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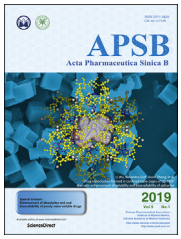

REVIEW

Research and development of Chinese anti-COVID-19 drugs

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KEY WORDS

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Abstract The outbreak and spread of coronavirus disease 2019 (COVID-19) highlighted the importance and urgency of the research and development of therapeutic drugs. Very early into the COVID-19 pandemic, China has begun developing drugs, with some notable progress. Herein, we summarizes the anti-COVID-19 drugs and promising drug candidates originally developed and researched in China. Furthermore, we discussed the developmental prospects, mechanisms of action, and advantages and disadvantages of the anti-COVID-19 drugs in development, with the aim to contribute to the rational use of drugs in COVID-19 treatment and more effective development of new drugs against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and the variants. Neutralizing antibody is an effective approach to overcome COVID-19. However, drug resistance induced by rapid virus mutation will likely to challenge neutralizing antibodies. Taking into account current epidemic trends, small molecule drugs have a crucial role in fighting COVID-19 due to their significant advantage of convenient administration and affordable and broad-spectrum. Traditional Chinese medicines, including natural products and traditional Chinese medicine prescriptions, contribute to the treatment of COVID-19 due to their unique mechanism of action. Currently, the research and development of Chinese anti-COVID-19 drugs have led to some promising achievements, thus prompting us to expect even more rapidly available solutions.

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1. Introduction

Coronavirus disease 2019 (COVID-19), a novel infectious disease, which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread all over the world[1]. The main symptoms of the patients affected by COVID-19 include fever, cough, renal failure, and dyspnea. Patients are mostly affected by respiratory disorders, some of which are characterized by acute respiratory distress syndrome (ARDS) as well as acute lung injury (ALI), occasionally leading to respiratory failure and death associated with severe forms of the infection[2].

SARS-CoV-2 can recognize and bind to host cell surface angiotensin-converting enzyme (ACE2) with its spike protein (S protein), and then mediate the fusion of virus and cells, finally completing the whole infection process[3,4]. The key proteins, enzymes and RNA of SARS-CoV-2 can be used as the potential targets for drugs against COVID-19, while the main action mechanisms include: inhibiting viral proteins and enzymes so as to prevent the replication and synthesis of RNA; acting upon the viral structural proteins, inhibiting self-assembly or blocking the virus from tethering to ACE2; targeting virulence factors and facilitating resuming innate immunity of the host; influencing human enzymes or receptors, and thus blocking viral entry.

Until now, there are no wonder drugs available for COVID-19 treatment. Various approaches have been used for the development of drugs for COVID-19, which can be summarized in the following three categories: drug repurposing (or repositioning), convalescent plasma therapy and novel drug development (such as small molecule drug, antibody and natural medicine, etc.)[5,6].

Very early into the pandemic, China has begun developing drugs for COVID-19. By analyzing the data obtained from the websites of "ClinicalTrials.gov", "Chinadrugtrials.org.cn" and "Chinese Clinical Trial Registry", as well as the scientific conferences, published reports, company press releases, investor presentations and other sources, we found more than 900 COVID-19 associated clinical trials that were conducted in China, among which some 260 anti-COVID-19 drug clinical trials involved over 160 drugs or prescriptions (listed in Tables 1 and 2). Due to a shortage of clinical cases and/or other reasons, the clinical trials of some Chinese anti-COVID-19 drugs were carried out abroad. Furthermore, the trials for some drug candidates are yet to begin. These research and development are steadily proceeding, gaining positive results: small-molecule drugs such as azvudine, VV116, FB2001 and SHEN26, etc.; traditional Chinese medicines such as Lianhua Qingwen capsule/granule, Xuebijing injection, Lung Cleaner and XuanFei Baidu prescription, as well as the natural products, *e.g.*, emetine, cephalotaxus fortune and hymecromone, etc.; protein drugs including human immunoglobulin pH4 and neutralizing antibodies BRII-196 and BRII-198, JS016 and JS026, DXP604, BDB-001, 9MW3311 and LY-CovMab, etc. (Table 3)[5,7]. Among the above-mentioned drugs, the combination therapy of neutralizing antibody BRII-196 and BRII-198 and the small molecule oral drug azvudine have been conditionally approved to be marketed in China.

Table 1 The number of anti-COVID-19 drug clinical trials in China and correlative drugs.

Drug type	Number of drugs	Number of clinical trials
Small molecule drug	48	95
Neutralizing antibody	19	30
Other protein drugs	13	14
Traditional Chinese medicine	66	106
Natural product	10	14
Other drugs	5	4
Total number	161	263

2. Small-molecule drugs

The proteins encoded by SARS-CoV-2 include structural proteins and non-structural proteins. Structural proteins mainly include nucleocapsid protein (N protein), an envelope protein (E protein), and spike protein (S protein); non-structural proteins mainly include Cathepsin L ($3CL^{pro}$, also known as M^{pro}), papain-like protease (PL^{pro}), helicase and RNA dependent RNA polymerase (RdRp)[8]. These non-structural proteins are key proteases in the replication cycle of the virus and the potential targets for the management of COVID-19 by small molecule drugs (as Fig. 1 shown).

Small-molecule drugs can block virus infection of host cells and replicate in host cells. They also have a clear mechanism, convenience in administration, easy large-scale manufacturing, affordable price, etc[9,10]. Additionally, small molecule drugs are not easy to encounter drug-resistant induced by various variant viral strains due to their broad-spectrum antiviral effects.

2.1. *Novel small molecule drugs*

ALD-R491 exerts antiviral and anti-inflammatory dual effects by targeting vimentin. Vimentin has a role in the entry, intracellular transport, and release of the virus, as well as an inflammatory response[11]. ALD-R491 can reduce endocytosis, endosomal transport and exosome release, thus preventing the virus from entering or leaving cells. ALD-R491 can also increase the microbicidal capability of macrophages, thereby promoting the clearance of the pathogen. Moreover, ALD-R491 can directly activates regulatory T cells to inhibit the excessive immune response. The *in vitro* studies indicated that ALD-R491 could effectively inhibit the SARS-CoV-2 infection mediated by viral spike protein and ACE2. The values of IC_{50} are 13.5, 34.7, and 64.9 nmol/L at multiplicities of infection (MOI) of 0.5, 5, and 50, respectively. The *in vivo* studies suggested that ALD-R491 significantly reduces the lung damage and fibrosis. The above results indicate that ALD-R491 can be used to treat COVID-19 and can also reduce the recurrence due to its effects on the prevention and treatment of lung damage[11].

VV116 is an oral nucleoside drug candidate for the treatment of COVID-19, which can be metabolized into maternal nucleoside 116-N1 *in vivo*. 116-N1 forms an active form of nucleoside three phosphoric acids in cells, after which it exerts an anti-SARS-CoV-2 effects by inhibiting RdRp. *In vitro* antivirus trial suggested that VV116 exerted a significant inhibitory effect against the SARS-CoV-2 prime strains and the South African variant virus strain (B.1.351). In the adenovirus-infected mice transduced with human ACE2, VV116 reduced the viral load and viral titer in the lungs in a dose-dependent and time-dependent manner. Additionally, VV116 significantly improved the pathological changes in the lung of mice. Compared with the positive control drug molnupiravir (Merck & Ridgeback), VV116 exhibited the same antiviral effect at a lower dosage[12]. Phase I clinical trials of VV116 have been completed in China, while two phase II/III international

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Table 2 The anti-COVID-19 drugs approved for clinical research in China.

Drug type	Drug
Small-molecule drug	Azvudine, Leflunomide, Acetylcysteine, Ambroxol hydrochloride, Heparin, Bromhexine hydrochloride tablet, Fabiravir, Baicalein, Vitamin C, Hydroxychloroquine sulfate, Aliskiren, Nifedipine, Danoprevir sodium tablet, Ritonavir, Celecoxib, ARBs, Nintedanib ethanesulfonate, Chloroquine phosphate, Pirfenidone, Ribavirin, Dexmedetomidine, Enoxaparin sodium, Ebastine, Thioctic acid, Jaktinib hydrochloride tablet, Dipyridamole, Sulamin sodium, Tranilast, Triazavirin, Polyinosinic-polycytidylic acid injection, Chloroquine, Methylprednisolone, Arbidol hydrochloride, ASC09, Ruxolitinib, Baloxavir marboxil, Darunavir, Cobicistat, Emtricitabine, Tenofovir alafenamide tablets, Remdesivir, Fingolimod, SSD8432, Nicotinamide, FB2001, RAY1216
Neutralizing antibody	BRII-196/BRII-198, Convalescent plasma (serum), Immunoglobulin, Ixekizumab, CMAB806, Adalimumab, PD-1, Tocilizumab, IBI314, Bevacizumab, MW33, JS026/JS016, Meplazumab, SCTA01, 2B11, JMB2002, YBSW015, BAT2022
Other protein drugs	Recombinant human interferon $\alpha 1\beta$, Gamma globulin, IFN-κ, Inflammation suppression factor TFF2, Interferon α/β-1b, viral macrophage inflammatory protein (vMIP), Recombinant cytokine gene derived protein, DAS181, rhACE2, MK-7110
Traditional Chinese medicine prescriptions	Buzhong Yiqi (plus and minus) formula, Huhuang Detoxicity Paste, Baimu Qingre Jiedu Paste, Jieji Xuanfei Chuyi granules, Sanhan Huashi granules, LianHuaQingWen capsules/granules, Liushen pill, Qingjin Huashi granules, Qingjin Yiqi granules, Chinese-herb-tea, Oviductus ranae, Lung Cleaner (QingfeiPaidu Decoction), XuanfeiBaidu granules, cure 14 (HuashiBaidu granules), Fuzheng Yiqing prescription, Jinyinhua oral liquid/ decoction, Shugan Jieyu capsule, Lianhua Qingke tablet, Juxin Junzi granules, Qibei Fuzheng granules, Jinhua Qinggan granules, Sancai granules, Shuanghuanglian oral Liquid, Ludangshen oral Liquid, Bufei Huoxue capsules, Xiaoyao capsules, Xiangsha Liujun pill, Shengmai oral liquid, Qimai feiluoping mixture, Danggui Shaoyao Powder, Kegan Liyan oral Liquid, Feiyan Yihao prescription, Toujie Quwen granules, Gushen Dingchuan pill, Yinqiao Huopu Tuire mixture, Jingfang Huopu Jiedu mixture, Huocao Songrong, Hanma capsule, *Dendrobium candidum*, Chushi Fangyi prescription, Pummelo Peel, Qingwen Shierwei pill, Secretio bufonis injection, Maxing Shigan decoction, Zedoary turmeric oil injection, Yiqi Huashi prescription, Compound Yuxingcao mixture, Xuebijing injection, Jingyin granules, Bupleurum Qingwen decoction, Qingfei Jiebiao decoction, Chibai Rougan decoction, Qingwen Baidu decoction, Shenfu injection, Antiviral Oral-Liquid, Wuzhi Fangguan decoction, KeSuTingTangJiang, Keqing capsule, Babao Dan, Tanreqing capsule/injection, KangBingDuKeLi, Shenqi Fuzheng injection, Jinye Baidu granules, GuBiaoJieDuLing, Fuzheng Jiedu granules, Fuzheng Huayu tablet, Hanshiyi formula, Reduning injection, Tanreqing injection
Natural product	Homoharringtonine, Artemisinin/dihydroartemisinin piperaquine tablets, Xiyanping injection, Diammonium glycyrrhizinate enteric-coated capsule, Sodium aescinate, Tetrandrine, Colchicine tablet, Berberine, Hymecromone, Artemisinin
Other drugs	microRNA2911 injection plasmid, *Clostridium butyricum* viable capsule, *Bacillus coagulans* viable tablet, Glucocorticoid, Newgen beta-gluten probiotic composite powder

multicenter clinical trials in patients with mild or moderate COVID-19 and severe COVID-19 are in progress, respectively.

