POTENSI OBAT HERBAL UNTUK SARS-COV-2

Muhammad Taher, PhD

Kulliyyah of Pharmacy

Outlines

- Plants as medicinal agent
- Covid-19 therapeutic strategy
- Computational study strategy
- Phytochemicals for covid-19
- Traditional Chinese medicine

Plants-traditional medicinal system

- Mesopotamia-2600 BCE
- Eqyptian Medicine-2900 BC
- Chinese Materia Medica-11000 BC
- Indian Ayurvedic- 1000 BC
- Roman- 100 CE
- Indonesian Jamu-?

Challenges in herbal medicines

- Preparation
- Delivery
- Side effects
- Standardization
- Toxicity/ Safety
- Regulatory

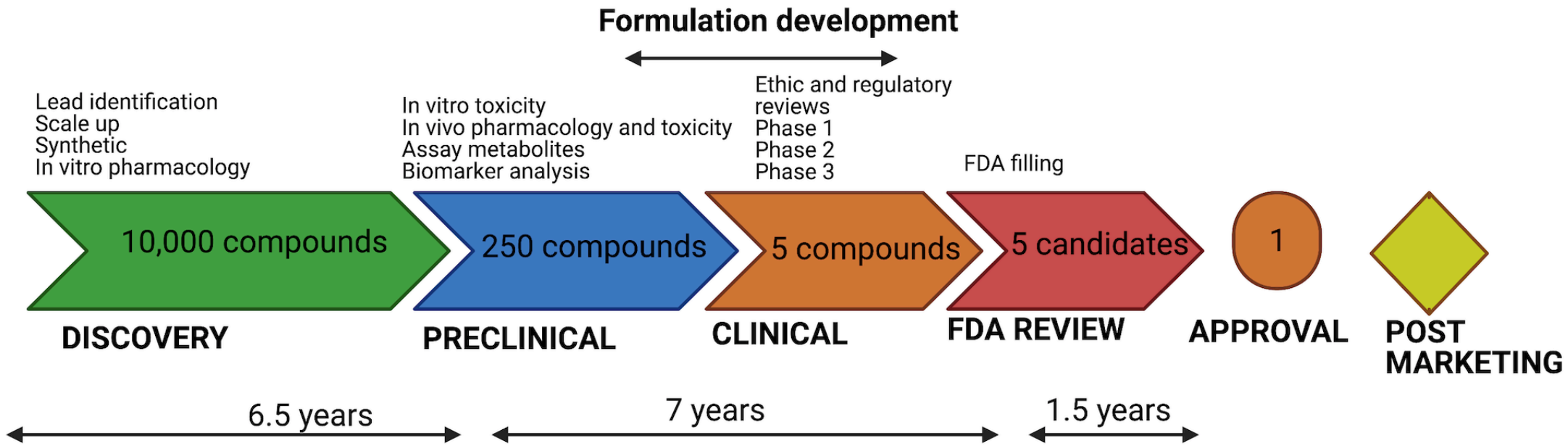
Role of traditional medicine

- ~ 80% of the population of the world relied on plant-derived traditional medicines for their primary health care (Martine Ekor, 2013)

Are herbal medicines still relevant?

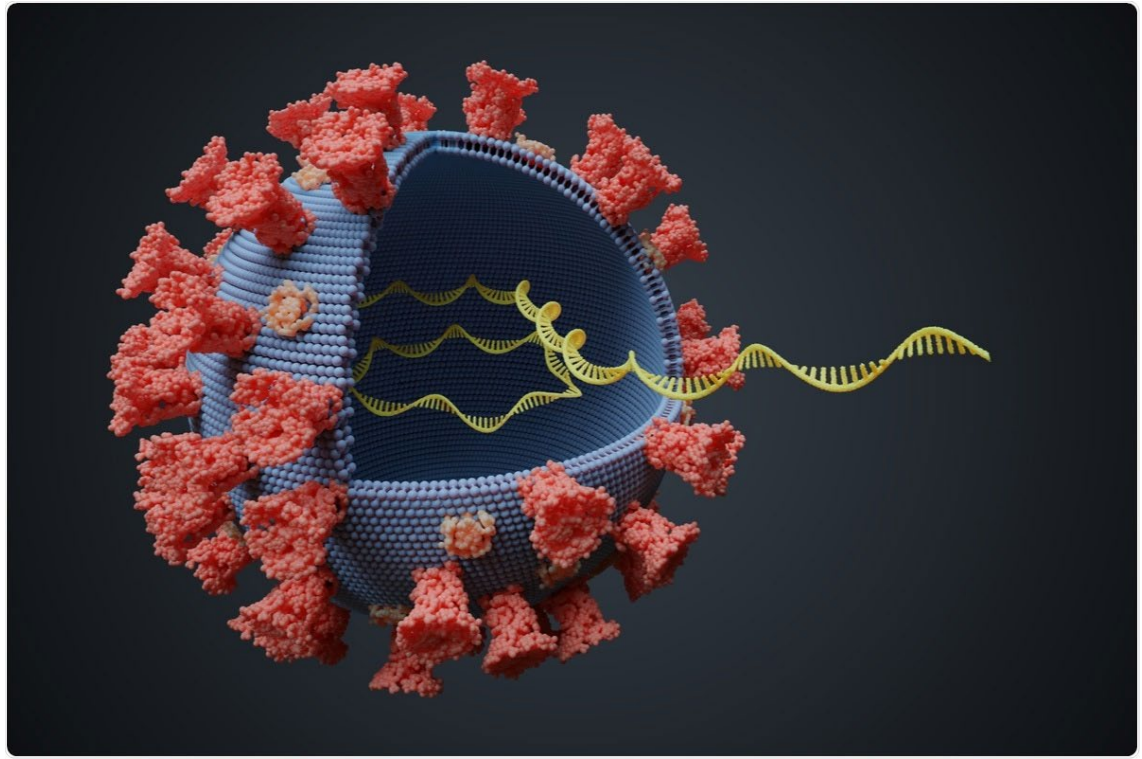
websource

Chart: Drug discovery and development



Challenges in SARS-COV-2 drug discovery

- Limited information
- Operational challenges
  - Facilities (handling)
  - Research materials



The ongoing coronavirus disease 2019 (COVID-19) global pandemic has affected more than 236 million people in over 220 countries and territories, resulting in more than 4.8 million deaths as of October 2021.

Currently, there is no effective treatment for COVID-19 to reduce mortality. The newly emerged viral pathogen causing COVID19 is the coronavirus SARS-CoV-2 (Hetrick, 2021)

COVID-19 Fact

https://www.worldometers.info/coronavirus/

(Oct 6,2021)

How to fight Covid-19

- Vaccines
- Medicines
- Monoclonal antibodies
- Interferon therapies
- Peptides
- Natural medicines

Target Sarcov-2

- Chemical structure of different natural compounds targeting Group Spike Protein; Helicase; Angiotensin-converting enzyme ACE2 receptor.
- Chemical structure of natural compounds targeting SARS-CoV 3CL protease.
- Chemical structure of natural compounds targeting papain- like cysteine protease (Khare, 2020).

