊

Key Messages

1. The herbal formula Kwan Du Bu Fei Dang transiently modulated the human immune system.
2. *Coriolus versicolor* had an immunostimulatory effect in mouse splenic lymphocytes.
3. *Ganoderma lucidum* inhibited SARS-CoV RNA-dependent RNA polymerase.
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Introduction

Severe acute respiratory syndrome (SARS) was a life-threatening form of pneumonia caused by SARS-coronavirus (SARS-CoV). Symptoms included cough, high fever and headache that could progress to interstitial infiltrates in the lung. From late 2002 to mid-2003, SARS affected more than 8000 persons worldwide, mostly in China. Due to the absence of definitive therapeutic western medicines, agents active against this disease are still needed.

The herbal formula Kwan Du Bu Fei Dang (抗毒補肺湯) [KDBFD] was an innovative product packaged in the form of sachets. It was based on two classical, popularly used formulae for treating influenza-like diseases known as Wan Bin (溫病). The formula was a combination of Sang Ju Yin (桑菊飲) and Yu Ping Feng San (玉屏風散) plus two other herbs with well-known antiviral properties. The herbs in the formula were Folium Mori (3.75 g), Flos Chrysanthemi (1.5 g), Semen Armeniacae Amarum (3.0 g), Fructus Forsythiae (2.5 g), Herba Menthae (1.25 g), Radix Platycodonis (3.0 g), Radix Glycyrrhizae (1.25 g), Rhizoma

Department of Chemical Pathology
CK Wong, WKC Lam
Institute of Chinese Medicine
BSC Lau

RFCID project number: 02040332

Principal applicant and corresponding author:
Prof Kwok Pui Fung
Institute of Chinese Medicine, Rm E203, Science Centre East Block, The Chinese University of Hong Kong, Shatin, NT, Hong Kong SAR, China
Tel: (852) 2609 6873
Fax: (852) 2603 5123
Email: kpfung@cuhk.edu.hk

double-blinded, placebo-controlled study. Only the results of the second study are reported. The results of the first study as well as the immunomodulatory and anti-SARS activities of HC have been published elsewhere.[1,2]

Volunteers were screened to ensure they were healthy, based on results of their complete blood count, levels of lactate dehydrogenase and creatine kinase, renal function and liver function. A total of 80 healthy subjects were enrolled. Each eligible subject was randomised to receive placebo or KDBFD treatment, according to a computer-generated code list. Neither the investigators nor subjects knew the treatments assigned. The placebo was prepared to appear, smell, and taste indistinguishable from the KDBFD, and was devoid of pharmacological activity and toxicity. Subjects were required to take one sachet of KDBFD (4 g) or placebo once per day for 7 days. Blood samples were collected from them on

immunostimulatory effect. They were found to stimulate the proliferation of $CD4^+$ helper T cells and $CD8^+$ cytotoxic T cells, which may in turn help to prevent the development of lymphopaenia and the pathogenesis of SARS.

SARS-CoV RNA-dependent RNA polymerase (RdRp) and SARS-CoV 3C-like protease ($3CL^{pro}$) are two enzymes important in the viral replication processes. RdRp is responsible for both positive and negative strand RNA synthesis. It is the essential enzyme in a replicase complex that contains additional viral and cellular proteins. In contrast, $3CL^{pro}$ is responsible for releasing the key replicative enzymes such as RdRp and helicase from the polyprotein precursors.[4] The functional importance of RdRp and $3CL^{pro}$ in the life cycle of SARS-CoV make them the key targets for the development of drugs directed against the virus.[5] From our results, GL and HC were the most potent TCM agents in inhibiting SARS-CoV RdRp and $3CL^{pro}$, respectively. They may be able to slow down viral growth and minimise its destructiveness.

From our results, GL and HC were the most potent TCM agents in inhibiting SARS-CoV RdRp and $3CL^{pro}$, respectively. They may be able to slow down viral growth and minimise its destructiveness.