Besides the above drugs, there are several agents, such as SHEN26, BH-103 and FB2001, etc., whose relevant study data have not been published in a peer-review article, but the press release of the preliminary data suggested that these drugs may be effective against COVID-19. Among them, SHEN26 is a new candidate oral drugs against COVID-19 developed by the research team of Henan Normal University, which exerts effects by targeting RdRp. The values of IC_{50} of SHEN26 for SARS-CoV-2 and variants of beta and delta are 1.36, 1.12 and 0.35 μmol/L, respectively.

The effective component of BH-103 is *N*-acetylneuraminic acid methyl ester (NANA-Me), an analog of *N*-acetylneuraminic acid. NANA-Me has good membrane permeability and can easily enter cells. NANA-Me participates in the synthesis and expression of intracellular sugar chains, which can repair the polysaccharide structure on the surface of lung damaged cells, and block the combination of pathogenic antibodies and autologous cells, so as to prevent and treat serious symptoms caused by antibody-dependent auto-attack (ADAA). Moreover, BH-103 can reduce the excessive immune response caused by respiratory virus infections such as cytokine storms. The "cytokine storm" is one of the main pathogenic mechanisms of COVID-19. The infected body produces and releases various inflammatory cytokines, which can cause cell and organ damage. Therefore, inhibiting the "cytokine storm" and improving the oxidative stress status can presumably could reduce the severity and mortality rate of the patients with COVID-19.

FB2001 is a peptide-like compound synthesized based on the three-dimensional structure of SARS-CoV-2 main protease. FB2001 can suppress $3CL^{pro}$ in the nanomolar grade, which has good broad-spectrum anti-virus activity *in vitro*. The IC_{50} of FB2001 against SARS-CoV-2 main protease Mpro is 0.053 μmol/L, and whose EC_{50} against SARS-CoV-2 is 0.42 μmol/L. Currently, the phase II/III international multicenter clinical trials of FB2001 have been approved in China.

SSD8432, which was developed by Jiangsu Simcere Pharmaceutical Co., Ltd., exerts an anti-COVID-19 effects by targeting $3CL^{pro}$. Moreover, VV993 (JUNSHI Biosciences Co., Ltd.), GDI-4405 (Global Health Drug Discovery Institute) and RAY1216 (RAYNOVENT Co., Ltd.) are also the anti-COVID-19 oral drugs targeting $3CL^{pro}$. Recently, the phase I clinical trials of SSD8432 and RAY1216 have been carried out in China. Phase II clinical trials of SSD8432 for the close contacts and patients also have been approved in China. Regrettably, two recent phase III clinical studies of Pfizer $3CL^{pro}$ inhibitor paxlovid on standard risk prophylaxis (EPIC-SR) and post-exposure prophylaxis (EPIC-PEP)

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Table 3 The main anti-COVID-19 drugs under research and development by China.

Drug type	Drug	R&D institution	Therapeutic targets	Route of administration	COVID indications	R&D stage	Therapeutic effects
Small-molecule drug	Azvudine (FNC)	Genuine Biotechnic Co., Ltd.	RdRp	Oral	Mild, moderate, severe	Gain conditional market approval in China	Antiviral effect
	VV116	JUNSHI Biosciences Co., Ltd.	RdRp	Oral	Mild, moderate, severe	Gain approval in Uzbekistan	Antiviral effect
	Proxalutamide	Kintor Pharmaceutical Co., Ltd.	ACE2, TMPRSS2	Oral	Mild, moderate, severe	Gain emergency use authorization in Uruguay	Antiviral effect; inhibit inflammation; control the cytokine storm
	FB2001	Frontier Biotechnologies Inc.	Cathepsin L	Intravenous injection	Moderate, severe	Phase II/III clinical study	Antiviral effect
	SHEN26	Kexing Biopharmaceutical Co., Ltd.	RdRp	Oral	Mild, moderate	Preclinical study	Antiviral effect
	SSD8432	Jiangsu Simcere Pharmaceutical Co., Ltd.	$3CL^{pro}$	Oral	Mild, moderate, post-exposure prophylaxis	Phase I/II clinical study	Antiviral effect
	RAY1216	RAYNOVENT Co., Ltd.	$3CL^{pro}$	Oral	Unreported	Phase I clinical study	Antiviral effect
	Carrimycin	Chinese Academy of Medical Sciences; Tonglian Group	Viral RNA, JAK/stat, ISGS, and PI3K Akt mTOR	Oral	Severe, critical	Phase III clinical study	
	Fenofibrate	Jiangsu Nhwa Pharmaceutical Co., Ltd.	S protein, ACE2	Oral	Severe	Phase II/III clinical study	Antiviral effect; inhibit inflammation; regulate immunity
	Danoprevir (Ganovo)	Ascletis Bioscience Co., Ltd.	Chymotrypsin-like protease	Oral	Mild, moderate	Phase IV clinical study	Antiviral effect
Neutralizing antibody	BRII-196&BRII-198	Brii Biosciences Co., Ltd.	S protein	Intravenous injection	Pre-exposure prophylaxis, post-exposure prophylaxis, mild, moderate, severe	Gain conditional market approval in China	Antiviral effect
	BDB-001	Staidson Pharmaceutical Co., Ltd.	C5a	Intravenous injection	Severe	Phase III clinical study	Antiviral effect; inhibit inflammation
	JS016	JUNSHI Biosciences Co., Ltd.	S protein	Intravenous injection	Post-exposure prophylaxis, mild, moderate	Phase II clinical study	Antiviral effect
	DXP604	DANXU Biopharmaceutical Co., Ltd.; China National Biotechnic Group	RBD, ACE2	Intravenous injection	Post-exposure prophylaxis, mild, moderate	Phase II clinical study	Antiviral effect
	JS016/JS026	JUNSHI Biosciences Co., Ltd.	S protein/S protein S1 subunit	Intravenous injection	Post-exposure prophylaxis, mild, moderate	Phase I clinical study	Antiviral effect
	HLX70	Fosun Pharmaceutical Co., Ltd.		Intravenous injection	Moderate, severe	Phase II clinical study	Antiviral effect
	pH4	China National	S protein, RBD,	Intravenous injection	Moderate, severe	Phase II/III clinical	Antiviral effect;

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		Biotechnic Group	N-terminal domain (NTD), N protein			study	regulate immunity
	LY-CovMab	Luye Pharmaceutical Co., Ltd.	RBD, ACE2	Intravenous injection	Mild, moderate	Gain approval of phase II clinical study	Antiviral effect
	IBI314	Innovent Biologics (Suzhou) Co., Ltd.	RBD, ACE2	Intravenous injection	Mild, moderate	Phase I/II clinical study	Antiviral effect; reduce pulmonary pathological damage
	YBSW015	Yabao Pharmaceutical Group Co., Ltd.	RBD	Intravenous injection	Unreported	Phase Ia clinical study	Antiviral effect
	BAT2022	Bio-Thera Solutions, Ltd.	S protein, ACE2	Intravenous injection	Unreported	Gain approval of phase I clinical study	Antiviral effect
	9MW3311	Mabwell (Shanghai) Bioscience Co., Ltd.	RBD	Intravenous injection	Mild, moderate	Phase II clinical study (suspended)	Antiviral effect
	MW33	Mabwell (Shanghai) Bioscience Co., Ltd.	RBD	Intravenous injection	Mild, moderate	Phase II clinical study	Antiviral effect
	SCTA01 (HB27)	Sinocelltech Ltd.	RBD	Intravenous injection	Severe	Phase II/III clinical study	Antiviral effect
	35B5	Zhejiang University	RBD	Nasal cavity	Unreported	A small-scale clinical trial on healthy subjects	Antiviral effect
	F61 and H121	China National Biotechnic Group	RBD, ACE2	Nasal cavity	Unreported	Preclinical study	Antiviral effect
	LQ050	Novamab Biopharmaceuticals Co., Ltd.	ACE2	Inhalation	Unreported	Preclinical study	Antiviral effect
Other protein drug	Novaferon	Genova Biotech Co., Ltd.	C-reactive protein (CRP), IL-6	Inhalation	Moderate, severe	Phase III clinical study	Antiviral effect
	HLX71	Fosun Pharmaceutical Co., Ltd.		Intravenous injection	Moderate, severe	Phase I clinical study	Antiviral effect
Natural product	Phillyrin	Jilin Yatai Pharmaceutical Co., Ltd.	$3CL^{pro}$	Oral	Mild, moderate	Phase II clinical study	Antiviral effect; inhibit inflammation
	Emetine	Institute for Viral Disease Control and Prevention	IL-6, TNF-α	Oral	Unreported	Preclinical study	Inhibit inflammation, control the cytokine storm
	Homoharringtonine	Minsheng Pharmaceutical Co., Ltd.	Host transfer RNA to host ribosome	Inhalation	Unreported	Preclinical study	Antiviral effect
	Tetrandrine	Kangenbei Pharmaceutical Co., Ltd.	TPC2	Oral	Unreported	Preclinical study	Antiviral effect; prevention and treatment of pulmonary fibrosis
	Baicalein	Kanion Pharmaceutical Co., Ltd.	$3CL^{pro}$	Oral	Mild, moderate	Exploratory clinical study	Antiviral effect
	Diammonium glycyrrhizinate and Glycyrrhizic acid	CHIA TAI TIANQING Pharmaceutical Co., Ltd.	ACE2, PGE2	Oral	Unreported	Exploratory clinical study	Antiviral effect; inhibit inflammation; protect from hepatic injury
	Hymecromone	Fudan University	Hyaluronic acid	Oral	Unreported	Exploratory clinical	Inhibit inflammation;

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Table 3 (*continued*)

Drug type	Drug	R&D institution	Therapeutic targets	Route of administration	COVID indications	R&D stage	Therapeutic effects
						study	control the cytokine storm
	Cepharanthine	Yigang Tong et al.	ACE2, NF-κB	Oral	Unreported	Preclinical study	Antiviral effect
	Artemisinin	Academy of Military Medicine Sciences	S protein, NF-κB, TGF-β	Oral	Unreported	Exploratory clinical study	Inhibit inflammation; inhibit ARDS; antiviral effect
	Berberine	Being recommended in guidelines issued by China National Health Commission for COVID-19	AP-1, NF-κB	Oral	Unreported	Phase IV clinical study	Inhibit inflammation; control the cytokine storm
Traditional Chinese medical prescription	Xuebijing injection	Chase Sun Pharmaceutical Co., Ltd.	$3CL^{pro}$, ACE2, etc.	Intravenous injection	Severe, critical	Being included in the diagnosis and treatment program of COVID-19	Antiviral effect; inhibit inflammation; regulate immunity
	Jinhua Qinggan granules	Juxiechang Pharmaceutical Co., Ltd.	MAPK, NF-κB, IL-6, etc.	Oral	Mild, moderate		Antiviral effect; inhibit inflammation;
	Lung Cleaner (QingfeiPaidu Decoction)	China academy of Chinese Medical sciences	IL-17, $3CL^{pro}$, ACE2, etc.	Oral	Mild, moderate		Antiviral effect; inhibit inflammation; control the cytokine storm
	LianHuaQingWen capsules	Yiling Pharmaceutical Co., Ltd.	NF-κB, IL-6, TNF-α, ACE2, etc.	Oral	Mild, moderate		Antiviral effect; control the cytokine storm
	XuanfeiBaidu granules	Buchang Pharmaceutical Co., Ltd.	IL-6/1β, MAPK, etc.	Oral	Mild, moderate		Inhibit inflammation; regulate immunity
	Cure 14 (HuashiBaidu granules)	EFONS Pharmaceutical Co., Ltd.	IL-6/17, MAPK, TNF, etc.	Oral	Mild, moderate, severe		Inhibit inflammation; control the cytokine storm
	FuzhengJiedu granules	Guangdong Provincial Hospital of Traditional Chinese Medicine	IL-2/6/17, NF-κB, MAPK, TNF, etc.	Oral	Mild, moderate, severe	Gain approval of emergency use	Antiviral effect; inhibit inflammation
	Hanshiyi formula	Xiaolin Tong, et al.	Mpro, ACE2	Oral	Mild, moderate	Being included in the diagnosis and treatment program of COVID-19	Reduce the progression to severe disease
	Reduning injection	Kanion Pharmaceutical Co., Ltd.	ACE2, $3CL^{pro}$, PL^{pro}, MAPK, PKC, NF-κB	Intravenous injection	Severe, critical		Antiviral effect; inhibit inflammation
	Tanreqing injection	Yongyan Wang, et al.; Shanghai KAIBAO Pharmaceutical Co., Ltd.	TNF, MAPK, NF-κB	Intravenous injection	Severe, critical		Improve lung injury, pulmonary infection, airway inflammation, and airway mucus hypersecretion