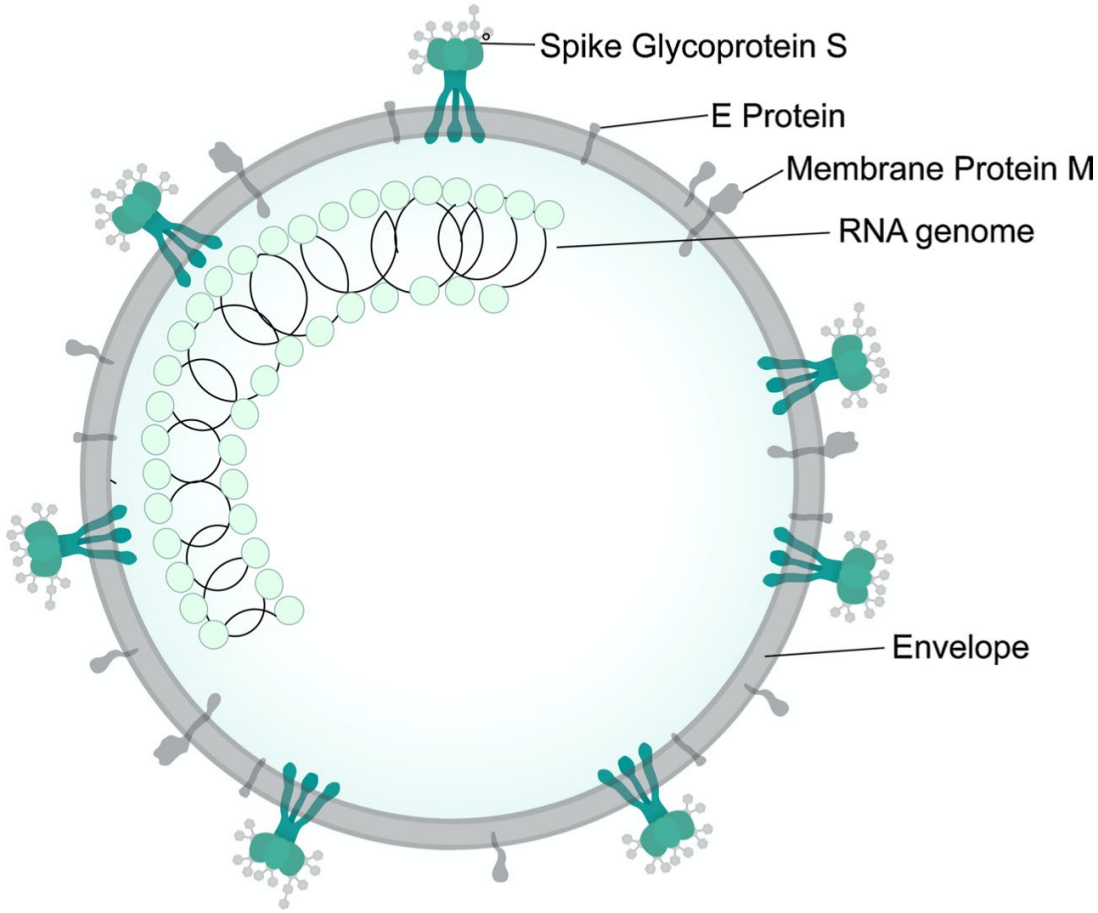
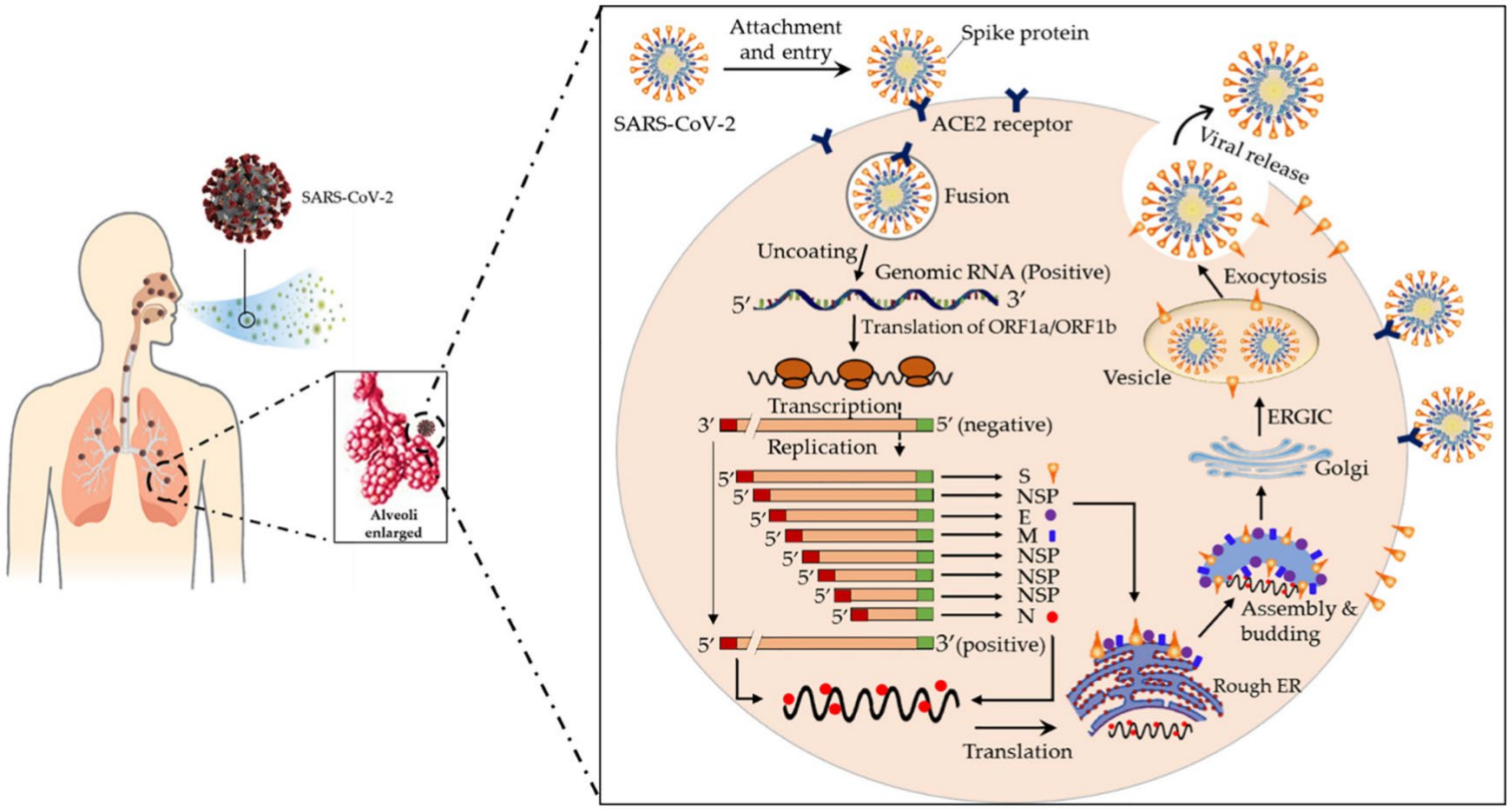
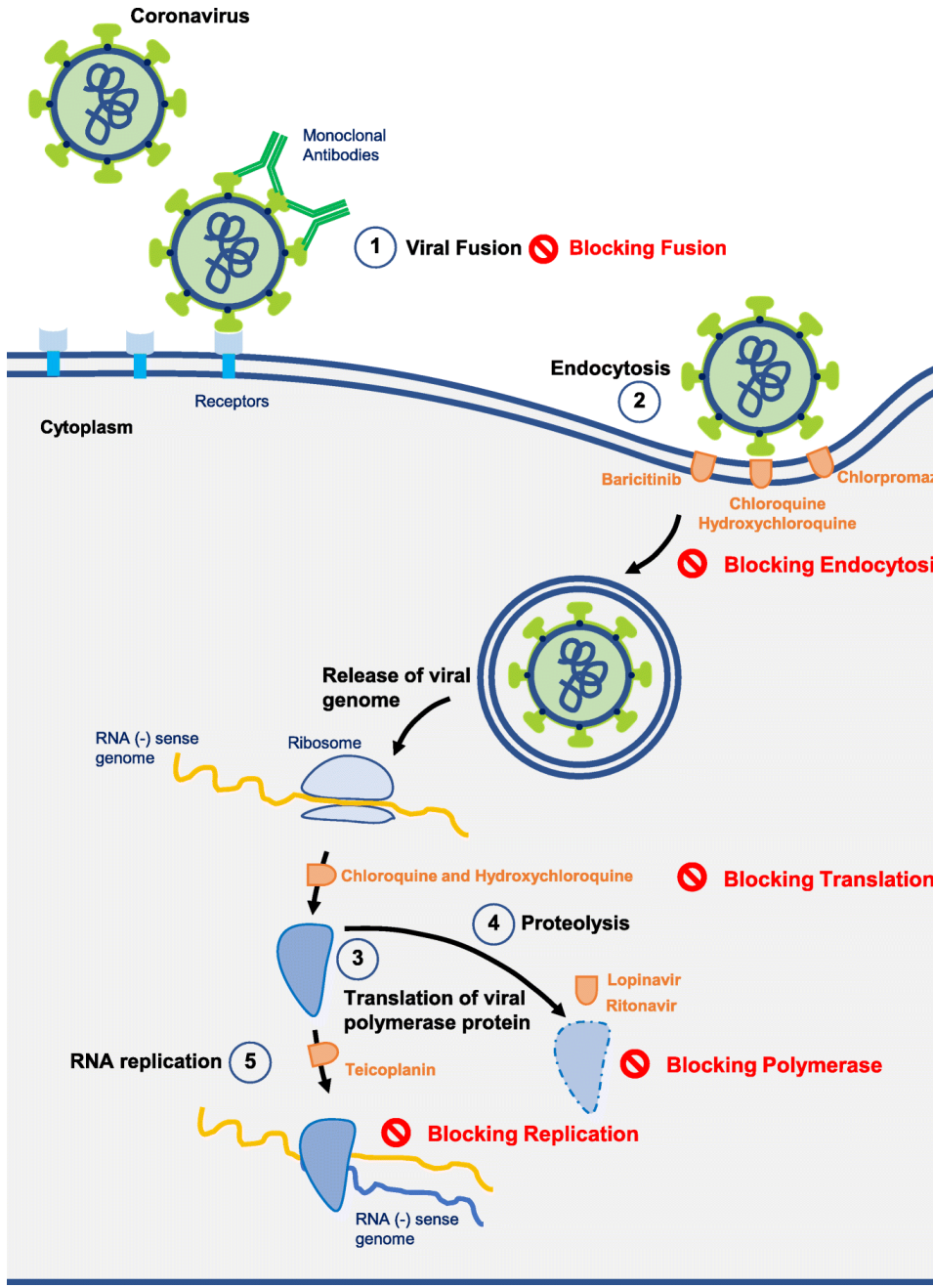


Fig. 1. The general structure of a coronavirus (reproduced from Wikipedia under CC licence 4.0). E protein = envelope protein.





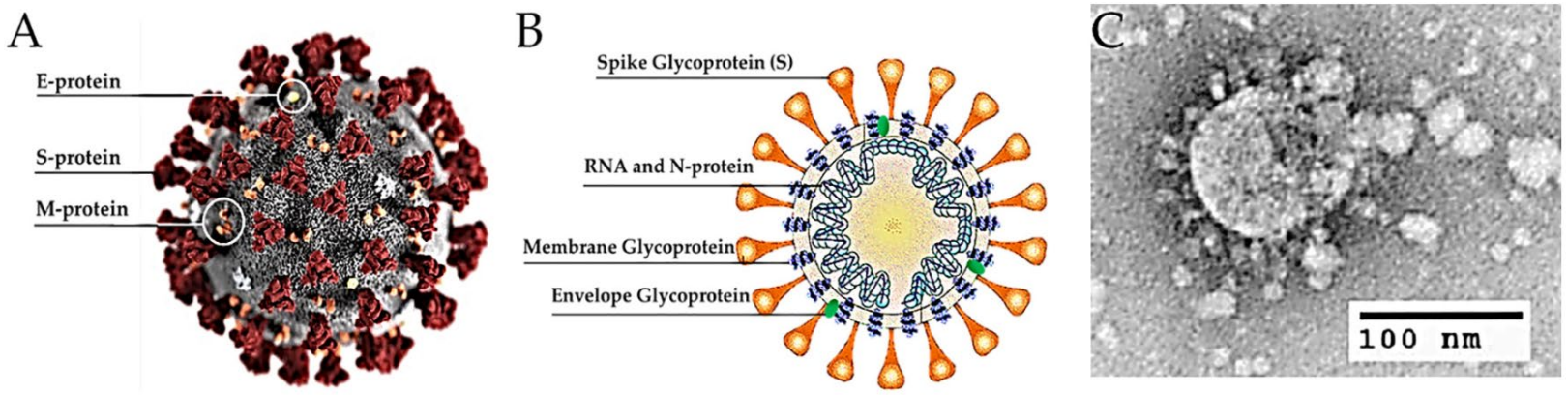
Understanding of the life cycle of SARS-CoV-2 in human lung cells (Abd E Aziz and Stockand, 2020) and possible target of therapy (Choudhary, 2021)