Acknowledgements

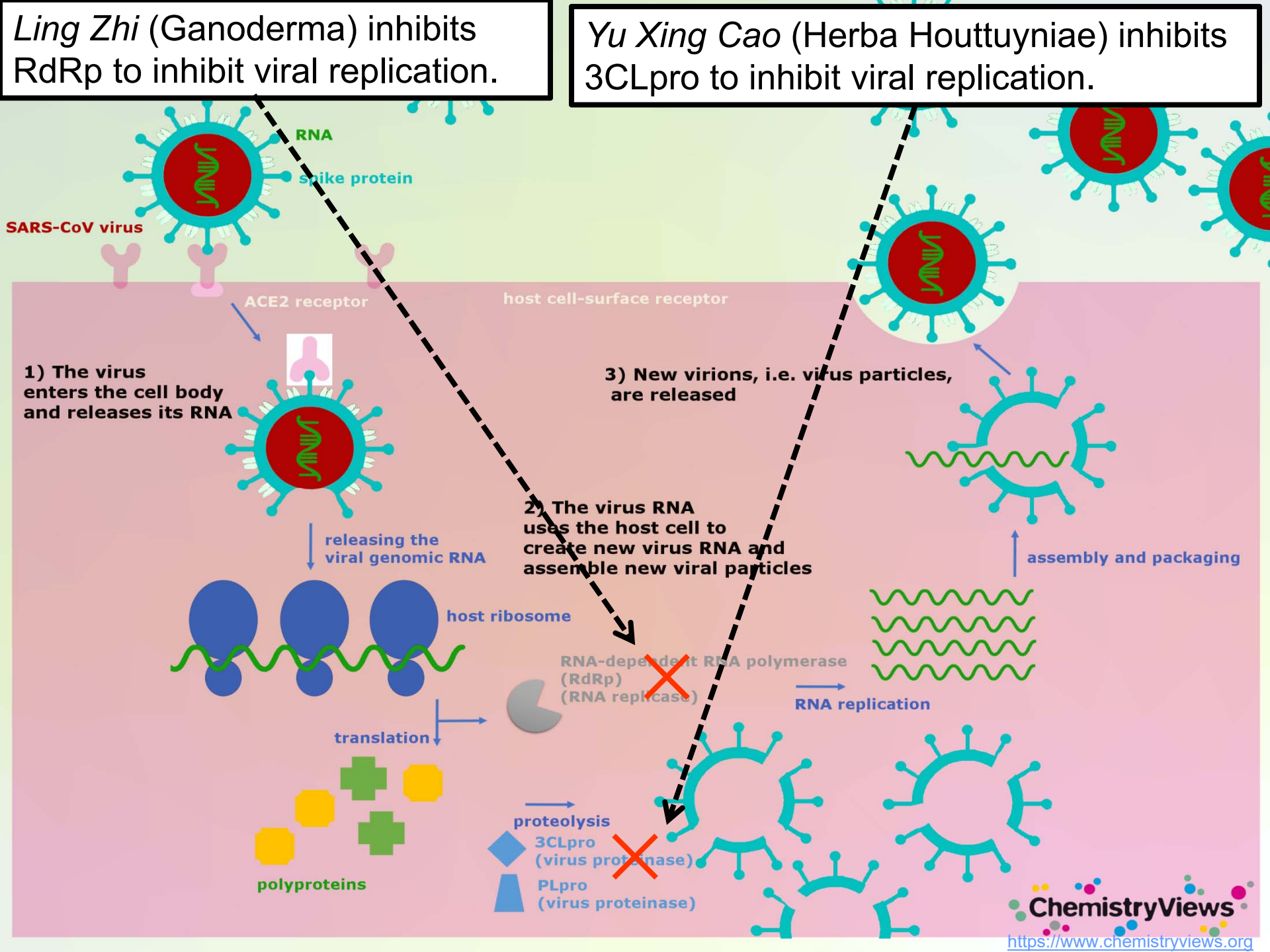
This study was supported by the Research Fund for the Control of Infectious Diseases, Food and Health Bureau, Hong Kong SAR Government (#02040332). The investigators thank Eu Yan Sang (HK) Limited.

References

1. Poon PM, Wong CK, Fung KP, et al. Immunomodulatory effects of a traditional Chinese medicine with potential antiviral activity: a self-control study. Am J Chin Med 2006;34:13-21.
2. Lau KM, Lee KM, Koon CM, et al. Immunomodulatory and anti-SARS activities of *Houttuynia cordata*. J Ethnopharmacol 2008;118:79-85.
3. O'Donnell R, Tasker RC, Roe MF. SARS: understanding the coronavirus: apoptosis may explain lymphopenia of SARS. BMJ 2003;327:620.
4. Thiel V, Ivanov KA, Putics A, et al. Mechanisms and enzymes involved in SARS coronavirus genome expression. J Gen Virol 2003;84:2305-15.
5. Gan YR, Huang H, Huang YD, et al. Synthesis and activity of an octapeptide inhibitor designed for SARS coronavirus main proteinase. Peptides 2006;27:622-5.