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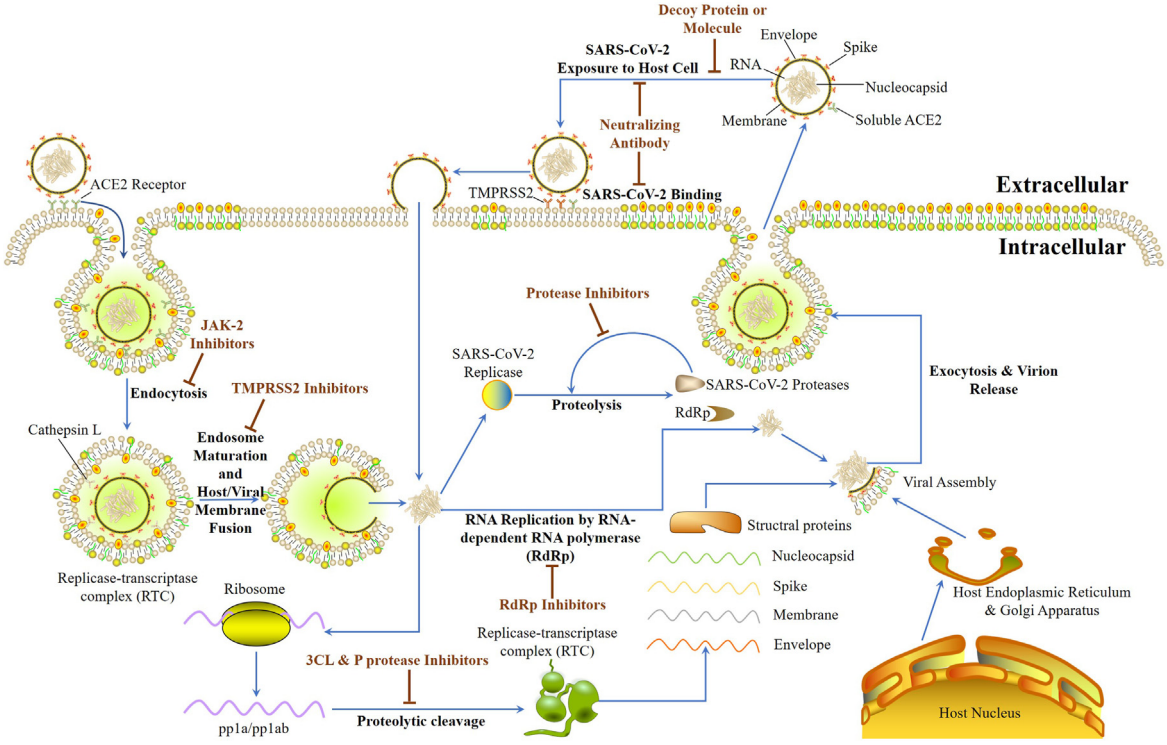

Figure 1 SARS-CoV-2 life cycle and potential therapeutic targets of anti-COVID-19 drugs.

failed successively. These defeats increased the uncertainty to the study of other 3CL protease inhibitors on the patients with risk factors for severe complications (SCORPIO-SR) during the Omicron variants epidemic.

2.2. *The repurposed (or repositioned) small-molecule drugs*

Besides developing the novel drugs, drug repurposing is also an effective approach for treating COVID-19. As a poly-ADP-ribose polymerase 1 (PARP1) inhibitor, CVL218 (mefuparib hydrochloride) can bind to the catalytic subunit nsp 12 in the N protein of SARS-CoV-2, thus inhibiting the process of the packaging, replication and transcription of SARS-CoV-2. In addition, CVL218 can target to SARS-CoV-2-N, thus interfering with the phase separation process of the N protein-viral RNA-nsp12 complex and making it easier for other antiviral drugs to enter the virus. Therefore, CVL218 can be used to treat COVID-19 as a single drug or in combination with other drugs[13].

S-Nitrosocaptopril (CapNO) is a stable captopril monohydrate that can rapidly decompose into NO and captopril in the respiratory tract. NO has a variety of clear therapeutic effects, such as relaxing pulmonary microvessels and tracheal smooth muscle, improving the alveolar blood gas exchange, alleviating ARDS, inhibiting viral RNA replication and palm glycosylation of viral spike protein, suppressing the fusion of virus and host ACE2, reducing pulmonary mucus viscosity, etc. CapNO atomizing agent has unique superiority in the treatment of COVID-19; it can suppress virus replication, inhibit virus entry into host cells, resist coagulation, improve blood oxygen level, relax pulmonary vessels, reduce pulmonary hypertension, and alleviate ARDS symptoms[14].

Carrimycin is the first macrolide compound developed by the synthetic biology technology. Previous studies found that carrimycin exerts efficacy after the virus enter cells, which can reduce the newly synthesized RNA level of coronavirus, indicating that carrimycin can play an anti-coronavirus role by affecting coronavirus RNA replication. In addition, Carrimycin can regulate the interferon signaling pathway JAK/stat, ISGS, and PI3K Akt mTOR signaling pathway[15]. A phase III clinical trials of carrimycin in hospitalized patients with severe COVID-19 have been completed.

Fenofibrate exhibits the therapeutic effect on COVID-19 by multiple mechanisms of action, which can effectively prevent SARS-CoV-2 infection mainly by blocking the combination of S protein and ACE2. Fenofibrate can also inhibit the replication of SARS-CoV-2 by affecting the lipid metabolism pathway of lung cells[16]. In addition, fenofibrate also has immunomodulatory and anti-inflammatory effects[17–20]. Phase II/III clinical trials of fenofibrate are in progress.

Danoprevir (Ganovo) was developed by Ascletis Bioscience Co., Ltd., which was a potent orally-administered antiviral agent to treat hepatitis C. The completed phase Ⅳ clinical trial results show that danoprevir, in combination with ritonavir, can effectively inhibit the viral replication of SARS-CoV-2 and improve the health condition of the patients with COVID-19[21,22].

Azvudine (FNC) is a novel nucleoside small molecule antiviral drug. Previous studies have indicated that the therapeutic target of azvudine is the RNA dependent RNA polymerase (RdRp) of the virus, which can effectively inhibit COVID-19 replication. In addition, azvudine can be enriched in the lymphatic system, effectively inhibiting virus replication and enhancing immune function, which may exert antiviral efficacy against SARS-CoV-2 by a double target mechanism[23–25]. The phase III clinical trials of azvudine in China, Russia, and Brazil have been completed. So far, azvudine obtained the approval for conditional marketing authorization as China's first self-developed oral small molecule anti-COVID-19 drug.

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Proxalutamide is a novel androgen receptor (AR) antagonist which can effectively reduce the expression of ACE2 and TMPRSS2, the two key proteins responsible for COVID-19 invading host cells[26]. Therefore, proxalutamide may inhibit the further infection of normal host cells (ACE2 positive cells) by affecting the S protein of SARS-CoV-2 to identify the ACE2 protein, thereby cutting off the replication and reproduction of the virus so as to achieve the effective treatment of COVID-19. Further mechanism study found that proxalutamide can activate the Nrf-2 pathway, thus reducing inflammatory injury and reducing the probability of cytokine storm. Phase III clinical trials of proxalutamide were conducted simultaneously in Brazil and the United States[27−29]. The interim results of phase III clinical trials indicated a statistically significant difference between the treatment and control groups.

HC-1119 is also an AR antagonis, its mechanism of treatment of COVID-19 are as follows: 1) prevent SARS-CoV-2 from infection of host cells; 2) inhibit the excessive inflammatory reaction; 3) reduce the platelet aggregation induced by COVID-19[30].

3. Neutralizing antibody and other protein drugs

Neutralizing antibodies are becoming increasingly attractive as the therapy for COVID-19, as they can be designed to specifically target viral antigens. The patients suffering COVID-19 without endogenous antibodies may benefit from neutralizing antibody therapy[31].

3.1. *Neutralizing antibody*

LQ050 is a monovalent nanobody phage developed by Novamab Biopharmaceuticals Co., Ltd., which exhibited the highest activity against authentic SARS-CoV-2 with a 50% neutralizing dose (ND_{50}) of 0.55 μg/mL. As a single domain antibody with a small size, LQ050 can be delivered to the site of infection through inhalation, which is supported by its high stability and its consistent post-nebulization stability profile[32].

The neutralizing antibodies F61 and H121 exhibited broad neutralizing activity against the SARS-CoV-2 wild strain and variants, including the beta, delta and omicron strains. F61 can block the virus binding with ACE2 through recognizing a linear epitope in ACE2-RBD binding domain, while H121 binds to an ACE2 conformational epitope located in a conserved side of RBD. Due to the different binding epitopes, the combination of F61 and H121 (1:1) exhibited synergistic neutralization. The *in vitro* studies indicated that the EC_{50} value of F61/H121 combination against omicron variant is 200 ng/mL. The *in vivo* studies suggested that the F61/H121 combination can induce significant prophylactic protection against lethal challenge with delta and omicron variants at the administration dose of 20 mg/kg. Moreover, F61 and H121 can be used as the nasal spray preparations in management of the COVID-19[33,34].

As a promising and pan-neutralizing monoclonal antibody, 35B5 can efficiently neutralize the wild-type and mutant SARS-CoV-2, including omicron variants both *in vitro* and *in vivo*. Furthermore, cryo-electron microscopy (cryo-EM) revealed that 35B5 neutralizes SARS-CoV-2 by targeting a unique epitope that avoids the prevailing mutation sites on RBD (receptor-binding domain) identified in circulating variant of concerns (VOCs), thus providing the molecular basis for its pan-neutralizing efficacy[35].

The monoclonal neutralizing antibody HLX70 and the ACE2 Fc fusion protein HLX71 have both been developed by Henlius Biopharmaceutical company. HLX70 is an IgG1 kappa immunoglobulin, which can target and recognize the spike protein on SARS-CoV-2. The binding site with the spike protein of HLX70 is the same as that of human angiotensin converting enzyme 2 (hACE2), which are the RBD regions on S1. Therefore, HLX70 possesses a high binding affinity with spike protein. HLX71 is a recombinant hACE2 protein with an IgG1 FC tag on its C-terminal. After binding to spike protein, both HLX70 and HLX71 can inhibit the virus binding to ACE2 on the host cell surface, thus exerting exert the antiviral effect. In addition, HLX71 exhibits ACE2 enzyme activity, which can inhibit the occurrence of inflammatory reactions by regulating the renin-angiotensin signaling pathway, and further enhance its therapeutic effect on COVID-19. Currently, phase I clinical trials of HLX70 and HLX71 are being carried out in the America. Moreover, the *in vitro* antiviral experiment indicated that HLX70 and HLX71 had synergistic effects in the combination ratio of 1:5 and 1:10[36].

BDB-001 is developed by Staidson biopharmaceuticals Co., Ltd., which is a monoclonal antibody against complement molecule C5a[37]. BDB-001 can specifically bind C5a and inhibit its receptor-binding activity, thus interrupting the biological functions induced by C5a, such as neutrophil chemotaxis, release of intracellular lysozyme, increase of inflammatory cytokine and oxygen production induced by respiratory burst, etc. Thus, BDB-001 can be used for preventing severe pneumonia induced by the inflammatory reaction caused by complement system activation for the treatment of COVID-19. Currently, phase II/III multicenter clinical trials of BDB-001 are being conducted in Spain, India, Indonesia and Bangladesh.