Potential drug therapies of COVID-19 (Wu et al., 2020)

1. Acting on the human immune system or human cells,
   - Blocking the signal pathways (ACE2 receptor and type-II transmembrane serine protease (TMPRSS2)
   - The innate immune system response
2. Acting on coronavirus itself
   - Preventing the synthesis of viral RNA (genetic material, enzymes binding, self-assembly process)

Enzyme targets

- 3-chymotrypsin-like protease ($3CL^{pro}$),
- Papain like protease (PL^{pro}),
- RNA-dependent RNA polymerase (RdRp)
- Protein spike (S) protein (Mani et al. 2020)



(A) Illustration of the SARS-CoV-2 (B) Schematic representation of the structure of SARS-CoV-2 (C) An electron microscopic image of a thin section of SARS-CoV-2 (Abd E Aziz and Stockand, 2020)

Strategies developing new Covid-19 drugs

- Using broad-spectrum antivirals: Interferons, ribavirin, and cyclophilin inhibitors used to treat coronavirus pneumonia fall into this category
- Using existing molecular databases to screen for molecules that may have therapeutic effect on coronavirus
- Using genomic information and pathological characteristics of different coronaviruses to develop new targeted drugs from scratch (Wu et al., 2020)

REPURPOSING DRUGS

- Available drugs used for RNA viruses (e.g. Ebola) may also be effective for treating COVID-19
  - Lopinavir–ritonavir (RdRp)
  - Favipiravir (RdRp)
  - Remdesivir (RdRp)
  - Arbidol (S protein)
  - Nafamostat (TMPRSS2)
  - Chloroquine/ hydroxychloroquine (ACE2)

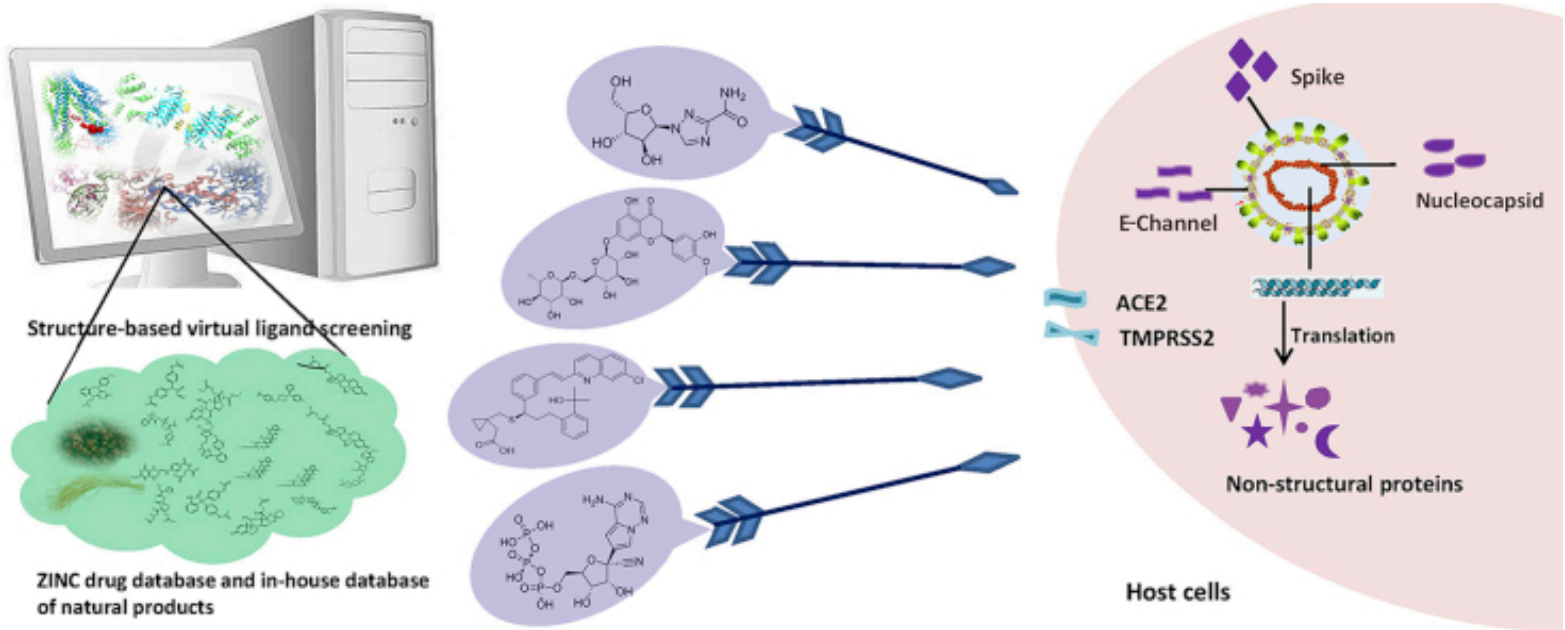
  - Etc….

Computational study

ZDD (ZINC drug database): 2924 compounds.

Natural products database: 1066 chemicals separated from traditional Chinese herbals

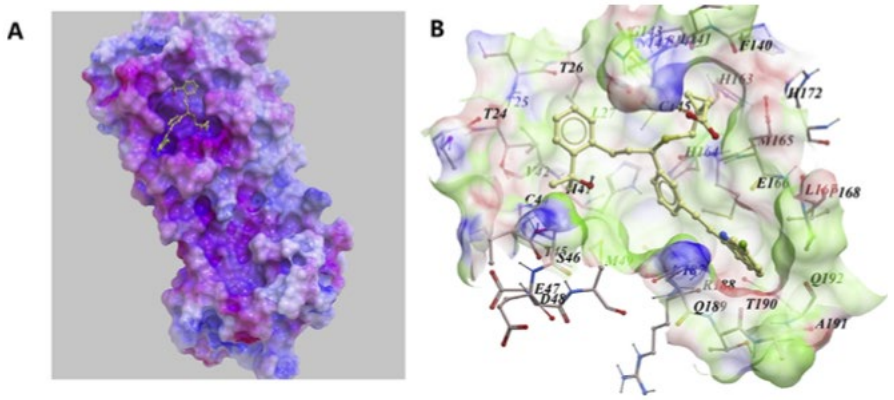
Anti-viral compounds library contains 78 known anti-viral drugs (WU, 2020)



Wu, 2020

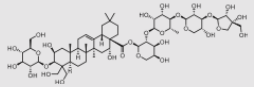
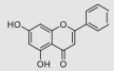
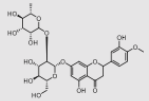
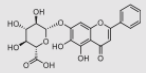
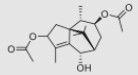
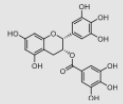
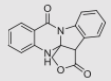
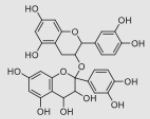
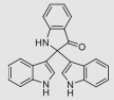
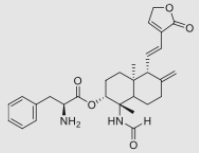
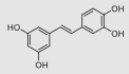
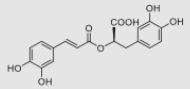
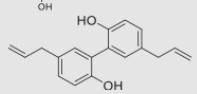
Papain-like proteinase (PLpro) (Montelukast)

Low-energy binding conformations of Montelukast bound to 3CLpro generated by molecular docking. (A) Montelukast was fitted well in the active pocket of SARS-CoV-2 3CLpro, 3CLpro was shown as electrostatic surface model. (B) Detailed view of montelukastin binding in the active pocket of 3CLpro (Supporting PDB file SARS_CoV-2_3CLpro_homo_Montelukast.pdb) (Wu, 202



Alignment of two protein sequences and subsequent homology modeling were performed by bioinformatics module of ICM 3.7.3 modeling software on an Intel i7 4960 processor (MolSoft LLC, San Diego, CA, USA).

Table 2 Potential PLpro inhibitors from in-house natural product database.