Ling Zhi (Ganoderma) inhibits RdRp to inhibit viral replication.

Yu Xing Cao (Herba Houttuyniae) inhibits 3CLpro to inhibit viral replication.



Journal of Ethnopharmacology 118 (2008) 79–85

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Immunomodulatory and anti-SARS activities of *Houttuynia cordata*

Kit-Man Lau[a,1], Kin-Ming Lee[a,1], Chi-Man Koon[a,1], Crystal Sao-Fong Cheung[b], Ching-Po Lau[a], Hei-Ming Ho[b], Mavis Yuk-Ha Lee[a], Shannon Wing-Ngor Au[b], Christopher Hon-Ki Cheng[b], Clara Bik-San Lau[c], Stephen Kwok-Wing Tsui[b], David Chi-Cheong Wan[b], Mary Miu-Yee Waye[b], Kam-Bo Wong[b], Chun-Kwok Wong[d], Christopher Wai-Kei Lam[d], Ping-Chung Leung[a], Kwok-Pui Fung[a,b,*]

[a] *Institute of Chinese Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China*
[b] *Department of Biochemistry, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China*
[c] *School of Pharmacy, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China*
[d] *Department of Chemical Pathology, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China*

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Anti-viral
3C-like protease
RNA-dependent RNA polymerase

ABSTRACT

Background: Severe acute respiratory syndrome (SARS) is a life-threatening form of pneumonia caused by SARS coronavirus (SARS-CoV). From late 2002 to mid 2003, it infected more than 8000 people worldwide, of which a majority of cases were found in China. Owing to the absence of definitive therapeutic Western medicines, *Houttuynia cordata* Thunb. (Saururaceae) (HC) was shortlisted by Chinese scientists to tackle SARS problem as it is conventionally used to treat pneumonia.

Aim of the study: The present study aimed to explore the SARS-preventing mechanisms of HC in the immunological and anti-viral aspects.

Results: Results showed that HC water extract could stimulate the proliferation of mouse splenic lymphocytes significantly and dose-dependently. By flow cytometry, it was revealed that HC increased the proportion of $CD4^+$ and $CD8^+$ T cells. Moreover, it caused a significant increase in the secretion of IL-2 and IL-10 by mouse splenic lymphocytes. In the anti-viral aspect, HC exhibited significant inhibitory effects on SARS-CoV 3C-like protease ($3CL^{pro}$) and RNA-dependent RNA polymerase (RdRp). On the other hand, oral acute toxicity test demonstrated that HC was non-toxic to laboratory animals following oral administration at 16 g/kg.