LY-CovMab is a monoclonal antibody against COVID-19, which belongs to the IgG4 subtype. The cryo-electron microscopy revealed that LY-CovMab had multiple advantages of high affinity and high activity. LY-CovMab occupies 13 amino acid epitopes on the SARS-CoV-2 spike protein, where nine coincide with the epitope of ACE2. Under cryo-electron microscopy, LY-CovMab can bind and block all three RBD on the spike protein. One LY-CovMab IgG molecule can simultaneously bind two RBD on the spike protein simultaneously. Furthermore, LY-CovMab can avoid the antibody-dependent enhancement (ADE) effect by designing and modifying the FC end of McAb. The preclinical study indicated that LY-CovMab could significantly reduce the viral titers in the lungs and tracheas of the BALB/c mice that received MAScp6 challenge compared with a vehicle control group. Phase I clinical study of LY-CovMab in China has been completed, revealing good safety and pharmacokinetic characteristics. At present, phase II clinical trials of LY-CovMab have been approved to be carried out in China[38].

JS016 (Etesevimab) is a potent anti-spike neutralizing monoclonal antibody isolated from COVID-19 survivors that can bind to the overlapping epitopes in RBD, which is a primary target for producing neutralizing monoclonal antibodies. The preclinical study results indicated that JS016 could bind to a different epitope from bamlanivimab (an authorized neutralizing monoclonal antibody specifically developed to treat COVID-19) and to neutralize resistant variants with mutations in the epitope bound by bamlanivimab[39]. So far, the phase II international multicenter clinical trials of JS016 have been completed. Neutralizing antibody JS026 has excellent neutralizing activity against SARS-CoV-2. In addition, the combination of JS026 and JS016 has synergistic effects, as their binding sites are complementary to the virus[40,41]. Phase I/II/IIIIII clinical trials of JS016 and JS026 have been approved in China.

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Neutralizing antibody DXP604 was screened from the plasma of convalescent patients infected with SARS-CoV-2 by high-throughput single-cell sequencing. In the preclinical study, the results of virus neutralization assay and the high-throughput yeast display technology indicated that DXP604 has broad-spectrum antivirus activity, as well as high neutralizing activity on wild-type and mutant SARS-CoV-2, including variants of delta and omicron. The results of the mutation pressure screening test showed that DXP604 has a strong escape ability against mutation. The high-throughput yeast display technology test data showed that DXP604 had a broad spectrum and was still effective for the omicron variant; however, its neutralization activity was reduced. In terms of clinical trials, phase I clinical trials have been completed in China and Australia[42,43]. At present, phase I clinical trials are being conducted in China.

9MW3311 is also a potent neutralizing monoclonal antibody isolated from COVID-19 survivors, which was screened by a B lymphocyte screening platform, and the FC end of the antibody was modified. The phase II clinical trials of 9MW3311 have been completed in the Philippines. The study is currently in a suspended state.

MW33, which was developed by Mabwell (Shanghai) Bioscience Co., Ltd., is a recombinant fully-humanized SARS-CoV-2 RBD-targeting monoclonal antibody. It is one of the IgG1κ subtypes, which exhibits high neutralization activity by disrupting the interaction of the RBD with the ACE2 receptor[44]. The phase II clinical trials of MW33 in patients with mild or moderate COVID-19 are currently in progress.

SCTA01 (HB27), a novel monoclonal antibody of the IgG1 subtype developed by Sinocelltech Ltd., which can inhibit SARS-CoV-2 by binding with the receptor-binding domain of the virus[45]. Phase II/III clinical trials of SCTA01 are being carried out in North America.

IBI314 is a new antibody cocktail therapy composed of the antibodies of p5-22 and p14-44 at the 1:1 ratio, which was screened by a yeast library expressing mutant RBDs of the spike protein. The crystal structure of the P5-22 and P14-44 indicated that IBI314 could bind two different RBDs on the spike protein and block the interaction of the RBDs with the ACE2 receptor. Moreover, *in vivo* study suggested that IBI314 can reduce the lung virus titer and pulmonary pathological damage in the SARS-CoV-2 infection mouse model[46]. Currently, the phase I/II clinical trials of IBI314 are in progress.

BRII-196 and BRII-198 were derived from patients who recovered from COVID-19; these two human neutralizing IgG (immunoglobulin G) monoclonal antibodies can inhibit the replication of SARS-CoV-2 and effectively counteract COVID-19. BRII-196 and BRII-198 bind distinct and complementary epitopes of the SARS-CoV-2 spike protein. The Fc regions of BRII-196 and BRII-198 are engineered with triple amino acid modifications (Met252Tyr, Ser254 Thr, and Thr256Glu) to extend half-life and reduce the binding affinity to Fc-γ receptors with the goal of reducing the potential for antibody-dependent enhancement[47]. The BRII-196/BRII-198 combination therapy obtained the approval for conditional marketing authorization as China's first self-developed neutralizing antibodies against COVID-19.

Advances in protein engineering technology have generated multiple bispecific antibodies (BsAbs), which can simultaneously and synergistically target two antigens or different epitopes of the same antigen as a single agent. Compared with monoclonal antibody, bispecific antibody possesses broader neutralizing breadth for resistance against viral evasion induced by mutation[48–50]. There are 14 bispecific antibodies against COVID-19 in development worldwide, of which eight are from China. Among the bispecific antibodies being developed in China, phase Ia clinical trials of YBSW015 (Yabao Pharmaceutical Group Co., Ltd.) are in progress. Recently, phase I clinical trials of BAT2022 (Bio-Thera Solutions, Ltd.) have been approved in China. BAT2022 simultaneously binds two independent epitopes on the spike protein, and prevents the virus binding with ACE2.

Convalescent plasma/serum is considered a viable option for COVID-19 treatment. Convalescent plasma/serum is an important source of neutralizing antibodies, whose action mechanism is similar to antibodies'[51,52]. However, using convalescent plasma/serum has certain limitations as it has to be obtained from COVID-19 survivors, and standardization of convalescent plasma is challenging as the neutralizing antibody titers vary depending on the different sources. Currently, approximately ten clinical trials on convalescent plasma/serum in patients with mild, moderate, severe, or critical COVID-19 are in progress.

Human immunoglobulin pH4, which was developed by Chinese firm Sinopharm, can rapidly improve the level of IgG in the blood, directly neutralize exogenous antigens, regulate a variety of immune functions, including regulating immune mediators, and improve the immune ability of natural immune cells and lymphocytes[53]. The phase II clinical trials of pH4 have been carried out in the United Arab Emirates.

3.2. *Other protein drugs*

Besides antibody drugs, other protein drugs are also employed for the treatment of COVID-19, such as polypeptides and nucleosides, etc. Novaferon is a novel unnatural protein based on 12 human interferons α subtype genes, which was obtained by gene shuttling and cell function screening technology. Novaferon was commonly used for the treatment of HBeAg positive chronic hepatitis B in clinic[54–56]. The *in vitro* antiviral experiment showed that it exhibited significant anti-virus activity against COVID-19 wild-type and mutant viruses, including omicron mutated strains. Novaferon can be administered through respiratory atomization inhalation and can be directly delivered to respiratory epithelial cells and alveolar tissues directly. The phase III clinical trials of novaferon are currently in progress.

4. Traditional Chinese medicine

4.1. *Natural products*

Natural product is an important source of drug development, which has an indispensable role in counteracting infectious diseases because numerous natural products possess antiviral activity against a broad range of pathogenic viruses, including HIV, influenza and SARS-CoV[57]. Therefore, it is of great significance to develop drugs for the treatment of COVID-19 based on natural products. To date, there are hundreds of natural products have been proposed to possess anti-SARS-CoV-2 activities, such as terpenoids, polyphenols, flavonoids, alkaloids and terpenoids. They exert antiviral effects through inhibiting the essential components of SARS-CoV-2, including Mpro, RdRp, ACE2 and TMPRSS2, etc.[58–61]. We summarized some representative natural products or those entered clinical stage as follows.

Emetine is an isoquinoline alkaloid extracted from plant rhizomes, which is used to treat amebiasis or is used as an emetic in

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clinic. Previous studies have shown that emetine has high antiviral activity and can accumulate in the virus-targeted organs. Moreover, *in vitro* anti-inflammatory experiments suggested that isoquinoline alkaloid has an anti-inflammatory effect and can reduce the release of interleukin 6 (IL-6) and tumor necrosis factor. Therefore, emetine may be used as a promising strategy for controlling the cytokine storm. The results of clinical trials suggested that emetine has certain curative efficacy on COVID-19, such as the negative conversion of nucleic acid, rapid recovery of blood oxygen concentration and improvement of cough symptoms. Additionally, emetine was found to have good safety during the treatment of COVID-19[62−65].

Cephalotaxus fortune is an endemic plant in China. Homoharringtonine (HHT) is a natural product extracted from *C. fortune*, which can limit protein translation by interfering with the binding of host transfer RNA to host ribosome. The genome of SARS-CoV-2 encode a protein of more than 8000 amino acids, which contain 16 non-structural proteins closely associated with virus replication. Once the translation process of non-structural proteins is interfered, the replication of SARS-CoV-2 is inhibited, which eventually helps to overcome COVID-19[64,66].

Tetrandrine is an antagonist of calmodulin, which may inhibit SARS-CoV-2 by blocking two-pore channel 2 (TPC2), which can suppress the release of the viral genome from the endolysosomal system[67]. In addition, tetrandrine can inhibit fibroblasts, thereby inhibiting pulmonary fibrosis. Tetrandrine can be potentially used to treat patients with mild and severe COVID-19, thereby reducing the disease progression and improving prognosis by reducing the incidence of pulmonary fibrosis during rehabilitation[68].

Baicalein (5,6,7-trihydroxyflavone) is a monomer flavonoid extracted from *Scutellaria baicalensis* or other plants. The previous study revealed that Baicalein has a therapeutic effect on COVID-19, as it can reduce cell damage *in vitro* and inhibit SARS-CoV-2 replication in mice[69]. A clinical trial of Baicalein in patients with mild or moderate COVID-19 has been completed in China.

Diammonium glycyrrhizinate and glycyrrhizic acid are the main bioactive components of *Glycyrrhiza uralensis*. Diammonium glycyrrhizinate can control inflammation by significantly inhibiting proinflammatory prostaglandin E2 (PGE2). Glycyrrhizic acid can exert an obvious antiviral effect on SARS-CoV-2 by binding to the angiotensin converting enzyme 2 (ACE2) receptor. Therefore, glycyrrhizic acid derivatives can be used to treat COVID-19[70,71]. In addition, critical COVID-19 patients are prone to sepsis, and severe hepatic injury is a key factor in sepsis and septic shock. Diammonium glycyrrhizinate participates in protecting hepatocyte membrane and ameliorating liver function, which may fight off the shock episodes from sepsis. Two exploratory clinical trials of diammonium glycyrrhizinate were approved in China for COVID-19 patients.

As a coumarin derivative, hymecromone is commonly used for the treatment of cholecystitis. According to previous research, hymecromone can inhibit the hyaluronic acid accumulation mediated by human identical sequence (HIS). Also, HIS can enhance the activation of inflammation-related genes of the non-immune cells in lung and blood vessels, thus suggesting that non-immune cells activated by COVID-19 may be an important cause of "cytokine storm". Hyaluronic acid can induce pulmonary ground-glass lesion in COVID-19 patients, which is closely related to inflammation[72]. Therefore, hymecromone can presumably be used to treat COVID-19, which is achieved by suppressing hyaluronic acid accumulation. In China, an exploratory clinical trial of hymecromone in patients with COVID-19 have been carried out.

As a key ingredient of *Forsythia suspensa*, phillyrin is demonstrated to have anti-inflammatory, anti-oxidant, and antiviral activities. *In vitro* studies indicated that phillyrin can significantly inhibit the replication of SARS-CoV-2. Additionally, phillyrin can markedly reduce the production of proinflammatory cytokines at the mRNA levels by regulating the activity of the NF-κB signaling pathway. Therefore, phillyrin may have the potential to fight COVID-19[73]. The phase II clinical trials of phillyrin are currently in progress.

