COVID-19: Antiviral Agents, Antibody Development and Traditional Chinese Medicine

Wenyi Guan1· Wendong Lan1 · Jing Zhang2 · Shan Zhao1 · Junxian Ou1 · Xiaowei Wu1 · Yuqian Yan1 · Jianguo Wu2 · Qiwei Zhang1,2

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Introduction

Since the end of 2019, an increasing cases of pneumonia were reported in Wuhan, followed by other cities and provinces in China as well as many other countries (Huang C et al. 2020). On 7 January 2020, a novel coronavirus (2019-nCoV) was initially isolated from a patient and then the complete genome was analyzed (Zhu et al. 2020). Later, this novel coronavirus was identified as the cause and named SARS-CoV-2 officially by the International Committee on Taxonomy of Viruses (ICTV). On January 30, 2020, WHO declared the coronavirus outbreak become a public-health emergency of international concern (PHEIC) (Ko et al. 2020). On February 11, 2020, WHO announced a name for this new coronavirus disease caused by SARS-CoV-2 infection: coronavirus disease 2019 (COVID-19) (Gorbalenya et al. 2020). Soon, the viruses have spread to many countries, including Asia, Europe, Americas, and Australia. On March 11, WHO characterized COVID-19 as a pandemic. As of September 2, 2020, 25,602,665 confirmed cases of COVID-19 have been reported globally and 852,758 people are dead due of COVID-19, with the estimated fatality rate of 3.33% (WHO 2020). This on-going COVID-19 pandemic has become the most serious threat to public health in recent times.

Given that large and increasing numbers of COVID-19 cases, the therapeutic options in response to the pandemic and effective interventions for severe cases are urgently needed. So far, there is no specific prescription drug available for its general use to alleviate the severity of COVID-19. SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA coronavirus belonging to the genus Betacoronavirus. As the genus also contains other similar high-pathogenic SARS-CoV and MERS-CoV (Chan et al. ...
2020), the experiences in the development of antiviral agents, network-based pharmacology research, antibody development and traditional Chinese medicine (Table 1).

Drug Repositioning

Given that the discovery and marketing of new compounds often require months to years, existing prescription drugs have matured synthetic processes, known safety and pharmacokinetic data, which greatly reduces costs and time (Guo 2020). Broad-spectrum antiviral drugs are the first choice for new use of old drugs. For example, SARS-CoV and SARS-CoV-2 share 96% RNA-dependent RNA polymerase (RdRp) sequence identity (Gao et al. 2020). Therefore, drugs targeting viral RdRp proteins of SARS-CoV are likely to be effective for SARS-CoV-2. In addition, human angiotensin-converting enzyme 2 (ACE2) inhibitors may also have an inhibitory effect on the virus because ACE2 is a cell surface receptor of both SARS-CoV and SARS-CoV-2. The inhibition of ACE2 can block virus invasion into cells (Gao et al. 2020).

Here, we summarize and discuss selected candidates with a focus on approved drugs or experimental agents that have already tested in clinical trials for other diseases, e.g., HIV, influenza, SARS and MERS. The potential to repurpose existing antiviral agents approved or in development for treating infections have been discussed.

Remdesivir

Remdesivir, targeting RNA-dependent RNA polymerase (RdRp), is a nucleotide analogue. It is a broad-spectrum antiviral drug developed by Gilead Science Inc. Remdesivir can be effectively metabolised to active nucleoside triphosphate in several human cell lines (Agostini et al. 2018). An in vitro study has demonstrated that nucleoside triphosphate works as an incorporation competitor with adenosine triphosphate, confuses viral RdRp, acts as a delayed RNA chain terminator against virus (Warren et al. 2016). It evades proofreading by viral exoribonuclease, and causes a decrease in viral RNA production (Agostini et al. 2018). In vitro tests, remdesivir has antiviral activity on various of viruses, including Ebola virus, coronavirus, hepatitis C virus, and HIV (Tchesnokov et al. 2019; Sheahan et al. 2020).

Recently, the antiviral activity of remdesivir was demonstrated at the stage after virus entry into Vero E6 cells, supporting its antiviral mechanism as a nucleotide analogue (Wang M et al. 2020). In February, 2020, the New England Journal of Medicine (NEJM) reported the first successful use of remdesivir to reverse the lung injury caused by COVID-19 (Holshue et al. 2020). Symptoms were significantly reduced the next day and oxygen saturation was 94% to 96%. Other symptoms except dry cough were eliminated and finally the patient was discharged from the hospital. Although this reported only one case, it brings great hope to the clinical cure of COVID-19 by remdesivir. The pharmacodynamics results of the remdesivir are as follows: EC50 = 0.77 μmol/L; CC50 > 100 μmol/L; selection index (SI) > 129.87; EC90 = 1.76 μmol/L. Cohen suggested in Science that the combination of remdesivir and monoclonal antibody is likely to be the ideal therapy for COVID-19 (Cohen 2020).