No.	Compound name	Structure	Pharmacological function	Source
1	Platycodin D		Anti-tumor, anti-inflammatory effect	*Platycodon grandiflorus*
2	Chrysin		Anti-virus, anti-inflammatory effect	*Scutellaria baicalensis*
3	Neohesperidin		Anti-tumor, anti-allergic effect	*Citrus aurantium* L.
4	Baicalin		Anti-tumor, anti-inflammatory, anti-bacterial, anti-virus effect	*Scutellaria baicalensis*
5	Sugetriol-3,9-diacetate		Anti-HBV, anti-HSV-1	*Cyperus rotundus*
6	(−)-Epigallocatechin gallate		Anti-oxidation, anti-tumor, treatment of depression	*Camellia sinensis*
7	Phaitanthrin D		Anti-virus	*Isatis indigotica* Fort.
8	2-(3,4-Dihydroxyphenyl)-2-[[2-(3,4-dihydroxyphenyl)-3,4-dihydro-5,7-dihydroxy-2*H*-1-benzopyran-3-yl]oxy]-3,4-dihydro-2*H*-1-benzopyran-3,4,5,7-tetrol		Anti-oxidant, anti-inflammatory, anti-tumor	*Vitis vinifera*
9	2,2-Di (3-indolyl)-3-indolone		Anti-virus	*Isatis indigotica* Fort.
10	(*S*)-(1*S*,2*R*,4a*S*,5*R*,8a*S*)-1-Formamido-1,4a-dimethyl-6-methylene-5-((*E*)-2-(2-oxo-2,5-dihydrofuran-3-yl)ethenyl) decahydronaphthalen-2-yl-2-amino-3-phenylpropanoate		Anti-virus, anti-inflammatory effect	Andrographolide derivatives
11	Piceatannol		Anti-tumor, anti-virus effect	*Vitis vinifera*
12	Rosmarinic acid		Anti-virus, anti-oxidant	*Salvia verticillata* L.
13	Magnolol		Anti-tumor, anti-microbial effect	*Magnolia officinalis*

Wu et al., 2020

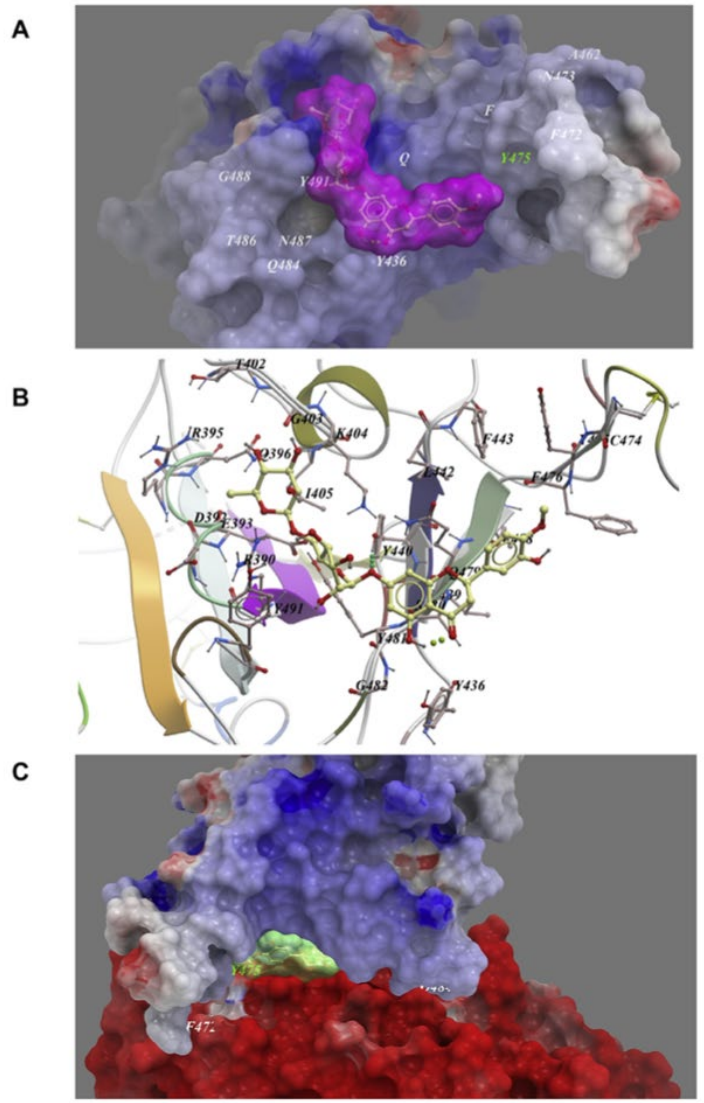
ACE2 inhibition (hesperidin)

Low-energy binding conformation of hesperidin bound to Spike RBD generated by molecular docking.

(A)Hesperidin was fitted into the shallow pocket in the surface of SARS-CoV-2 Spike RBD.

(B)Detailed view of hesperidin binding in the pocket of Spike RBD.

(C)Hesperidin blocks the interface of ACE2 and Spike RBD binding (Supporting PDB file SARS_CoV-2 _Spike_RBD_homo_Hesperidin.pdb) (Wu, 2020)



Herbal constituents with possible mechanisms to combat SARS-CoV-2 (Choudhary, 2021)

Compounds	Possible target in SARS-CoV-2
Quercetin	Inhibits $3CL^{pro}$ and interacts with viral HA protein to inhibit virus entry into the cell
Andrographolide	Inhibits $3CL^{pro}$ and virus-induced activation of RLRs signaling pathway
Glycyrrhizin	Inhibits replication, adsorption, and penetration of the virus
Baicalin	Inhibits 3CLpro and HIV-1 Env protein-mediated fusion with cells expressing CD4/CXCR4 or CD4/CCR5
Patchouli alcohol	Inhibits activation of PI3K/Akt and ERK/MAPK signaling pathways to block viral infection and replication
Luteolin	Inhibits 3CLpro and the expression of the coat protein I complex and interferes with viral replication at an early stage of infection
Hesperidin	Inhibits $3CL^{pro}$
Emodin	Blocks the SARS-CoV spike protein and ACE2 inter- action and inhibits 3a protein to reduces virus release

Herbal constituents with possible mechanisms to combat SARS-CoV-2 (Choudhary, 2021)

Compounds	Possible target in SARS-CoV-2
Resveratrol	Inhibits RNA and nucleocapsid expression
Kaempferol	Inhibits 3a channel protein
Lignan	Inhibits virus replication and $3CL^{pro}$
Betulinic acid	Inhibits virus replication and $3CL^{pro}$
Tanshinone	Inhibits $3CL^{pro}$ and PL^{pro}
Cryptotanshinone	Inhibits $3CL^{pro}$ and PL^{pro}
Dihydrotanshinone I	Inhibits $3CL^{pro}$ and PL^{pro}
Tanshinone IIA	Inhibits $3CL^{pro}$ and PL^{pro}
Curcumin	Inhibits virus replication and $3CL^{pro}$
Shikonin	Inhibits $3CL^{pro}$
Matrine	Improves abnormal laboratory parameters and clinical symptoms inpatients, and significantly shortens the time to nucleic acid conversion