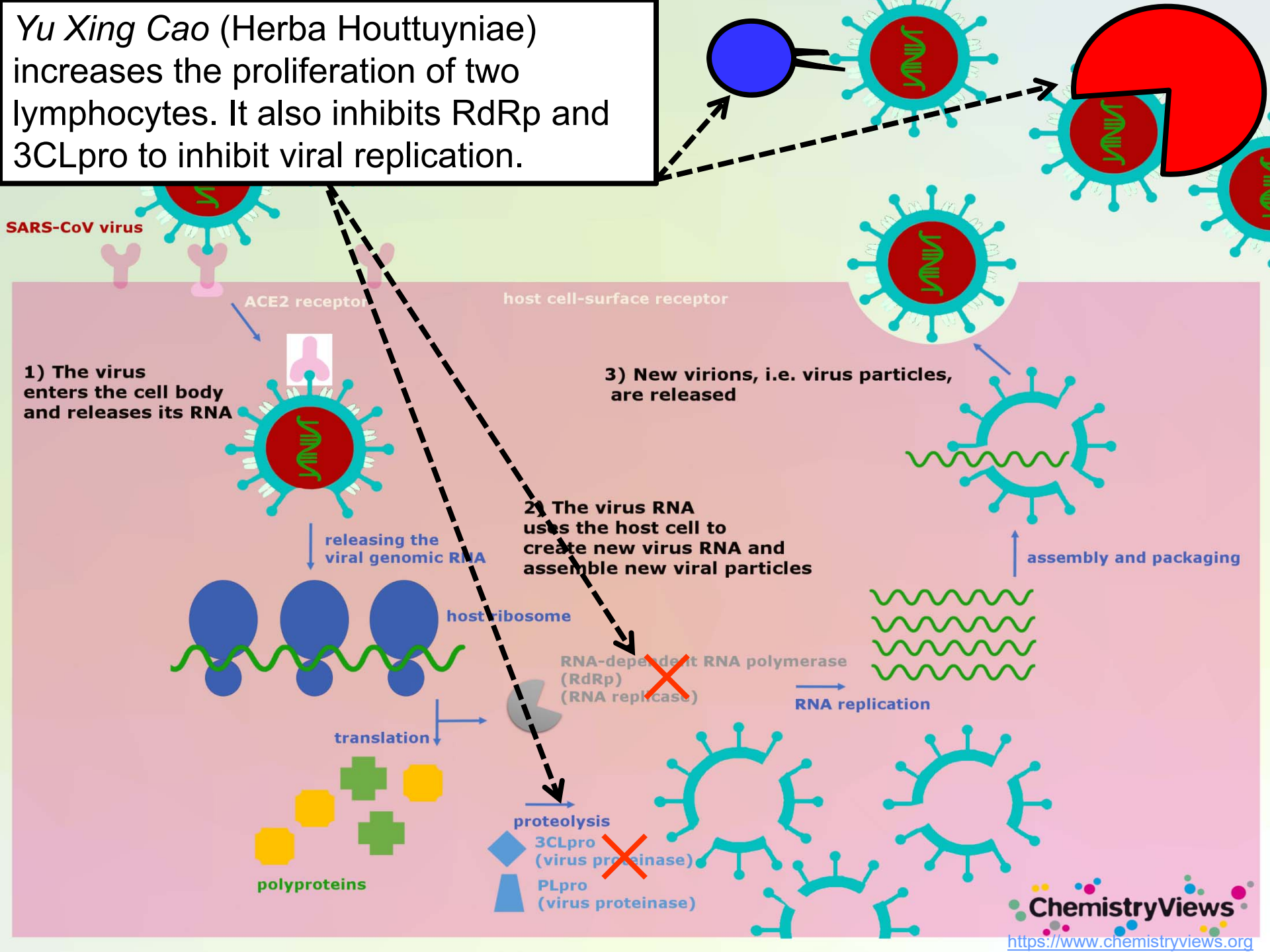
Conclusion: The results of this study provided scientific data to support the efficient and safe use of HC to combat SARS.

Yu Xing Cao (Herba Houttuyniae)

- *Yu Xing Cao* increases the proliferation of two lymphocytes:
  - CD8+ cytotoxic T lymphocytes
  - CD4+ helper T lymphocytes
- *Yu Xing Cao* blocks SARS-CoV replicaiton by inhibiting 3C-like protease ($3CL^{Pro}$) and RNA-dependent RNA polymerase (RdRp).

- Lau KM, et al. Immunomodulatory and anti-SARS activities of Houttuynia cordata. Institute of Chinese Medicine, The Chinese University of Hong Kong, Shatin, Hong Kong SAR, China. J Ethnopharmacol. 2008 Jun 19;118(1):79-85.

Yu Xing Cao (Herba Houttuyniae) increases the proliferation of two lymphocytes. It also inhibits RdRp and 3CLpro to inhibit viral replication.



Yu Fang

預防

Prevention

Shang Han

伤寒

(Cold Damage)

Wen Bing

温病

(Warm Disease)

Hui Fu

恢复

Recovery

Shā Shēn Mài Dōng Tāng 沙參麥冬湯 (Glehnia and Ophiopogonis Decoction)

- *Sha Shen* (Radix Glehniae seu Adenophorae) 9g
- *Mai Dong* (Radix Ophiopogonis) 9g
- *Yu Zhu* (Rhizoma Polygonati Odorati) 6g
- *Tian Hua Fen* (Radix Trichosanthis) 4.5g
- *Sang Ye* (Folium Mori) 4.5g
- *Bai Bian Dou* (Semen Lablab Album) 4.5g
- *Gan Cao* (Radix et Rhizoma Glycyrrhizae) 3g

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Shā Shēn Mài Dōng Tāng 沙參麥冬湯 (Glehnia and Ophiopogonis Decoction)