Cepharanthine is a biscoclaurine alkaloid derived from *Stephania cepharantha* Hayata, which possesses the antiviral, anti-infammatory, antioxidative and immunomodulating properties. Cepharanthine was found to have significant antiviral effects on SARS-CoV-2 by binding to the spike protein and interfering with viral engagement to ACE2. *In vitro* study indicated that viral RNA yield in cells treated with 10 mmol/L cepharanthine was 15,393-fold lower than that in the untreated cells[74]. Moreover, cepharanthine can inhibit NF-κB, lipid peroxidation, NO production, cyclooxygenase, and expression of cytokine production[75,76]. As a potential drug candidate, further clinical trials will be required for the identification of the efficacy of cepharanthine.

As a well-known anti-malarial compound, artemisinin is isolated from the herbs of *Artemisia apiacea* (Qinghao). Artemisinin and its derivatives including artesunate, arteannuin B, arteether, dihydroartemisinin and lumefantrine are found to be effective against COVID-19 due to their ability to inhibit NF-κB signaling pathway leading to reduce TNF-α and IL-6 which are the key mediators of ARDS[77,78]. Among its derivatives, arteannuin B exerted the highest anti-SARS-CoV-2 activity with an EC_{50} of 10.28 μmol/L[79], while lumefantrine presented favorable PK characters owing to its high plasma and lung concentrations after multiple administrations[80]. In addition, artesunate is proven effective in a faster recovery of COVID-19 in a prospective, controlled clinical study[81]. An open-label non-randomized study indicated that COVID-19 patients received standard of care therapy combined with artemisinin plus piperaquine showed a faster clearance of SARS-CoV-2 than the patients only received standard of care therapy[82]. These clinical trials suggested that artemisinin may contribute to therapy of COVID-19.

Berberine is a quaternary ammonium alkaloid isolated from Rhizoma Coptidis, which can inhibit AP-1 and NF-κB, the key factors in cell signal transduction, thereby reducing the inflammatory response. Berberine can be used to treat COVID-19 by blocking "cytokine storms" and maintaining intestinal microenvironment balance[83,84]. A phase IV clinical trial of berberine in severe patients with COVID-19 has been completed in China.

4.2. *Traditional Chinese medicine prescriptions*

Traditional Chinese medicine was found to achieve satisfactory results in the treatment of COVID-19. According to some reports, the condition of over 92% patients received traditional Chinese medicine treatment was improved, while only 5% of them were in critical condition[7]. Traditional Chinese medicine has the advantage of a full course of treatment and a full range of treatments[85]. As early prevention and early treatment can reduce the mortality rate, improve symptoms (including fever, fatigue, cough, dry and/or sore throat, breathing difficulties, myalgia, and so on)[86−90], and decrease the occurrence of complications and recurrence, they have broad application prospects[60,91].

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The traditional Chinese medicine prescriptions such as Jinhua qinggan granule[92], Lianhua Qingwen capsule/granule[93], Xuebijing injection[94], Lung Cleaner (Qingfei Paidu decoction)[95], cure 14 (Huashi Baidu granules)[96], XuanFei Baidu granules[97–99] are collectively termed "three medicines and three formulas". Besides the above six prescriptions, other traditional Chinese medicine prescriptions, such as Fuzheng Huayu tablets[100], Buzhong Yiqi decoction[101], Hanshiyi formula[102,103], Reduning injection[104–106], Tanreqing injection[107,108] and FuzhengJiedu granules[109,110], etc. were reported to be effective in the treatment of COVID-19.

The possible mechanisms of traditional Chinese medicine for the treatment of COVID-19 mainly include the following aspects: antivirus, anti-inflammation, immunoregulation, and others. Xuebijing injection[111] and Lung Cleaner[112] exerted antiviral effect by regulating PI3K−Akt. Jinhua qinggan granule[113], Lianhua Qingwen capsule/granule[114,115], Hanshiyi formula[103] and Reduning injection[106] can inhibit SARS-CoV-2 by targeting Mpro or ACE2. Furthermore, Jinhua qinggan granule, Lung Cleaner, cure 14, Xuebijing injection and Tanreqing injection, etc. could affect signaling pathways such as TNF, MAPK, NF-κB, thus alleviating the "cytokine storm"[116–119]. Virus-infected cells release signals to recruit and activate immune cells. These immune cells secrete a variety of cytokines and chemokines to recruit more immune cells to the lesion site. However, this can lead to excessive immune responses and damage the body. Traditional Chinese medicines do not only exert antiviral effects, but by improving human immunity to treat COVID-19. Viral infection may induce host humoral and cellular immunities, which play an important role in fighting the virus[120].

5. Discussion

The risks of outbreaks of coronavirus remain clear and present. Thus, it is imperative that work continues to develop effective broad-spectrum drugs against coronaviruses to respond to current and future global challenges. Most Chinese pharmaceutical groups and R&D teams are striving for their anti-COVID-19 drugs in development being approved as soon as possible. Complete and accurate clinical data and real-world verification are essential for approval, and a "head-to-head" comparison with the anti-COVID-19 drugs that have been approved in the world is more convincing. However, the success of drug development cannot only be measured by the speed of approval, and the efficacy and safety are the most important.

An ideal antiviral drug for the therapy of COVID-19 should have the following features: 1) convenient administration; 2) high efficiency and low toxicity; 3) affordability and easily accessible; 4) be effective against SARS-CoV-2 variants. However, these requirements are difficult to achieve concurrently at present. For instance, the neutralizing antibodies have high clinical efficacy against COVID-19, but they are mostly confined to mildly affected the COVID-19 patients with high risk factors due to their administration methods (as Fig. 2 shown). Furthermore, most action mechanisms of neutralizing antibodies preventing viral infection of SARS-CoV-2 focus on inhibiting interference with virus entry, virus protein maturation, and viral RNA synthesis. Thus, treatment with neutralizing antibodies is more likely to encounter the challenge of drug resistance induced by rapid virus mutation[42]. Therefore, research and development of the broad-spectrum antiviral oral agents, *e.g.*, the small molecule antiviral drugs, are among the most important research directions for treating COVID-19. So far, the original research and development of small molecule drugs and neutralizing antibodies in China have made encouraging progress, and the process is speeding up. In addition to the drugs in clinical phases, some potential drug candidates in development exhibited promising efficacy in preclinical trials, such as SSD8432, VV993, GDI-4405, SHEN26 and RAY003, etc. The pathogenesis of COVID-19 is complex; however, few drugs that can act concurrently on multiple targets are being developed. Therefore, combined medication is an effective way to fight against COVID-19. The combination of different sorts of drugs can reduce the adverse events. Moreover, the drug combination can simultaneously alleviate clinic symptoms and kill the virus[121]. One challenge for the therapy of COVID-19 is the time window for the treatment. The earlier treatment is started, the better effects can be achieved. Clinical trials showed that antiviral drugs should be used in the earlier virus replication phase of COVID-19. Thus, the pre- and post-exposure prophylactic effects of anti-COVID-19 drugs should be given more attention, and more relevant clinical trials should be conducted.

Due to pressure from the high infectivity and mortality of COVID-19, there is insufficient time to develop novel drugs and conduct clinical trials. Consequently, some drugs that are currently in use as investigational therapeutic agents for the treatment of COVID-19 are the repurposed (or repositioned) medications, *e.g.*, azvudine and proxalutamide, which are usually used for treating other diseases[122]. Drug repurposing is a rapid and effective measure for managing COVID-19, as these drugs have already been approved for use in other indications. The main advantage of drug repurposing is that the approved drugs are already well documented in terms of their safety and pharmacokinetics, etc. Thus, if the efficacy against COVID-19 is demonstrated, the repurposed drugs can be directly tested in phase II/III clinical trials without conducting the preclinical or phase I clinical trials.

Traditional Chinese medicine has been widely used for fighting against COVID-19 in China, as its safety and efficacy have been confirmed. Traditional Chinese medicine should have a valuable and active role in confronting the worldwide COVID-19 pandemic. Traditional Chinese medicine may not be the best strategy for directly eliminating the virus, but it is effective in the early phase and treatment phase of SARS-CoV-2 infection. Traditional Chinese medicine can be used in a full course of treatment and a full range of treatments due to its multiple components that exert different efficacy *via* multiple mechanisms and multi-targets. Among the multiple mechanisms, the regulation of various immune functions has an important role in treating COVID-19. Traditional Chinese medicine can regulate the host immune response to achieve balanced immunity through two important approaches: 1) regulating the innate immune system and enhancing the body's resistance to viruses; 2) inhibiting inflammatory reaction and reducing lung damage, which contributes to control and eliminate viral infection[123]. In addition, other molecular targets of traditional Chinese medicine may also be involved in the pathogenesis of COVID-19 and thus may have other benefits that may not yet be known. However, there are many unsolved issues for COVID-19 treatment with traditional Chinese medicine. One main characteristic of traditional Chinese medicine treatment is that the components and dosages of prescriptions often change due to the different syndromes of different patients. Therefore, the standardization of traditional Chinese medicines therapy needs to be concerned. The mechanisms, active ingredients and *in vivo* pharmacokinetic properties (absorption, distribution, metabolism, and excretion) of most traditional Chinese medicines are unclear, which still needs further explored.

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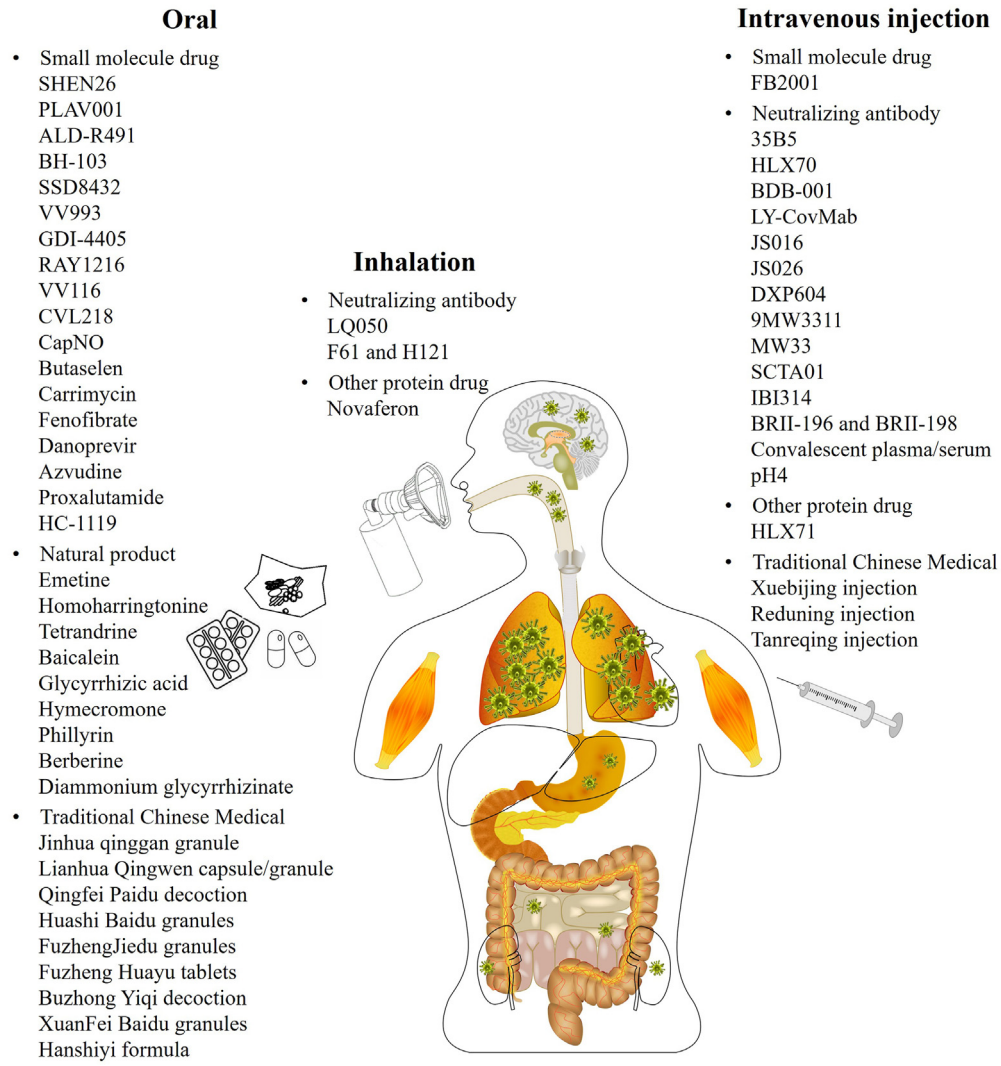

Figure 2 The routes of administration of anti-COVID-19 drugs.