Computational of covid 19

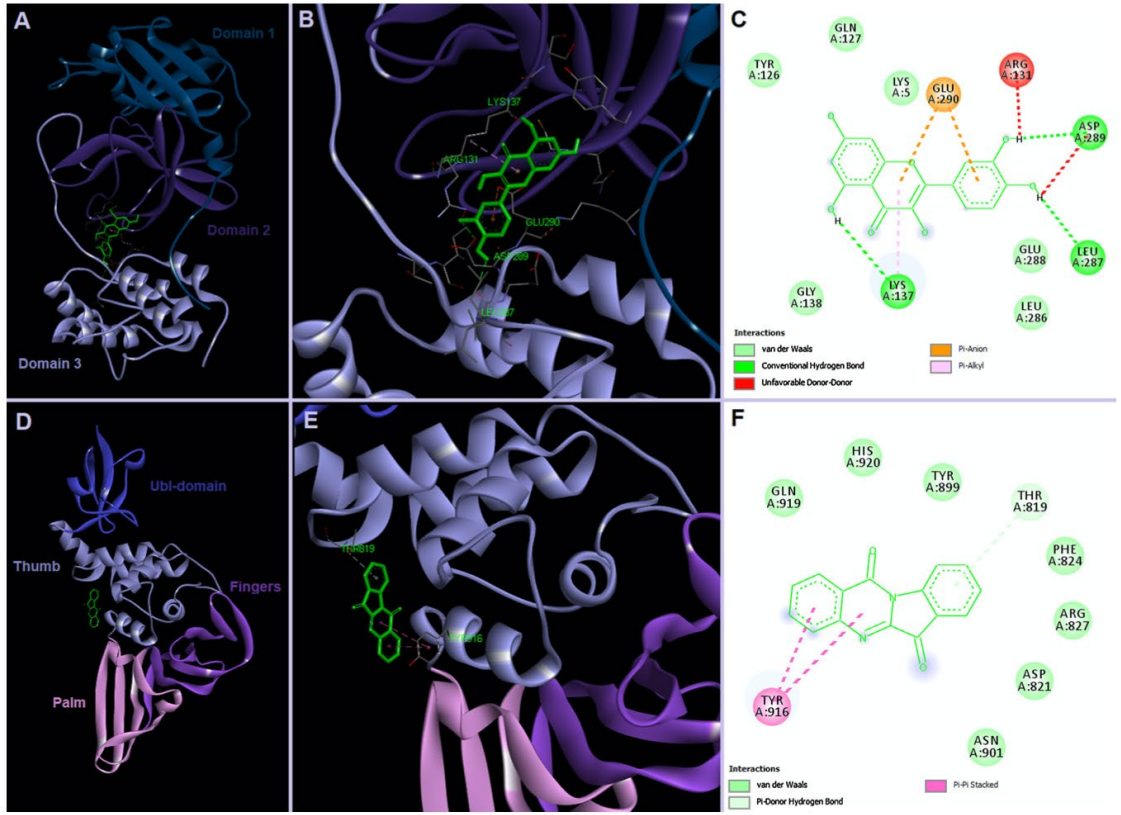
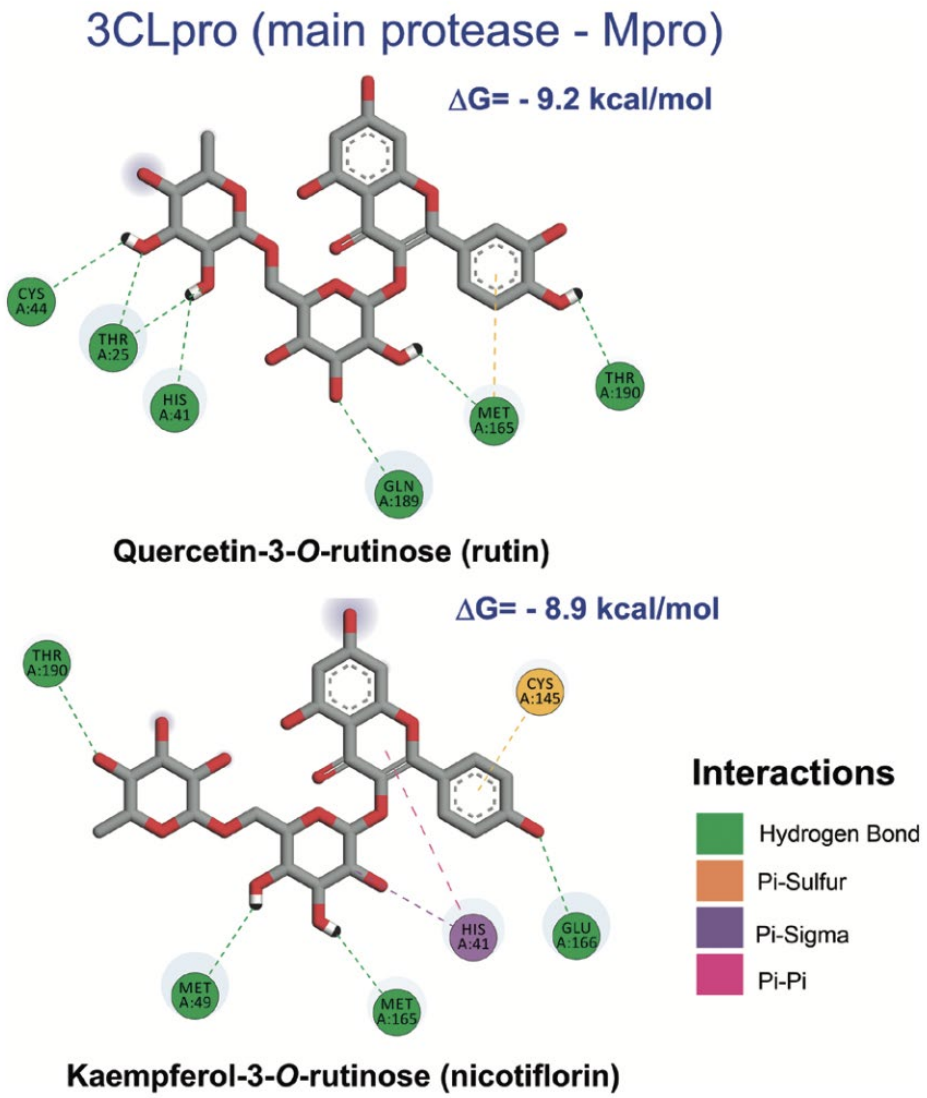
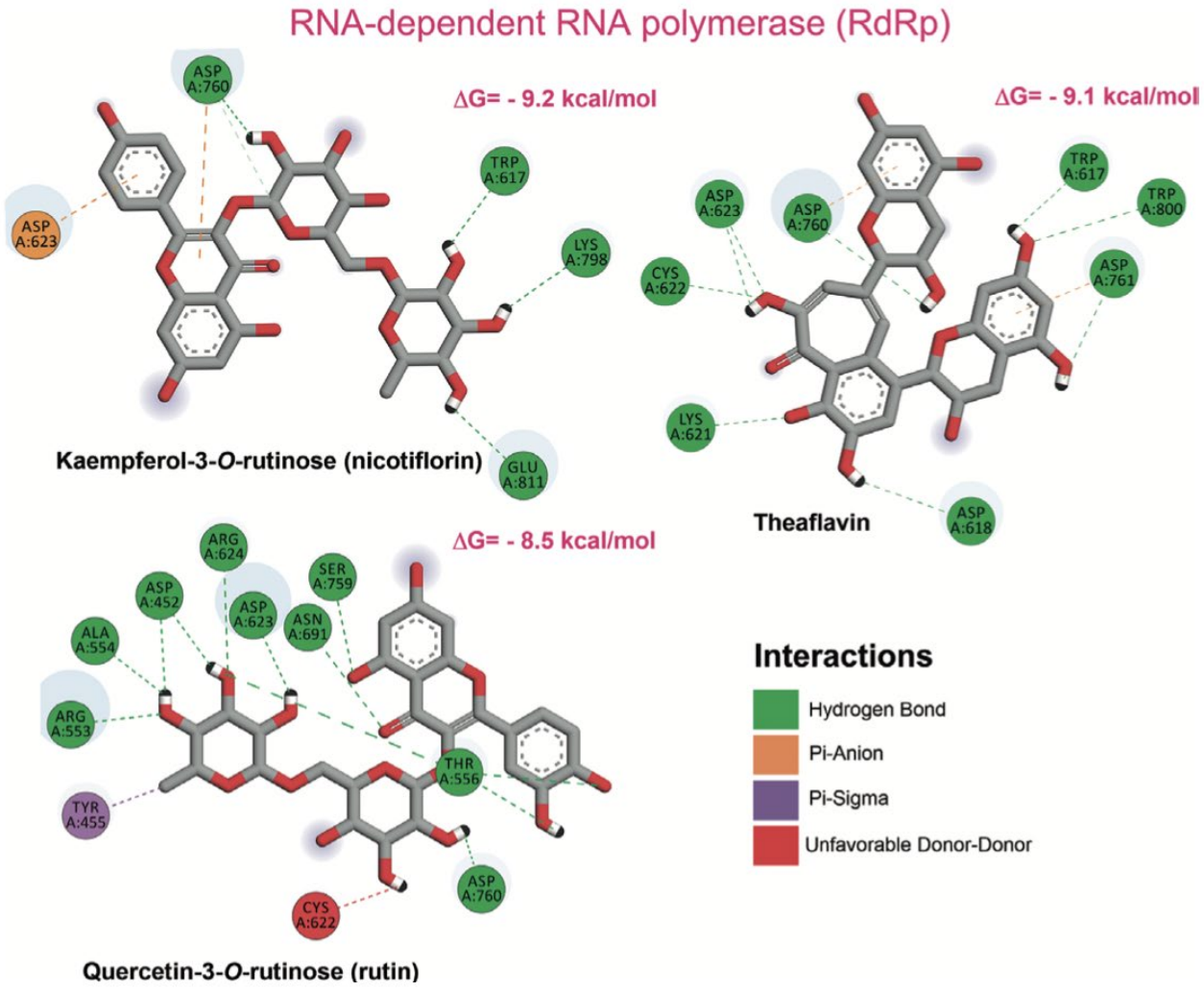


Fig. 3. Possible binding sites of quercetin in SARS-CoV-2 3CLpro and tryptanthrin in PLpro. Docking was performed in AutoDock Vina 1.1.2 (Trott and Olson, 2010) against target proteins generated by SWISS-MODEL (https://swissmodel.expasy.org/repository/species/2697049).

Mani et al., 2020

Binding activity of flavonoid glycoside on 3CLpro and RdRp (Da Silva et al., 2020)





Use of herbal in Covid-19 treatment

- TCM was used as a treatment for 91.5% of the COVID-19 cases in China

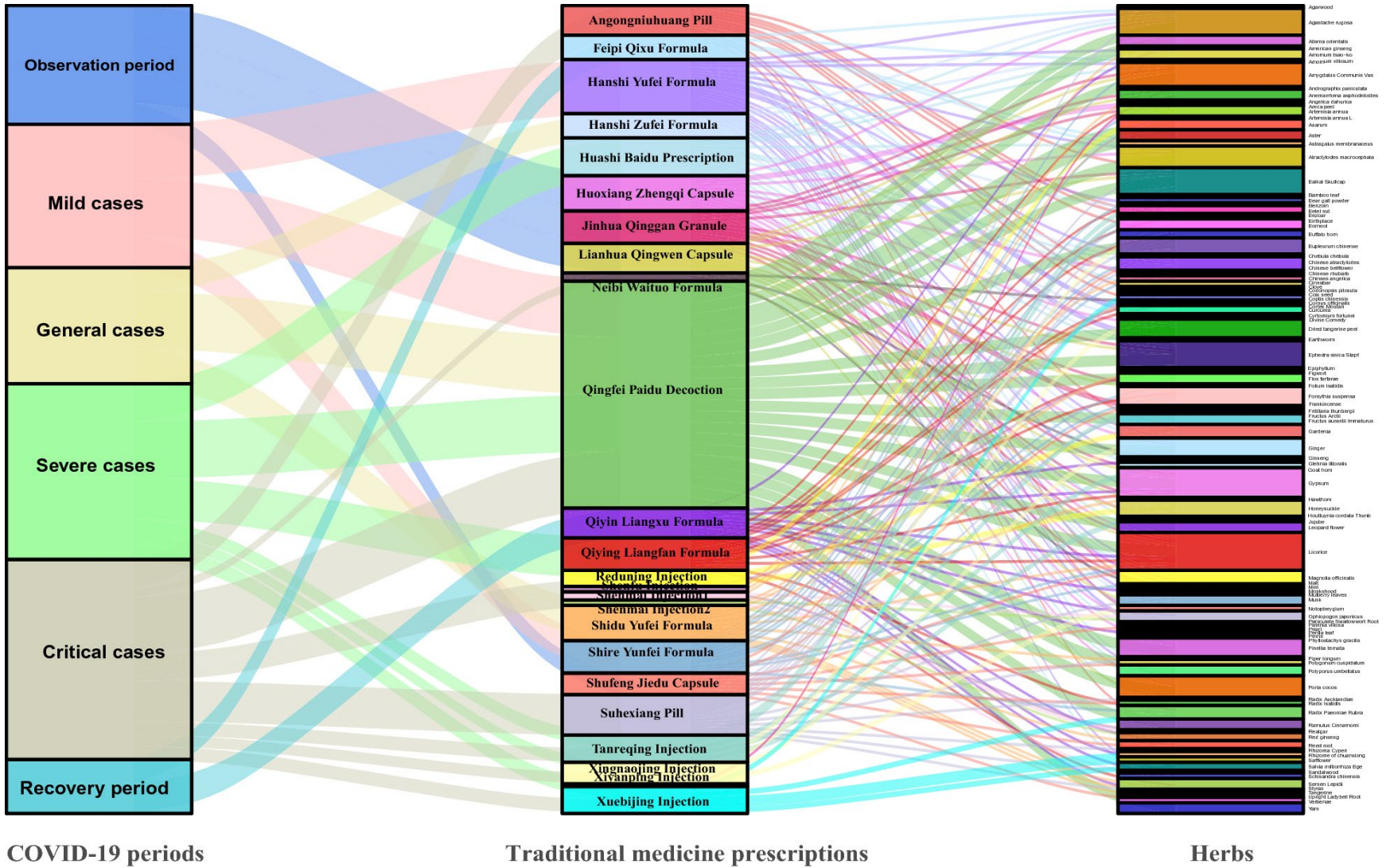
- Promising results in improving symptoms and reducing disease deterioration, mortality and recurrence rates (Luo, 2020