Two phase III trials were initiated in early February to evaluate intravenous remdesivir (200 mg on day 1 and 100 mg once daily for 9 days) in patients with COVID-19 (Wang M et al. 2020). Preliminary results indicate that patients who received remdesivir had a 31% faster time to recovery than those who received placebo (P < 0.001). Specifically, the median time to recovery was 11 days for patients treated with remdesivir compared with 15 days for those who received placebo. Results also suggested a survival benefit, with a mortality rate of 8.0% for the group receiving remdesivir versus 11.6% for the placebo group (P = 0.059). The result shows remdesivir was better than placebo from the perspective of the primary endpoint, time to recovery, a metric often used in influenza trials. Recovery in this study was defined as being well enough for hospital discharge or returning to normal activity level (NIH 2020). But this dose regimen of intravenous remdesivir did not provide significant clinical or antiviral effects in seriously ill patients with COVID-19. However, we could not exclude clinically meaningful differences and saw numerical reductions in some clinical parameters. Ongoing studies with larger sample sizes will continue to inform our understanding of the effect of remdesivir on COVID-19 (Wang YM et al. 2020).

Chloroquine/Hydroxychloroquine

Chloroquine was a front-line drug for the treatment and prophylaxis of malaria and is one of the most prescribed drugs worldwide (White et al. 2014). Yet the activity of the molecule is not limited to malaria and the control of inflammatory processes, as illustrated by its broad-spectrum activity against a range of bacterial, fungal and viral infections (Raoult et al. 1990, 1999; Boulos et al. 2004; Rolain et al. 2007). Studies have shown that
| Name                        | Original indication                                                                 | Target                                                                 | Clinical trials reported | Dose/administration                                                                 | Toxicities/side effects                                                                 |
|-----------------------------|--------------------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
| **Western medicine**        |                                                                                      |                                                                        |                          |                                                                                      |                                                                                        |
| Remdesivir                  | Ebola virus disease (Phase II); RNA-dependent RNA polymerase inhibitor                | Yes                                                                    | A 10-day course of remdesivir treatment, 200 mg intravenously on day 1, 100 mg for next 9 days | None noted (similar to placebo in severe COVID patients)                                |
| Chloroquine/Hydroxychloroquine | Malaria treatment Caps hemozoin to prevent biocrystallization of heme, PLpro inhibitor | Yes                                                                    | Chloroquine: 500 mg daily for 10 days HCQ: weight > 50 kg, 500 mg × 2/d for 7 days; weight < 50 kg, 500 mg × 2/d on days 1 ~ 2, 500 mg/d on days 3 ~ 7; | Hemolytic anemia, cardiomyopathy, neutropenia, GI disturbances, retinopathy, rash, QT prolongation |
| Lopinavir/ritonavir          | A fixed dose combination for HIV/AIDS treatment Lopinavir: protease inhibitor Ritonavir: protease inhibitor and inhibitor of CYP3A4 | Yes                                                                    | Oral, 400 mg/100 mg, twice daily | QT prolongation, CV events, dyslipidemia, liver injury, GI disturbances               |
| Arbidol                     | Influenza treatment Inhibits viral entry by interfering with clathrin-dependent trafficking | Yes                                                                    | 200 mg × 3/d for no more than 10 d | No significant differences between ARB-treated and control groups does not have dose-related adverse effects in the dose range 3–10 mg/kg mild hypertension, cytotoxicity and bone damage |
| Teicoplanin                 | A glycopeptide antibiotic to treat bacterial infection Inhibits viral entry by inhibiting the activity of cathepsin L | No                                                                    |                          |                                                                                      |                                                                                        |
| Glycyrrhizic Acid           | An extract of a traditional Chinese herb to treat coughs, colds and disturbed digestion Regulate immune function, can bind to ACE2 | Yes                                                                    | 250 mg standardized extract (25% Glycyrrhizic—62.5 mg) for 10 days |                                                                                      |                                                                                        |
| Darunavir                   | A fixed dose combination for HIV/AIDS treatment 3CL protease inhibitor, substrate of CYP3A4 | Yes                                                                    | 800 mg/days              | Liver injury, dyslipidemia, sulfonamide allergy                                       |
| Forsythina and Chlorogenic acid | Extract of a traditional Chinese herb to treat influenza ACE2 inhibitor | No                                                                    |                          |                                                                                      |                                                                                        |
| Tocilizumab                 | Commonly used for rheumatoid arthritis (RA) and cytokine-release syndrome induced by chimeric antigen receptor-T cell therapy FCG3RA, IL6R, CD69,GALNT18 | Yes                                                                    | 4–8 mg/kg body weight     | Thrombocytopenia, liver injury, neutropenia, rash, hypertension, infection            |
| Interferon beta-1b          | Pharmacogenomics determinants are not well-delineated for IFN-β1b                     | Yes                                                                    | 8 million IU (0.25 mg) on alternate days | Liver injury, depression, heart failure, leukopenia, and flu-like symptoms, etc.     |
chloroquine has inhibitory activity on SARS-CoV and MERS-CoV infection in vitro (Vincent et al. 2005; Savarino et al. 2006; Dyall et al. 2014).