Moreover, unique theoretical system of traditional Chinese medicine also limits in the global promotion of traditional Chinese medicine against COVID-19.

In COVID-19 patients, especially the elderly, the high viral load of virus at an early stage of the disease often results in a poor outcome[124]. The shortened time of SARS-CoV-2 ribonucleic acid turned negative is often used as an indicator of efficacy of anti-COVID-19 drugs. The shorter turning-to-negative time reflects viral load decreases faster, but the improvement of symptoms (*e.g.*, decrease in the proportion of severe cases) is also critical for efficacy evaluation. Thus, researchers should pay more attention to the therapeutic effects of anti-COVID-19 drugs on reducing the incidence of severe cases and death in clinical study.

The knowledge of COVID-19 has increased greatly with the in-depth study, which give a boost to the continuous development of candidate drugs in COVID-19 treatment. For instance, several original findings on the pathogenesis of COVID-19 reported by Chinese researchers indicated that some inhibitors of signaling pathways may also be used in combating SARS-CoV-2[125−128]. It was reported that SARS-CoV-2 N protein is a key mediator for acute kidney injury (AKI), which can induce AKI *via* the Smad 3-dependent G1 cell cycle arrest mechanism[127]. As a Smad3 inhibitor, SIS3 is able to protect kidneys from SARS-CoV-2 N-induced cell death through the G1 cell cycle arrest[129,130]. Furthermore, some preclinical studies suggested that N protein can aggravate lung injury, accelerates death in sepsis and acute inflammation induced upon SARS-CoV-2 infection, and promotes IL-1β and IL-6 activation in mouse models[131]. MCC950 (a specific inhibitor of NLRP3) and Ac-YVAD-cmk (an inhibitor of caspase-1) can block N-induced lung injury and cytokine production[126]. HIF-1α plays an extensive role in facilitating SARS-CoV-2 infections and aggravating inflammatory responses to COVID-19, which can be inhibited by BAY87-2243 (a HIF-1α inhibitor)[125]. The repression of NF-κB signaling pathway has therapeutic applications in inflammatory diseases and virus-induced cytokine storms[132]. Treatment with NF-κB inhibitors caffeic acid phenethyl ester and parthenolide were found they can improve the survival rate of mice infected with SARS-CoV[133]. Although these inhibitors have not be subjected to clinical trials so far, they also offer more choices for coping with COVID-19.

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Author contributions

Xiwei Ji, Yimin Cui conceived, designed, and revised the manuscript; Xiwei Ji, Yimin Cui wrote and revised the manuscript; Xiwei Ji, Xiangrui Meng, Xiao Zhu, Qingfeng He and Yimin Cui analyzed the data and discussed.

Conflicts of interest

The authors state no conflict of interest and have received no payment in preparation of this manuscript.

References

1. Andersen KG, Rambaut A, Lipkin WI, Holmes EC, Garry RF. The proximal origin of SARS-CoV-2. *Nat Med* 2020;**26**:450−2.
2. Hu B, Guo H, Zhou P, Shi ZL. Characteristics of SARS-CoV-2 and COVID-19. *Nat Rev Microbiol* 2021;**19**:141−54.
3. Monteil V, Kwon H, Prado P, Hagelkruys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020;**181**:905−913.e7.
4. Bian J, Li Z. Angiotensin-converting enzyme 2 (ACE2): SARS-CoV-2 receptor and RAS modulator. *Acta Pharm Sin B* 2021;**11**:1−12.
5. McKee DL, Sternberg A, Stange U, Laufer S, Naujokat C. Candidate drugs against SARS-CoV-2 and COVID-19. *Pharmacol Res* 2020;**157**:104859.
6. Liu L, Wang P, Nair MS, Yu J, Rapp M, Wang Q, et al. Potent neutralizing antibodies against multiple epitopes on SARS-CoV-2 spike. *Nature* 2020;**584**:450−6.
7. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese medicine in the treatment of patients infected with 2019-new coronavirus (SARS-CoV-2): a review and perspective. *Int J Biol Sci* 2020;**16**:1708−17.
8. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science* 2020;**368**:779−82.
9. Xiang R, Yu Z, Wang Y, Wang L, Huo S, Li Y, et al. Recent advances in developing small-molecule inhibitors against SARS-CoV-2. *Acta Pharm Sin B* 2022;**12**:1591−623.
10. Ghosh AK, Brindisi M, Shahabi D, Chapman ME, Mesecar AD. Drug development and medicinal chemistry efforts toward SARS-coronavirus and COVID-19 therapeutics. *ChemMedChem* 2020;**15**:907−32.
11. Li Z, Wu J, Zhou J, Yuan B, Chen J, Wu W, et al. A vimentin-targeting oral compound with host-directed antiviral and anti-inflammatory actions addresses multiple features of COVID-19 and related diseases. *mBio* 2021;**12**:e0254221.
12. Xie Y, Yin W, Zhang Y, Shang W, Wang Z, Luan X, et al. Design and development of an oral remdesivir derivative VV116 against SARS-CoV-2. *Cell Res* 2021;**31**:1212−4.
13. Abubaker Bagabir S, Ibrahim NK, Abubaker Bagabir H, Hashem Ateeq R. COVID-19 and artificial intelligence: genome sequencing, drug development and vaccine discovery. *J Infect Public Health* 2022;**15**:289−96.
14. Lin M, Dong HY, Xie HZ, Li YM, Jia L. Why do we lack a specific magic anti-COVID-19 drug? Analyses and solutions. *Drug Discov Today* 2021;**26**:631−6.
15. Yan H, Sun J, Wang K, Wang H, Wu S, Bao L, et al. Repurposing carrimycin as an antiviral agent against human coronaviruses, including the currently pandemic SARS-CoV-2. *Acta Pharm Sin B* 2021;**11**:2850−8.
16. Pawar A, Pal A, Goswami K, Squitti R, Rongiolettie M. Molecular basis of quercetin as a plausible common denominator of macrophage-cholesterol-fenofibrate dependent potential COVID-19 treatment axis. *Results Chem* 2021;**3**:100148.
17. Buschard K. Fenofibrate increases the amount of sulfatide which seems beneficial against COVID-19. *Med Hypotheses* 2020;**143**:110127.
18. Davies SP, Mycroft-West CJ, Pagani I, Hill HJ, Chen YH, Karlsson R, et al. The hyperlipidaemic drug fenofibrate significantly reduces infection by SARS-CoV-2 in cell culture models. *Front Pharmacol* 2021;**12**:660490.
19. Feher M, Joy M, Munro N, Hinton W, Williams J, de Lusignan S. Fenofibrate as a COVID-19 modifying drug: laboratory success *versus* real-world reality. *Atherosclerosis* 2021;**339**:55−6.
20. Yasmin F, Zeeshan MH, Ullah I. The role of fenofibrate in the treatment of COVID-19. *Ann Med Surg (Lond)* 2022;**74**:102974.
21. Chen H, Zhang Z, Wang L, Huang Z, Gong F, Li X, et al. First clinical study using HCV protease inhibitor danoprevir to treat COVID-19 patients. *Medicine (Baltim)* 2020;**99**:e23357.
22. Zhang Z, Wang S, Tu X, Peng X, Huang Y, Wang L, et al. A comparative study on the time to achieve negative nucleic acid testing and hospital stays between danoprevir and lopinavir/ritonavir in the treatment of patients with COVID-19. *J Med Virol* 2020;**92**:2631−6.
23. Ren Z, Luo H, Yu Z, Song J, Liang L, Wang L, et al. A randomized, open-label, controlled clinical trial of azvudine tablets in the treatment of mild and common COVID-19, a pilot study. *Adv Sci* 2020:2001435.
24. Yu B, Chang J. Azvudine (FNC): a promising clinical candidate for COVID-19 treatment. *Signal Transduct Targeted Ther* 2020;**5**:236.
25. Zhang JL, Li YH, Wang LL, Liu HQ, Lu SY, Liu Y, et al. Azvudine is a thymus-homing anti-SARS-CoV-2 drug effective in treating COVID-19 patients. *Signal Transduct Targeted Ther* 2021;**6**:414.
26. Hoffmann M, Kleine-Weber H, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell* 2020;**181**:271−280.e8.
27. Cadegiani FA, McCoy J, Gustavo Wambier C, Vano-Galvan S, Shapiro J, Tosti A, et al. Proxalutamide significantly accelerates viral clearance and reduces time to clinical remission in patients with mild to moderate COVID-19: results from a randomized, double-blinded, placebo-controlled trial. *Cureus* 2021;**13**:e13492.
28. Frontiers Editorial O. Expression of concern: proxalutamide reduces the rate of hospitalization for COVID-19 male outpatients: a randomized double-blinded placebo-controlled trial. *Front Med* 2021;**8**:831449.
29. McCoy J, Goren A, Cadegiani FA, Vano-Galvan S, Kovacevic M, Situm M, et al. Proxalutamide reduces the rate of hospitalization for COVID-19 male outpatients: a randomized double-blinded placebo-controlled trial. *Front Med* 2021;**8**:668698.
30. Li X, Cheng K, Li X, Zhou Y, Liu J, Zeng H, et al. Phase I clinical trial of HC-1119: a deuterated form of enzalutamide. *Int J Cancer* 2021;**149**:1473−82.
31. Shanmugaraj B, Siriwattananon K, Wangkanont K, Phoolcharoen W. Perspectives on monoclonal antibody therapy as potential therapeutic intervention for coronavirus disease-19 (COVID-19). *Asian Pac J Allergy Immunol* 2020;**38**:10−8.
32. Gai J, Ma L, Li G, Zhu M, Qiao P, Li X, et al. A potent neutralizing nanobody against SARS-CoV-2 with inhaled delivery potential. 2020 *MedComm* 2021;**2**:101−13.
33. Qu Y, Zhang X, Wang M, Sun L, Jiang Y, Li C, et al. Antibody cocktail exhibits broad neutralization activity against SARS-CoV-2 and SARS-CoV-2 variants. *Virol Sin* 2021;**36**:934−47.
34. Lu J, Yin Q, Pei R, Zhang Q, Qu Y, Pan Y, et al. Nasal delivery of broadly neutralizing antibodies protects mice from lethal challenge with SARS-CoV-2 delta and omicron variants. *Virol Sin* 2022;**37**:238−47.
35. Wang X, Hu A, Chen X, Zhang Y, Yu F, Yue S, et al. A potent human monoclonal antibody with pan-neutralizing activities directly dislocates S trimer of SARS-CoV-2 through binding both up and down forms of RBD. *Signal Transduct Targeted Ther* 2021;**7**:114.
36. Liu J, Chen Q, Yang S, Li Y, Dou Y, Deng YQ, et al. hACE2 Fc-neutralization antibody cocktail provides synergistic protection