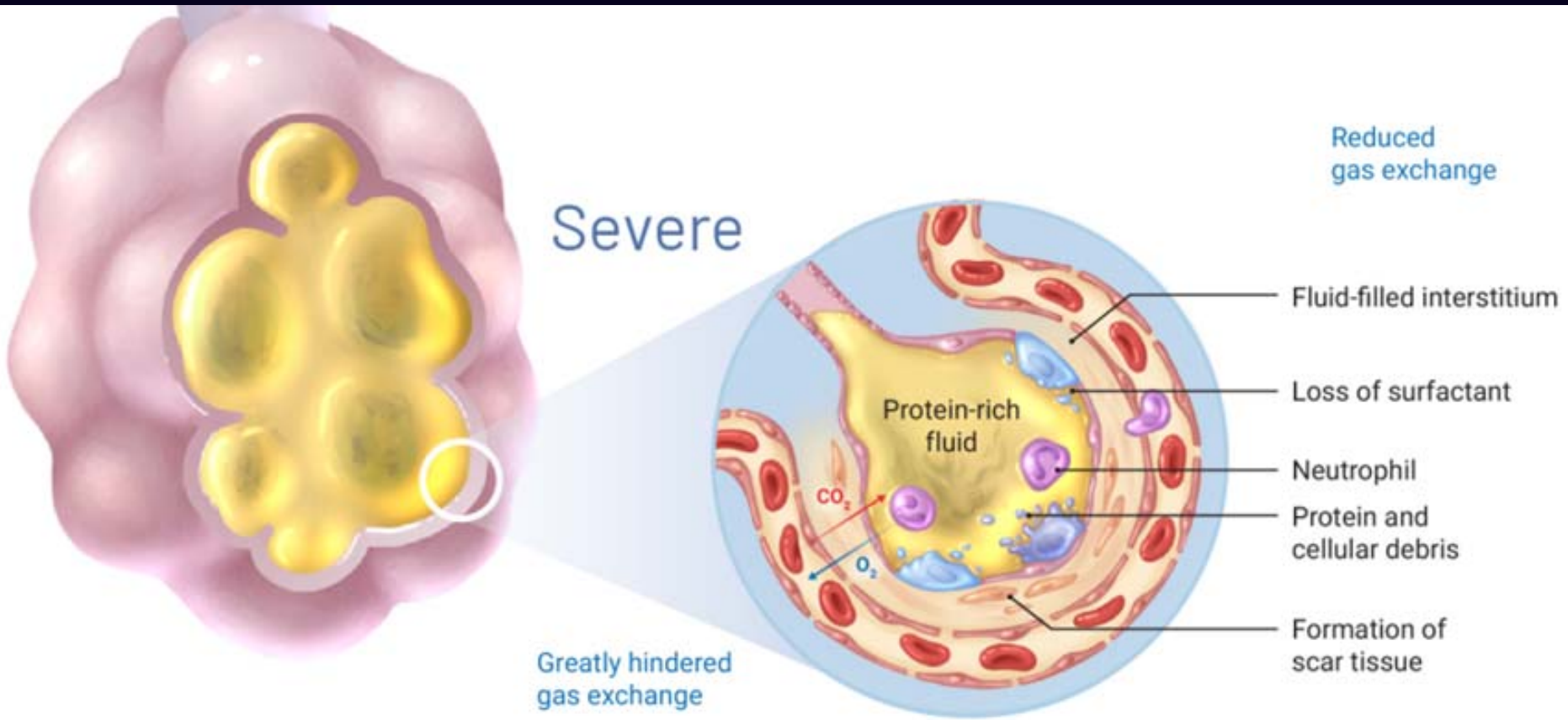
- Clears and nourishes the Lung and Stomach
- Promotes secretion of body fluids and moistens dryness

Original Source: *Wen Bing Tiao Bian* (Systematic Differentiation of Warm Disease) by Wu Ju-Tong in 1798

Shā Shēn Mài Dōng Tāng 沙參麥冬湯 (Glehnia and Ophiopogonis Decoction)

- Indications (TCM): Dryness damaging Lung and Stomach yin: dry throat, thirst, fever, dry coughing, and dry, sticky sputum.