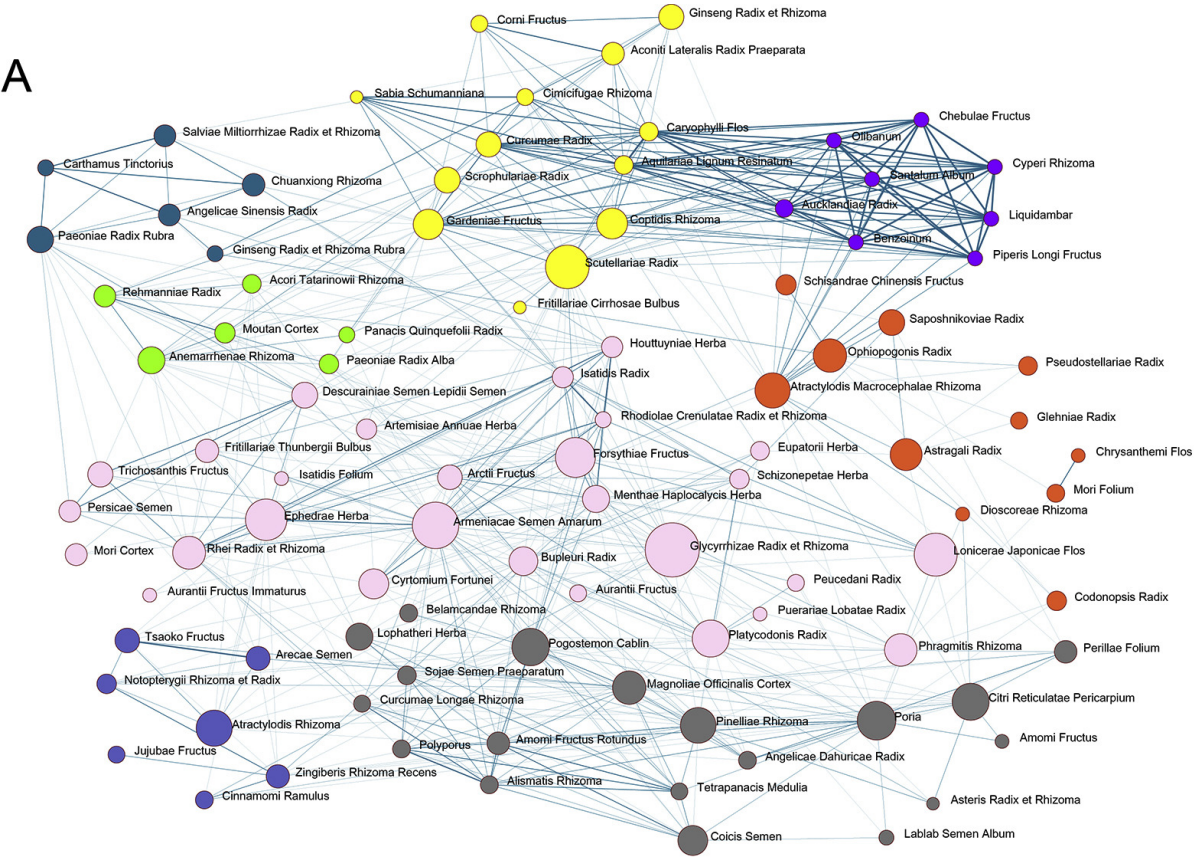
Herbal preparation used in Covid-19

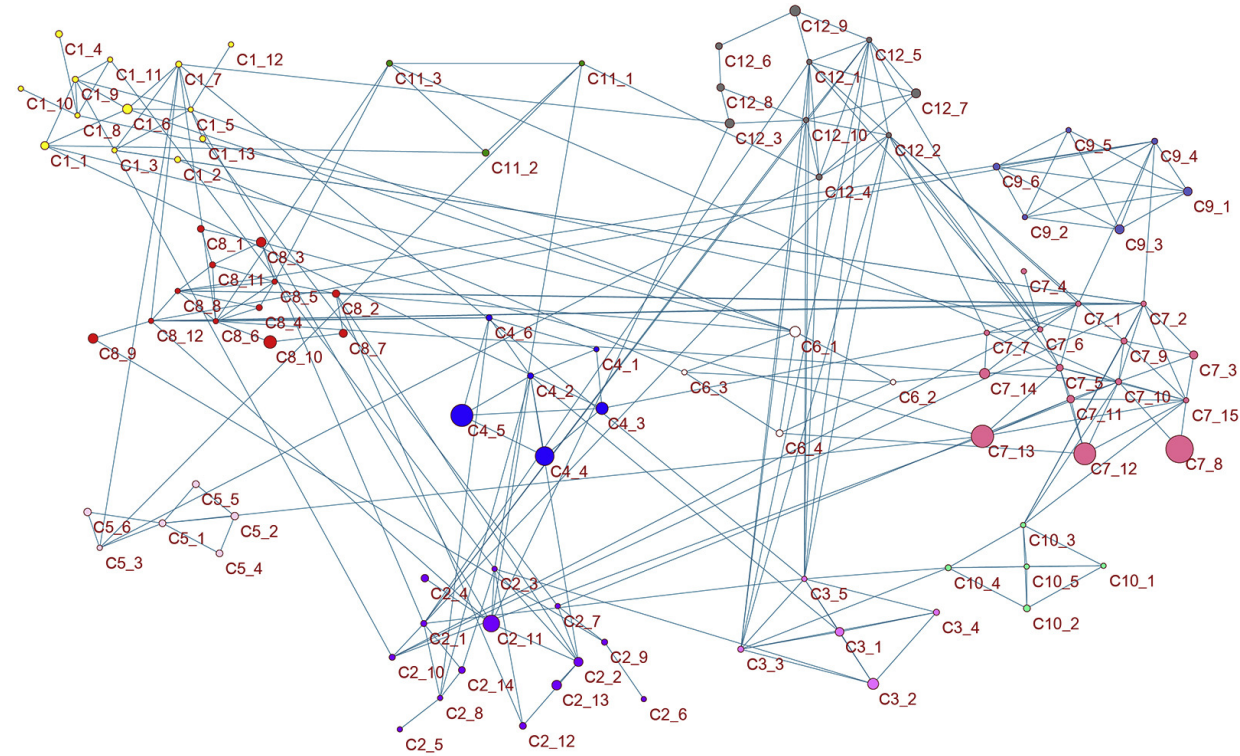
Mostly based on Traditional Chinese Medicine.

Traditional Chinese Medicie prescriptions against covid-19 (Xia et al., 2021)

- 24 TCM prescriptions with 105 herbs







Network analyses of core herbal combinations and chemical components. (A) Network analysis of 8 core combinations of herbs. (B) Network analysis of 12 core combinations of chemical components (Luo et al, 2020)

1. Three formulas (Qingfeipaidu Decoction, Huashibaidu Decoction and Xuanfeibaidu Decoction)

- Developed from Chinese Classical Formula (CCF) have been selected as general effective medicines for the treatment of COVID-19 and approved as new medicines in 2021 (Luo, 2021).

1.a. Qingfei Paidu decoction

- An open-label, single-arm pilot study was conducted using 19 healthy uninfected individuals as subjects, and the effects of QFPD ingestion at a dose lower than that recommended for therapeutic use on hematological and immunological parameters.
- Results: Low-dose QFPD ingestion significantly increased the plasma levels of pro-inflammatory cytokines, tumor necrosis factor (TNF)-α , interleukin (IL)-1β, IL-18, IL-2 and IL-8 , key mediators of a broad spectrum of antiviral immunity

Kageyama et al, 2021

1.b. Huashi Baidu Decoction (HSBD)

- 11 main active compounds of Huashi Baidu Decoction (HSBD): quercetin, luteolin, kaempferol, naringenin, b-sitosterol, delphini- din, isorhamnetin, aloe-emodin, irisolidone, baicalein and (+)-catechin (Zhu et al., 2021)
- Results: HSBD might treat severe COVID-19 through 45 potential target genes, among them, there were 13 hub target genes: RELA, TNF, IL6, IL1B, MAPK14, TP53, CXCL8, MAPK3, MAPK1, IL4, MAPK8, CASP8, STAT1.