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against SARS-CoV-2 and its spike RBD variants. *Cell Discov* 2021; **7**:54.
37. Patel MR, Tolcher AW, Rasco DW, Johnson ML, Andtbacka R. BDB001, an intravenously administered toll-like receptor 7 and 8 (TLR7/8) agonist, in combination with pembrolizumab in advanced solid tumors: phase 1 safety and efficacy results. *J Clin Oncol* 2021; **39**:2512.
38. Zhang Q, Zhou R, Yang J, Dou C, Gan T, Liu F, et al. A randomized, double-blind, placebo-controlled, first-in-human clinical trial to assess safety, tolerability, and pharmacokinetics of LY-CovMab, a potent human neutralizing antibody against SARS-CoV-2. *Infect Dis Ther* 2022;**11**:405−22.
39. Nathan R, Shawa I, De La Torre I, Pustizzi JM, Haustrup N, Patel DR, et al. A narrative review of the clinical practicalities of bamlanivimab and etesevimab antibody therapies for SARS-CoV-2. *Infect Dis Ther* 2021;**10**:1933−47.
40. Dong R, Jiang L, Yang T, Wang C, Zhang Y, Chen X, et al. Efficacy and safety of SARS-CoV-2 neutralizing antibody JS016 in hospitalized Chinese patients with COVID-19: a phase 2/3, multicenter, randomized, open-label, controlled trial. *Antimicrob Agents Chemother* 2022;**66**:e0204521.
41. Wang F, Li L, Dou Y, Shi R, Duan X, Liu H, et al. Etesevimab in combination with JS026 neutralizing SARS-CoV-2 and its variants. *Emerg Microb Infect* 2022;**11**:548−51.
42. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. *Nature* 2022;**602**:657−63.
43. Cui Z, Liu P, Wang N, Wang L, Fan K, Zhu Q, et al. Structural and functional characterizations of infectivity and immune evasion of SARS-CoV-2 omicron. *Cell* 2022;**185**:860−71.e13.
44. Meng X, Wang P, Xiong Y, Wu Y, Lin X, Lu S, et al. Safety, tolerability, pharmacokinetic characteristics, and immunogenicity of MW33: a phase 1 clinical study of the SARS-CoV-2 RBD-targeting monoclonal antibody. *Emerg Microb Infect* 2021;**10**:1638−48.
45. Li Y, Qi L, Bai H, Sun C, Xu S, Wang Y, et al. Safety, tolerability, pharmacokinetics, and immunogenicity of a monoclonal antibody (SCTA01) targeting SARS-CoV-2 in healthy adults: a randomized, double-blind, placebo-controlled, phase I study. *Antimicrob Agents Chemother* 2021;**65**:e0106321.
46. Zou J, Li L, Zheng P, Liang W, Hu S, Zhou S, et al. Ultrapotent neutralizing antibodies against SARS-CoV-2 with a high degree of mutation resistance. *J Clin Invest* 2022;**132**:e154987.
47. Group AC-TfIwC-S. Efficacy and safety of two neutralising monoclonal antibody therapies, sotrovimab and BRII-196 plus BRII-198, for adults hospitalised with COVID-19 (TICO): a randomised controlled trial. *Lancet Infect Dis* 2021;**22**:622−35.
48. Cho H, Gonzales-Wartz KK, Huang D, Yuan M, Peterson M, Liang J, et al. Bispecific antibodies targeting distinct regions of the spike protein potently neutralize SARS-CoV-2 variants of concern. *Sci Transl Med* 2021;**13**:eabj5413.
49. De Gasparo R, Pedotti M, Simonelli L, Nickl P, Muecksch F, Cassaniti I, et al. Bispecific antibody neutralizes circulating SARS-CoV-2 variants, prevents escape and protects mice from disease. *bioRxiv* 2021. Available from: https://doi.org/10.1101/2021.01.22.427567.
50. Li C, Zhan W, Yang Z, Tu C, Hu G, Zhang X, et al. Broad neutralization of SARS-CoV-2 variants by an inhalable bispecific single-domain antibody. *Cell* 2022;**185**:1389−401.e18.
51. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with COVID-19 with convalescent plasma. *JAMA* 2020;**323**:1582−9.
52. Wang Y, Huo P, Dai R, Lv X, Yuan S, Zhang Y, et al. Convalescent plasma may be a possible treatment for COVID-19: a systematic review. *Int Immunopharm* 2021;**91**:107262.
53. Binson G, Venisse N, Sauvaget A, Bacle A, Lazaro P, Dupuis A. Preparation and physicochemical stability of 50 mg/mL hydroxychloroquine oral suspension in SyrSpend® SF PH4 (dry). *Int J Antimicrob Agents* 2020;**56**:106201.
54. Janapala RN, Patel J, Belfaqeeh O, Alhashmi A, Pourmand A. Novaferon, treatment in COVID-19 patients. *Int J Infect Dis* 2021; **103**:297.
55. Li M, Rao C, Pei D, Wang L, Li Y, Gao K, et al. Novaferon, a novel recombinant protein produced by DNA-shuffling of IFN-alpha, shows antitumor effect *in vitro* and *in vivo*. *Cancer Cell Int* 2014;**14**:8.
56. Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, et al. SARS-CoV-2 clearance in COVID-19 patients with Novaferon treatment: a randomized, open-label, parallel-group trial. *Int J Infect Dis* 2020;**99**: 84−91.
57. Huang J, Tao G, Liu J, Cai J, Huang Z, Chen JX. Current prevention of COVID-19: natural products and herbal medicine. *Front Pharmacol* 2020;**11**:588508.
58. Santana FPR, Thevenard F, Gomes KS, Taguchi L, Camara NOS, Stilhano RS, et al. New perspectives on natural flavonoids on COVID-19-induced lung injuries. *Phytother Res* 2021;**35**: 4988−5006.
59. Boozari M, Hosseinzadeh H. Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies. *Phytother Res* 2021;**35**:864−76.
60. Lyu M, Fan G, Xiao G, Wang T, Xu D, Gao J, et al. Traditional Chinese medicine in COVID-19. *Acta Pharm Sin B* 2021;**11**:3337−63.
61. Luo L, Jiang J, Wang C, Fitzgerald M, Hu W, Zhou Y, et al. Analysis on herbal medicines utilized for treatment of COVID-19. *Acta Pharm Sin B* 2020;**10**:1192−204.
62. Kumar R, Afsar M, Khandelwal N, Chander Y, Riyesh T, Dedar RK, et al. Emetine suppresses SARS-CoV-2 replication by inhibiting interaction of viral mRNA with eIF4E. *Antivir Res* 2021;**189**:105056.
63. Snoussi M, Redissi A, Mosbah A, De Feo V, Adnan M, Aouadi K, et al. Emetine, a potent alkaloid for the treatment of SARS-CoV-2 targeting papain-like protease and non-structural proteins: pharmacokinetics, molecular docking and dynamic studies. *J Biomol Struct Dyn* 2021;**13**:1−14.
64. Sohrab SS, Suhail M, Kamal MA, Azhar EI. Natural products homoharringtonine and emetine alkaloids as SARS-CoV-2 treatment options. *Curr Pharm Des* 2021;**27**:3444−53.
65. Wang A, Sun Y, Liu Q, Wu H, Liu J, He J, et al. Low dose of emetine as potential anti-SARS-CoV-2 virus therapy: preclinical *in vitro* inhibition and *in vivo* pharmacokinetic evidences. *Mol Biomed* 2020;**1**:14.
66. Choy KT, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication *in vitro*. *Antivir Res* 2020;**178**:104786.
67. Heister PM, Poston RN. Pharmacological hypothesis: TPC2 antagonist tetrandrine as a potential therapeutic agent for COVID-19. *Pharmacol Res Perspect* 2020;**8**:e00653.
68. Hsu YC, Chiu YT, Cheng CC, Wu CF, Lin YL, Huang YT. Antifibrotic effects of tetrandrine on hepatic stellate cells and rats with liver fibrosis. *J Gastroenterol Hepatol* 2007;**22**:99−111.
69. Song J, Zhang L, Xu Y, Yang D, Zhang L, Yang S, et al. The comprehensive study on the therapeutic effects of baicalein for the treatment of COVID-19 *in vivo* and *in vitro*. *Biochem Pharmacol* 2021;**183**:114302.
70. Yu S, Zhu Y, Xu J, Yao G, Zhang P, Wang M, et al. Glycyrrhizic acid exerts inhibitory activity against the spike protein of SARS-CoV-2. *Phytomedicine* 2021;**85**:153364.
71. Bailly C, Vergoten G. Glycyrrhizin: an alternative drug for the treatment of COVID-19 infection and the associated respiratory syndrome?. *Pharmacol Ther* 2020;**214**:107618.
72. Andonegui-Elguera S, Taniguchi-Ponciano K, Gonzalez-Bonilla CR, Torres J, Mayani H, Herrera LA, et al. Molecular alterations prompted by SARS-CoV-2 infection: induction of hyaluronan, glycosaminoglycan and mucopolysaccharide metabolism. *Arch Med Res* 2020;**51**:645−53.
73. Lai Y, Han T, Lao Z, Li G, Xiao J, Liu X. Phillyrin for COVID-19 and influenza co-infection: a potential therapeutic strategy targeting host based on bioinformatics analysis. *Front Pharmacol* 2021;**12**: 754241.