- Indications (WM): Atrophic gastritis, epigastric pain, lung cancer, pneumonia, bronchitis, dry cough, cough and wheezing in children, and diabetes mellitus



https://www.visualcapitalist.com/visualizing-what-covid-19-does-to-your-body/

NIH U.S. National Library of Medicine

ClinicalTrials.gov

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Condition or disease COVID x

Other terms TCM x

Country

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11 Studies found for: **tcm | covid-19**

Your search included: **COVID**

Learn more about clinical studies related to COVID-19:

- **ClinicalTrials.gov**: Federally-funded clinical studies related to COVID-19
- **WHO Trial Registry Network**: COVID-19 studies from the ICTRP database
- **CDC**: Information for Clinicians on Therapeutic Options for COVID-19 Patients

Fuzheng Huayu (Support the Righteousness and Resolve Stasis)

Study Design Go to

Study Type :	Interventional (Clinical Trial)
Estimated Enrollment :	136 participants
Allocation:	Randomized
Intervention Model:	Parallel Assignment
Masking:	Double (Participant, Investigator)
Primary Purpose:	Treatment
Official Title:	A Randomized, Placebo-Controlled, Multi-Center Study on the Efficacy and Safety of Fuzheng Huayu on Pulmonary Fibrosis Due to 2019-nCoV
Estimated Study Start Date :	February 15, 2020
Estimated Primary Completion Date :	December 2022
Estimated Study Completion Date :	December 2022

Fuzheng Huayu (Support the Righteousness and Resolve Stasis)

Arm	Intervention/treatment
Experimental: Basic Treatment+Fuzheng Huayu Tablet Capcule with N-acetylcysteine+ Tablet with Fuzheng Huayu	Drug: N-acetylcysteine+ Fuzheng Huayu Tablet The subjects will be taking 1 N-acetylcysteine capcule and 4 Fuzheng Huayu tablets three times a day for 24 weeks.
Placebo Comparator: Basic Treatment+Placebo Capcule with N-acetylcysteine+ Tablet with starch	Drug: N-acetylcysteine+Placebo The subjects will be taking 1 N-acetylcysteine capcule and 4 Placebo tablets three times a day for 24 weeks.

Fuzheng Huayu (Support the Righteousness and Resolve Stasis)

- *Dan Shen* (Radix et Rhizoma Salviae Miltiorrhizae)
- *Song Hua Fen* (Pollen Pini)
- *Tao Ren* (Semen Persicae)
- *Jiao Gu Lan* (Rhizoma seu Herba Gynostemmatis)
- *Dong Chong Xia Cao* (Cordyceps)
- *Wu Wei Zi* (Fructus Schisandrae Chinensis)

Yu Fang

預防

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(Cold Damage)

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(Warm Disease)

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恢复

Recovery

Summary

WM	Covid-19	TCM
✓	Prevention	✓+
	Mild (81%)*	✓
✓	Moderate (14%)*	✓
✓	Severe (<5%)*	
	Recovery	✓

Marco Cascella; Michael Rajnik; Arturo Cuomo; Scott C. Dulebohn; Raffaela Di Napoli.Features, Evaluation and Treatment Coronavirus (COVID-19). StatPearls Publishing; April 6, 2020.

References (WHO, NIH, CDC, FDA)

Organization	Link
WHO	**https://www.who.int/emergencies/diseases/novel-coronavirus-2019**
NIH	**https://www.nih.gov/health-information/coronavirus**
CDC	https://www.cdc.gov/coronavirus/2019-ncov/about/index.html
FDA	https://www.fda.gov/emergency-preparedness-and-response/mcm-issues/novel-coronavirus-2019-ncov

References (WM)

Organization	Link
Elsevier	https://www.elsevier.com/connect/coronavirus-information-center
Johns Hopkins University	https://coronavirus.jhu.edu/
New England Journal of Medicine	https://www.nejm.org/doi/full/10.1056/NEJMoa2001017
JAMA	https://jamanetwork.com/journals/jama/pages/coronavirus-alert
The Lancet	https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(20)30305-6/fulltext
Internet Book of Critical Care	https://emcrit.org/ibcc/covid19/?fbclid=IwAR31Xy-vkhL39xSWNAqkx3fECRR2yQLVbyWD2EOOoDG7FYv2WXqdQm7Lu_U#biology

References (TCM)

Organization	Link
Lotus Institute	https://www.elotus.org/articles
Guidance of Covid-19 7th Edition	https://mp.weixin.qq.com/s/Wikq6hrnKIZl7Iumg2bq5A
Guidance of Covid-19 English Edition	https://mp.weixin.qq.com/s/nOAmosQ4YqkXHKdJbBE9GA
Acupuncture in the Treatment of COVID-19	https://www.journalofchinesemedicine.com/acupuncture-in-the-treatment-of-covid-19-an-exploratory-study.html?fbclid=IwAR2dUlmkqaEHnjjP5-jcJepRq6G2R8BkSWnTE510-axx57HJdRaszd1pgJQ