1.c.Xuanfeibaidu Decoction (XBD)

- 42 patients with COVID-19 were randomly assigned to XBD plus conventional medicine(n = 22) and conventional medicine alone (n = 20). Both groups were treated for 1 week. The primary end point was the disappearance rate of main symptoms (fever, cough, and fatigue)
- Results: XBD combined with conventional medicine may significantly improve patient's clinical symptoms, increase the number of white blood cells and lymphocytes to improve immunity, and also significantly reduce C-reactive protein and erythrocyte sedimentation rate to play an anti-inflammatory effect. (Xiong et al., 2020)

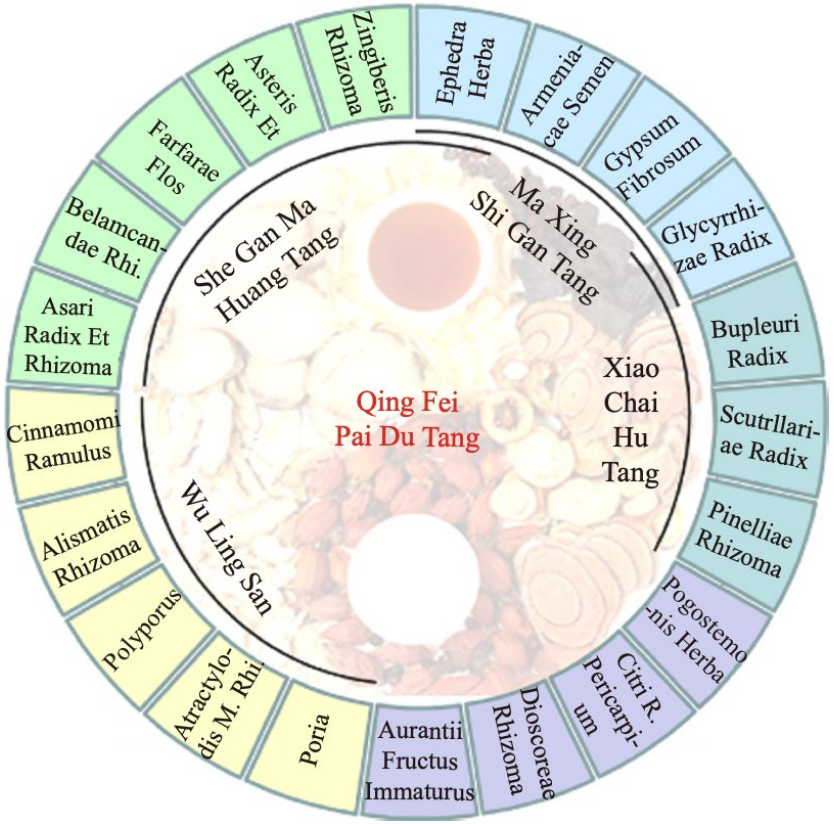
2. Lianhua Qingwen capsule/granule

- An innovative Chinese medicine for the treatment of colds and influenza developed under the guidance of the traditional Chinese Medicine (TCM) collateral disease theory.
- It is composed of 13 herbs:
  1. Forsythia fruit (Forsythia suspensa(Thunb.) Vahl),
  2. Honey suckle flower (Lonicera japonicaThunb.),
  3. Fried ephedra stem (Ephedra sinica Stapf),
  4. Dryopteris root(Dryopteris crassirhizomaNakai),
  5. Isatis root (Isatis indigotica Fort.),
  6. Gypsum (Crystalline gypsum),
  7. Patchouli (Pogostemon cablin (Blanco) Benth.),
  8. Integripetal rhodiola herb (Rhodiola saera (Prain)Fu),
  9. Houttuynia (Houttuynia cordataThunb.),
  10. Rhubarb root andrhizome (Rheum palmatumL.),
  11. Fried apricot seed (Prunus armeniaca L. var. ansu Maxim.),
  12. Licorice root (Glycyrrhiza uralensis Fisch.),
  13. Menthol.

Traditional Chinese Medicine

Lianhuaqingwen

a Chinese patent medicine composed of 13 herbs, has played a positive role in the treatment of SARS-CoV-2



The composition of the prescription—Qing Fei Pai Du Tang

142 document results

TITLE-ABS-KEY ("Lianhua Qingwen") AND (covid-19)

Edit Save Set alert

Search within results...

Refine results

Limit to Exclude

Open Access

- All Open Access (123)
- Gold (64)
- Hybrid Gold (7)

Documents Secondary documents Patents

View Mendeley Data (3)

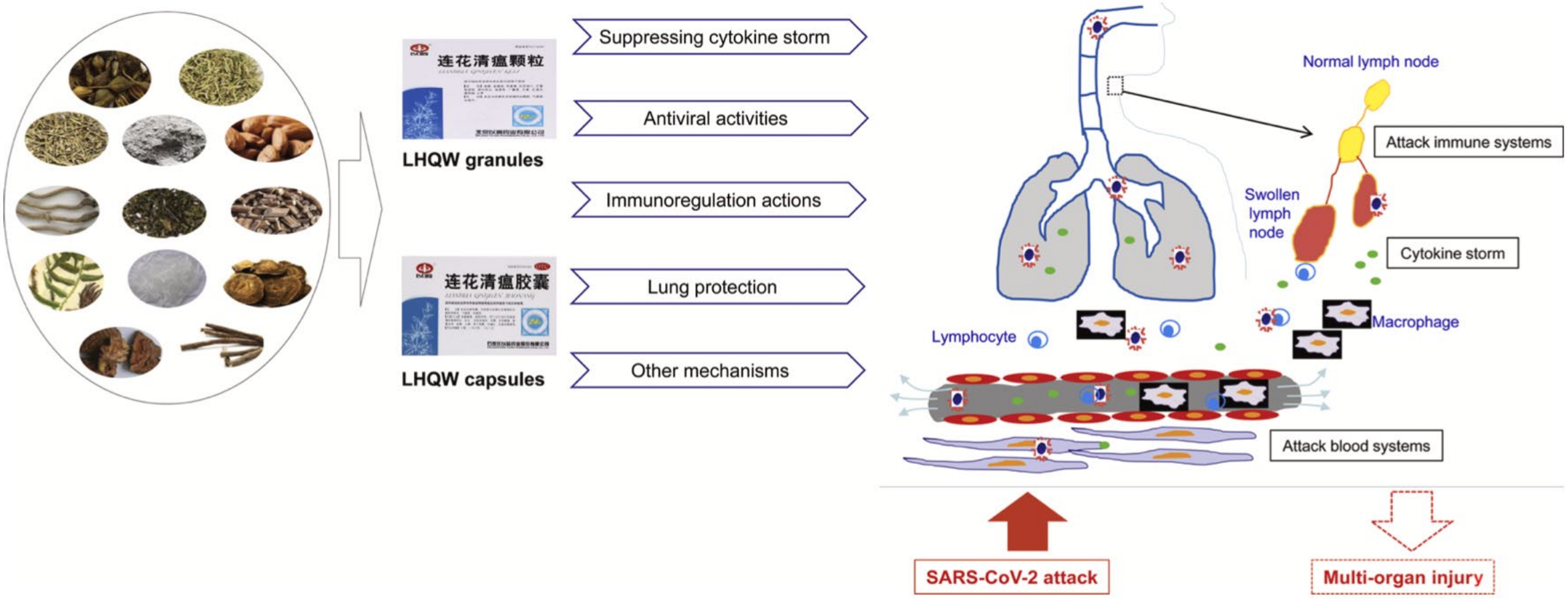
Analyze search results

Show all abstracts Sort on: Date (newest)

All Export Download View citation overview View cited by Add to List •••

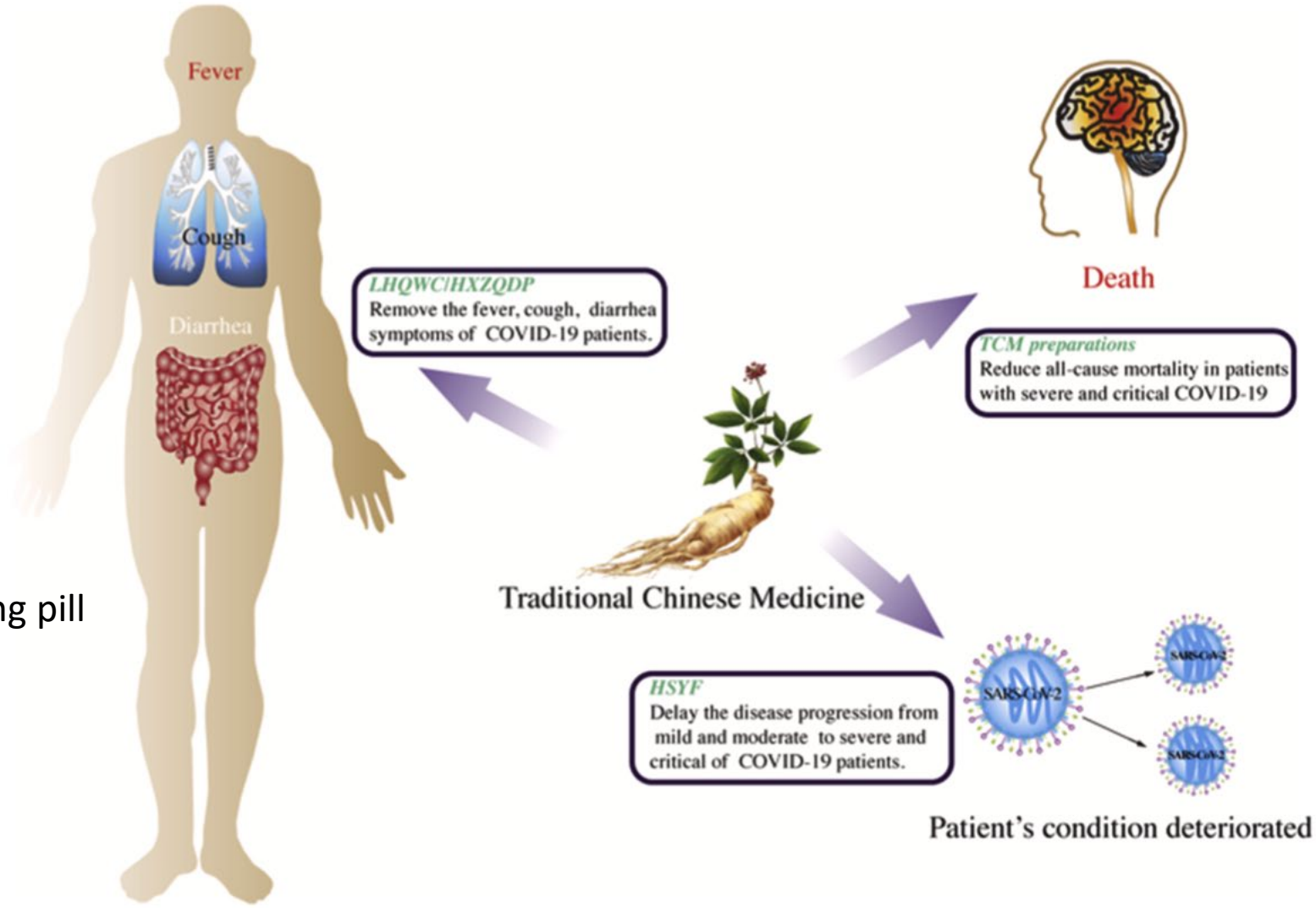
	Document title	Authors	Year	Source	Cited by
1	Current status of traditional Chinese medicine for the treatment of COVID-19 in China *Open Access*	Chu, L., Huang, F., Zhang, M., Huang, B., Wang, Y.	2021	Chinese Medicine (United Kingdom) 16(1),63	0