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74. Fan HH, Wang LQ, Liu WL, An XP, Liu ZD, He XQ, et al. Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus-related coronavirus model. *Chin Med J (Engl)* 2020;**133**:1051−6.
75. Ohashi H, Watashi K, Saso W, Shionoya K, Iwanami S, Hirokawa T, et al. Potential anti-COVID-19 agents, cepharanthine and nelfinavir, and their usage for combination treatment. *iScience* 2021;**24**:102367.
76. Rogosnitzky M, Okediji P, Koman I. Cepharanthine: a review of the antiviral potential of a Japanese-approved alopecia drug in COVID-19. *Pharmacol Rep* 2020;**72**:1509−16.
77. Li T, Chen H, Yang Z, Liu XG, Zhang LM, Wang H. Evaluation of the immunosuppressive activity of artesunate *in vitro* and *in vivo*. *Int Immunopharm* 2013;**16**:306−12.
78. Jiang W, Cen Y, Song Y, Li P, Qin R, Liu C, et al. Artesunate attenuated progression of atherosclerosis lesion formation alone or combined with rosuvastatin through inhibition of pro-inflammatory cytokines and pro-inflammatory chemokines. *Phytomedicine* 2016;**23**:1259−66.
79. Cao R, Hu H, Li Y, Wang X, Xu M, Liu J, et al. Anti-SARS-CoV-2 potential of artemisinins *in vitro*. *ACS Infect Dis* 2020;**6**:2524−31.
80. Borrmann S, Sallas WM, Machevo S, Gonzalez R, Bjorkman A, Martensson A, et al. The effect of food consumption on lumefantrine bioavailability in African children receiving artemether-lumefantrine crushed or dispersible tablets (Coartem) for acute uncomplicated *Plasmodium falciparum* malaria. *Trop Med Int Health* 2010;**15**:434−41.
81. Lin Y, Wu F, Xie Z, Song X, Zhu Q, Wei J, et al. Clinical study of artesunate in the treatment of coronavirus disease 2019. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue* 2020;**32**:417−20.
82. Li G, Yuan M, Li H, Deng C, Wang Q, Tang Y, et al. Safety and efficacy of artemisinin-piperaquine for treatment of COVID-19: an open-label, non-randomised and controlled trial. *Int J Antimicrob Agents* 2021;**57**:106216.
83. Wang ZZ, Li K, Maskey AR, Huang W, Toutov AA, Yang N, et al. A small molecule compound berberine as an orally active therapeutic candidate against COVID-19 and SARS: a computational and mechanistic study. *FASEB J* 2021;**35**:e21360.
84. Zhang BY, Chen M, Chen XC, Cao K, You Y, Qian YJ, et al. Berberine reduces circulating inflammatory mediators in patients with severe COVID-19. *Br J Surg* 2021;**108**:e9−11.
85. Wu X, Li W, Qin Z, Xue L, Huang G, Luo Z, et al. Traditional Chinese medicine as an adjunctive therapy for mild and common COVID-19: a systematic review and network meta-analysis. *Medicine (Baltim)* 2021;**100**:e27372.
86. Hu K, Guan WJ, Bi Y, Zhang W, Li L, Zhang B, et al. Efficacy and safety of Lianhuaqingwen capsules, a repurposed Chinese herb, in patients with coronavirus disease 2019: a multicenter, prospective, randomized controlled trial. *Phytomedicine* 2021;**85**:153242.
87. Xiong WZ, Wang G, Du J, Ai W. Efficacy of herbal medicine (Xuanfei Baidu decoction) combined with conventional drug in treating COVID-19: a pilot randomized clinical trial. *Integr Med Res* 2020;**9**:100489.
88. Liu Z, Li X, Gou C, Li L, Luo X, Zhang C, et al. Effect of Jinhua Qinggan granules on novel coronavirus pneumonia in patients. *J Tradit Chin Med* 2020;**40**:467−72.
89. Xiao M, Tian J, Zhou Y, Xu X, Min X, Lv Y, et al. Efficacy of Huoxiang Zhengqi dropping pills and Lianhua Qingwen granules in treatment of COVID-19: a randomized controlled trial. *Pharmacol Res* 2020;**161**:105126.
90. Xin S, Cheng X, Zhu B, Liao X, Yang F, Song L, et al. Clinical retrospective study on the efficacy of Qingfei Paidu decoction combined with Western medicine for COVID-19 treatment. *Biomed Pharmacother* 2020;**129**:110500.
91. Ren JL, Zhang AH, Wang XJ. Traditional Chinese medicine for COVID-19 treatment. *Pharmacol Res* 2020;**155**:104743.
92. Huang K, Zhang P, Zhang Z, Youn JY, Wang C, Zhang H, et al. Traditional Chinese Medicine (TCM) in the treatment of COVID-19 and other viral infections: efficacies and mechanisms. *Pharmacol Ther* 2021;**225**:107843.
93. Li LC, Zhang ZH, Zhou WC, Chen J, Jin HQ, Fang HM, et al. Lianhua Qingwen prescription for coronavirus disease 2019 (COVID-19) treatment: advances and prospects. *Biomed Pharmacother* 2020;**130**:110641.
94. Xing Y, Hua YR, Shang J, Ge WH, Liao J. Traditional Chinese medicine network pharmacology study on exploring the mechanism of Xuebijing Injection in the treatment of coronavirus disease 2019. *Chin J Nat Med* 2020;**18**:941−51.
95. Chen J, Wang YK, Gao Y, Hu LS, Yang JW, Wang JR, et al. Protection against COVID-19 injury by qingfei paidu decoction *via* antiviral, anti-inflammatory activity and metabolic programming. *Biomed Pharmacother* 2020;**129**:110281.
96. Tao Q, Du J, Li X, Zeng J, Tan B, Xu J, et al. Network pharmacology and molecular docking analysis on molecular targets and mechanisms of Huashi Baidu formula in the treatment of COVID-19. *Drug Dev Ind Pharm* 2020;**46**:1345−53.
97. Wang Y, Wang X, Li Y, Xue Z, Shao R, Li L, et al. Xuanfei Baidu Decoction reduces acute lung injury by regulating infiltration of neutrophils and macrophages *via* PD-1/IL17A pathway. *Pharmacol Res* 2022;**176**:106083.
98. Wang Y, Sang X, Shao R, Qin H, Chen X, Xue Z, et al. Xuanfei Baidu Decoction protects against macrophages induced inflammation and pulmonary fibrosis *via* inhibiting IL-6/STAT3 signaling pathway. *J Ethnopharmacol* 2022;**283**:114701.
99. Li F, Li Y, Zhang J, Li S, Mao A, Zhao C, et al. The therapeutic efficacy of Xuanfei Baidu Formula combined with conventional drug in the treatment of coronavirus disease 2019: a protocol for systematic review and meta-analysis. *Medicine (Baltim)* 2021;**100**:e24129.
100. Tan SZ, Liu CH, Zhang W, Lu X, Ye WC, Cai ZZ, et al. Effects of Fuzheng Huayu recipe on MMP-2 activity and type IV collagen expression at fibrotic lung. *China J Chin Mater Med* 2007;**32**:835−9.
101. Bian YQ, Ma J, Ren Y, Zhang YL, Qiao YJ. Discovery of intervention effect of Chinese herbal formulas on COVID-19 pulmonary fibrosis treated by VEGFR and FGFR inhibitors. *China J Chin Mater Med* 2020;**45**:1481−7.
102. Tian J, Yan S, Wang H, Zhang Y, Zheng Y, Wu H, et al. Hanshiyi Formula, a medicine for SARS-CoV2 infection in China, reduced the proportion of mild and moderate COVID-19 patients turning to severe status: a cohort study. *Pharmacol Res* 2020;**161**:105127.
103. Han L, Wei XX, Zheng YJ, Zhang LL, Wang XM, Yang HY, et al. Potential mechanism prediction of Cold-Damp Plague Formula against COVID-19 *via* network pharmacology analysis and molecular docking. *Chin Med* 2020;**15**:78.
104. Ma Q, Xie Y, Wang Z, Lei B, Chen R, Liu B, et al. Efficacy and safety of ReDuNing injection as a treatment for COVID-19 and its inhibitory effect against SARS-CoV-2. *J Ethnopharmacol* 2021;**279**:114367.
105. Xu X, Zhang J, Zheng W, Yang Z, Zhao X, Wang C, et al. Efficacy and safety of Reduning injection in the treatment of COVID-19: a randomized, multicenter clinical study. *Ann Palliat Med* 2021;**10**:5146−55.
106. Jia S, Luo H, Liu X, Fan X, Huang Z, Lu S, et al. Dissecting the novel mechanism of reduning injection in treating coronavirus disease 2019 (COVID-19) based on network pharmacology and experimental verification. *J Ethnopharmacol* 2021;**273**:113871.
107. Liu W, Zhang X, Mao B, Jiang H. Systems pharmacology-based study of Tanreqing injection in airway mucus hypersecretion. *J Ethnopharmacol* 2020;**249**:112425.
108. Liu W, Jiang HL, Cai LL, Yan M, Dong SJ, Mao B. Tanreqing injection attenuates lipopolysaccharide-induced airway inflammation through MAPK/NF-kappaB signaling pathways in rats model. *Evid Based Complement Alternat Med* 2016;**2016**:5292346.
109. Yang X, Feng Y, Liu Y, Ye X, Ji X, Sun L, et al. Fuzheng Jiedu Xiaoji formulation inhibits hepatocellular carcinoma progression in patients

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by targeting the AKT/CyclinD1/p21/p27 pathway. *Phytomedicine* 2021;**87**:153575.
110. Xu H, Liu C, Li M, Wang C, Liu G, Wang H, et al. *In vitro* antibacterial experiment of Fuzheng Jiedu Huayu decoction against multidrug-resistant pseudomonas aeruginosa. *Front Pharmacol* 2019;**10**:1682.
111. He TM, Duan CC, Li XF, Zhang JY. Potential mechanism of Xuebijing injection in treatment of coronavirus pneumonia based on network pharmacology and molecular docking. *Chin J Mod Appl Pharm* 2020;**37**:398−405.
112. Peng XJ, Yang XJ, Gang XU, Chen YB, Yang CH, Gong WL, et al. Investigating clinical efficacy and mechanism of Qingfei Paidu Decoction for treatment of COVID-19 based on integrative pharmacology. *Chin J Exp Tradit Med Formulae* 2020;**26**:6−13.
113. Shen F, Fu ZY, Wu YR, LI L, Zhao YD, Xia Y, et al. The potential molecular mechanism of active compounds binding SARS-CoV-2 specific target proteins in Huaqing granules treat COVID-19 based on network pharmacology and high-throughput molecular docking fellowship. *Modern Tradit Chin Med Mater Med-World Sci Technol* 2020;**22**:622−31.
114. Ling XY, Tao JL, Sun X, Yuan B. Exploring material basis and mechanism of Lianhua Qingwen Prescription against coronavirus based on network pharmacology. *Chin Tradit Herb Drugs* 2020;**51**:1723−30.
115. Chen X, Wu Y, Chen C, Gu Y, Zhu C, Wang S, et al. Identifying potential anti-COVID-19 pharmacological components of traditional Chinese medicine Lianhuaqingwen capsule based on human exposure and ACE2 biochromatography screening. *Acta Pharm Sin B* 2021;**11**:222−36.
116. Mao Y, Su YX, Xue P, Li LL, Zhu SJ. Discussion on the mechanism of Jinhua Qinggan granules in the treatment of corona virus disease 2019. *J Chin Med Mater* 2020;**11**:2843−9.
117. Sun X, Tao JL, Xu SJ, Yuan B. The molecular mechanism of treating COVID-19 with Huashi Baidu formula based on network pharmacology. *J Chin Med Mater* 2020;**8**:2047−52.
118. Gao H, Yao XS. Strengthen the research on the medicinal and edible substances to advance the development of the comprehensive healthcare industry. *Chin J Nat Med* 2019;**17**:1−2.
119. Kong Y, Lin LL, Chen Y, Lai S, Wu H, Chen J. Mechanism of XueBiJing Injection on treatment of coronavirus disease 2019 based on network pharmacology. *Moder Tradi Chin Med Mater Med* 2020;**22**:552−60.
120. Florindo HF, Kleiner R, Vaskovich-Koubi D, Acurcio RC, Carreira B, Yeini E, et al. Immune-mediated approaches against COVID-19. *Nat Nanotechnol* 2020;**15**:630−45.
121. Ni L, Chen L, Huang X, Han C, Xu J, Zhang H, et al. Combating COVID-19 with integrated traditional Chinese and Western medicine in China. *Acta Pharm Sin B* 2020;**10**:1149−62.
122. Pandey A, Nikam AN, Shreya AB, Mutalik SP, Gopalan D, Kulkarni S, et al. Potential therapeutic targets for combating SARS-CoV-2: drug repurposing, clinical trials and recent advancements. *Life Sci* 2020;**256**:117883.
123. Ma HD, Deng YR, Tian Z, Lian ZX. Traditional Chinese medicine and immune regulation. *Clin Rev Allergy Immunol* 2013;**44**:229−41.
124. Tsukagoshi H, Shinoda D, Saito M, Okayama K, Sada M, Kimura H, et al. Relationships between viral load and the clinical course of COVID-19. *Viruses* 2021;**13**:304.
125. Tian M, Liu W, Li X, Zhao P, Shereen MA, Zhu C, et al. HIF-1 alpha promotes SARS-CoV-2 infection and aggravates inflammatory responses to COVID-19. *Signal Transduct Targeted Ther* 2021;**6**:308.
126. Pan P, Shen M, Yu Z, Ge W, Chen K, Tian M, et al. SARS-CoV-2 N protein promotes NLRP3 inflammasome activation to induce hyperinflammation. *Nat Commun* 2021;**12**:4664.
127. Wang W, Chen J, Hu D, Pan P, Liang L, Wu W, et al. SARS-CoV-2 N protein induces acute kidney injury *via* smad3-dependent G1 cell cycle arrest mechanism. *Adv Sci* 2022;**9**:e2103248.
128. Yin J, Li C, Ye C, Ruan Z, Liang Y, Li Y, et al. Advances in the development of therapeutic strategies against COVID-19 and perspectives in the drug design for emerging SARS-CoV-2 variants. *Comput Struct Biotechnol J* 2022;**20**:824−37.
129. Lai W, Tang Y, Huang XR, Ming-Kuen Tang P, Xu A, Szalai AJ, et al. C-reactive protein promotes acute kidney injury *via* Smad 3-dependent inhibition of CDK2/cyclin. *E. Kidney Int* 2016;**90**:610−26.
130. Fu S, Tang Y, Huang XR, Feng M, Xu AP, Lan HY. Smad 7 protects against acute kidney injury by rescuing tubular epithelial cells from the G1 cell cycle arrest. *Clin Sci (Lond)* 2017;**131**:1955−69.
131. Kayagaki N, Wong MT, Stowe IB, Ramani SR, Gonzalez LC, Akashi-Takamura S, et al. Noncanonical inflammasome activation by intracellular LPS independent of TLR4. *Science* 2013;**341**:1246−9.
132. Yu H, Lin L, Zhang Z, Zhang H, Hu H. Targeting NF-kappaB pathway for the therapy of diseases: mechanism and clinical study. *Signal Transduct Targeted Ther* 2020;**5**:209.
133. DeDiego ML, Nieto-Torres JL, Regla-Nava JA, Jimenez-Guardeno JM, Fernandez-Delgado R, Fett C, et al. Inhibition of NF-kappaB-mediated inflammation in severe acute respiratory syndrome coronavirus-infected mice increases survival. *J Virol* 2014;**88**:913−24.

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