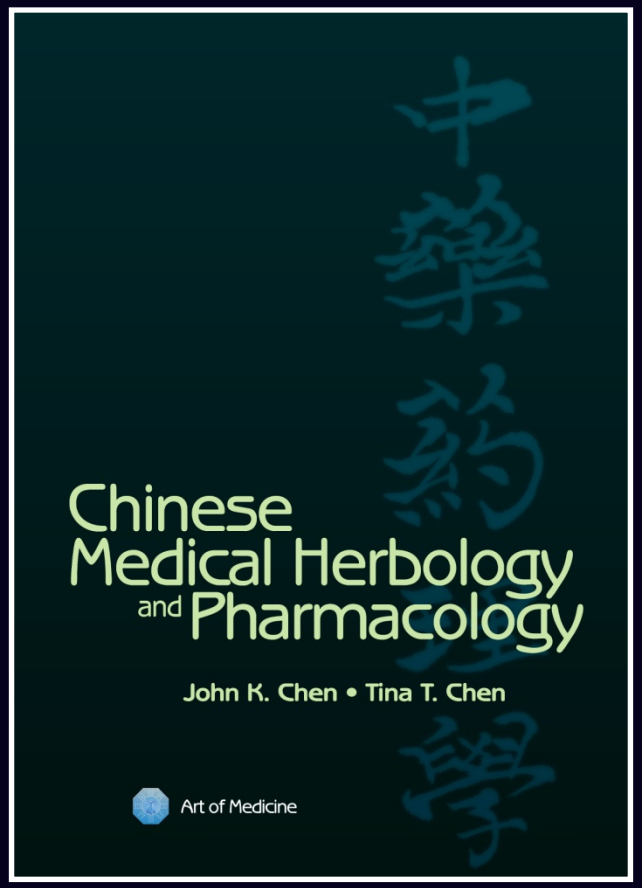
Contact

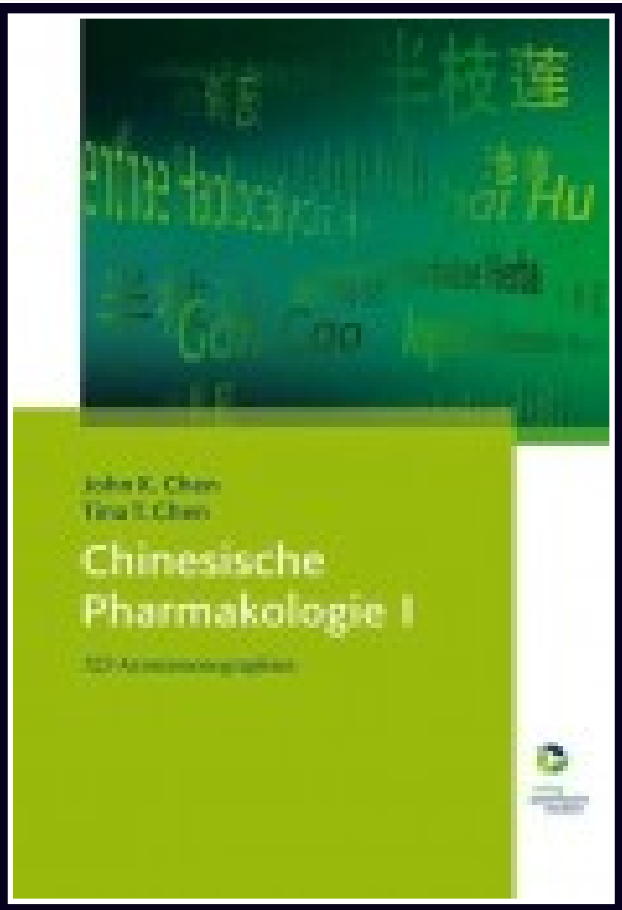
- Lotus Institute of Integrative Medicine
- www.eLotus.org

- Art of Medicine Press
- www.aompress.com

- John K. Chen, Ph.D., Pharm.D., O.M.D., L.Ac.
- drjohnchen@gmail.com

Single/Individual Herbs





Herbal Formulas