Role of Lianhua Qingwen in the treatment of COVID-19. Li et al., 2021



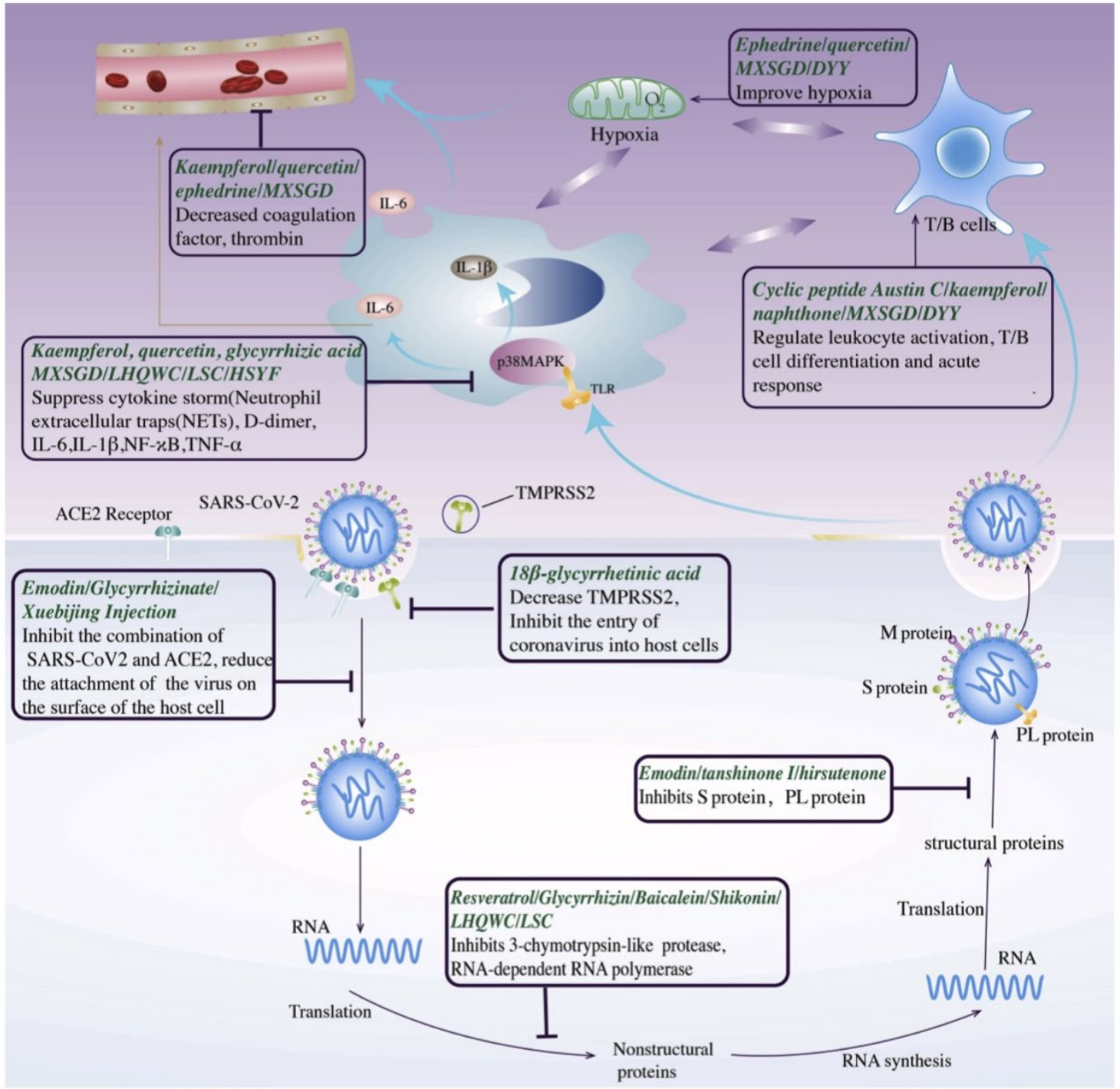
Advantages of TCM in the treatment of COVID-19 based on clinical evidence.

Biomedicine & Pharmacotherapy 137 (2021)

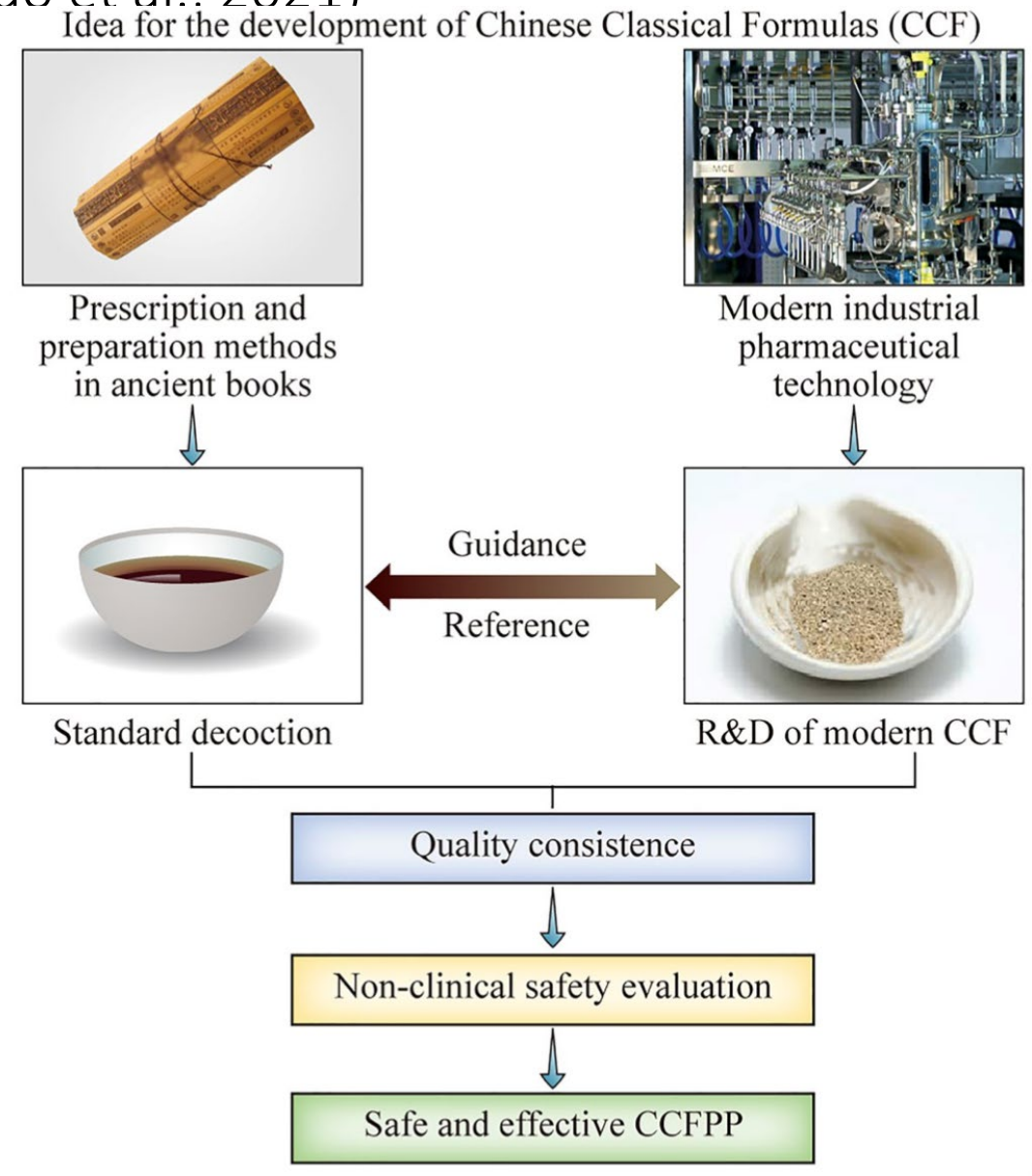


Abbreviation:
LHQWC: Lianhua Qingwen capsules
HXZQDP: Huoxiang Zhengqi dropping pill
HSYF: Hanshiyi formula.
(An et al., 2021)

The mechanism of TCM in the treatment of COVID-19.
(An et al., 2021)



The guidance for the development of Chinese Classical Formula pharmaceutical preparations (CCFPP) (Luo et al., 2021)



CONCLUSION

- There are some clinical evidences showing the effectiveness of herbal preparation against COVID-19
- Some of the compounds and plants discussed here have not yet been tested for clinical efficacy for SAR Cov-2.
- The computational model (in silico) predictions of each single compound still need confirmation via laboratory testing and experimentation

Email: mtaher@iium.edu.my

Editor-in-Chief: Journal of Pharmacy
(https://journals.iium.edu.my/ktn/index.php/jp/index)