Researchers tested the pharmacodynamics of chloroquine against SARS-CoV-2 in vitro, and the results showed that EC50 = 1.13 μmol/L; EC90 = 6.90 μmol/L (Wang M et al. 2020). Due to its tolerability, rare toxicity reports, inexpensive cost and immunomodulatory properties (Savarino et al. 2003), chloroquine is currently among the best available candidates to impact the severity of SARS-CoV-2 infections in humans. Chloroquine phosphate has also been recommended in “Guideline on diagnosis and treatment of COVID-19 (Trial 7th edition)” (National Health Commission of the People’s Republic of China 2020b; in Chinese). Currently, at least ten clinical trials are testing chloroquine as an anti-COVID-19 therapy (Harrison 2020). However, the study by Boulware et al. reporting a randomized trial testing hydroxychloroquine as postexposure prophylaxis for COVID-19 showed that hydroxychloroquine failed to show efficacy for COVID-19 prophylaxis (Boulware et al. 2020). The recent study published in Lancet reported a multinational, observational, real-world study of patients with COVID-19 requiring hospitalization, and found that the use of a regimen containing hydroxychloroquine or chloroquine (with or without a macrolide) was associated with no evidence of benefit, but instead was associated with an increase in the risk of ventricular arrhythmias and a greater hazard for in-hospital death with COVID-19 (Mehra et al. 2020). However, on 4 June 2020, the Lancet published an update that the study authors retracted the study for publication due to lack of access to the databases needed for the investigation. The major doubts of the Lancet’s retracted paper included: (1) The study was not a strict randomized double-blind

Table 1 (continued)

| Name                          | Original indication                                                                 | Target                                                                 | Clinical trials reported | Dose/administration                              | Toxicities/side effects                                      |
|-------------------------------|------------------------------------------------------------------------------------|----------------------------------------------------------------------|--------------------------|--------------------------------------------------|-------------------------------------------------------------|
| Dexamethasone                 | First-line treatment for immune-related complications                              | Suppresses the immune system by inhibiting naive T cell proliferation and differentiation | Yes                      | 6 mg once daily for 10 days                     | Mild increase of blood glucose level, ocular hypertension, and cataract, mood and behavior change, osteoporosis |
| Qingfei Paidu Decoction       | A traditional Chinese medicine for treating exogenous fever caused by cold evil    | The network pharmacology analysis showed that QPD has an overall regulatory effect via multi-component and multi-target | Yes                      |                                                  |                                                             |
| Qingfei dayuan granules & Chaihu daxiong mixture | For COVID-19 patients with severe cough, sputum, and wheezing                      | Eliminate inflammation, improve immunity                             | No                       |                                                  |                                                             |
| Huashi Baidu Granules         | First approval drug of traditional Chinese medicine for the clinical treatment of COVID-19 | Inhibits the SARS-CoV-2 replication, affects virus morphology and exerts anti-inflammatory activity in vitro | Yes                      | 4 capsules, 3 times a day, after meal           | No toxic side effects in mice                               |
| Lianhuaqingwen                | As traditional Chinese medicine formula to treat influenza                         |                                                                      | Yes                      |                                                  |                                                             |

The information is retrieved from the Chinese Clinical Trial Registry (http://www.chictr.org.cn/index.aspx) and Clinicaltrials.gov as of May 27th, 2020.
control; (2) The study did not indicate the patient’s health status before the trial; (3) The daily dosage of hydroxychloroquine exceeded the standard of 600 mg (U.S. official recommended dosage is less than 500 mg); (4) The data from Australian medical institutions is inaccurate; (5) The original data lacks transparency.

On May 28, 2020, Dr. Nanshan Zhong’s research team published a clinical study of multi-center chloroquine treatment of COVID-19 in *National Science Review*. They found that after 500 mg chloroquine oral administration twice a day (full dose), COVID-19 patients can clear the virus faster, allowing patients to recover body temperature more quickly; and the adverse events occurred were not different from the control group, and no serious adverse events occurred. 500 mg chloroquine once a day (half dose) is also effective, and the adverse events are 40% lower than the full dose group. Therefore, the researchers believed that chloroquine is effective in treating patients with COVID-19 (Huang M et al. 2020). On June 3, 2020, WHO Director-General Dr. Tedros said at a press conference that the WHO “Solidarity clinical trial” executive team agreed to continue the trial of hydroxychloroquine against COVID-19.

These different findings suggest that the drug regimens should be used with caution and urgent confirmation of anti-COVID-19 efficacy by randomized clinical trials in different age groups is needed.

**Lopinavir/Ritonavir and Interferons**

A report suggested that the anti-HIV drugs ritonavir and lopinavir may have a therapeutic effect on SARS-CoV-2. A member of the expert group of the National Health Commission, Dr. Guangfa Wang, who visited Wuhan and was infected by SARS-CoV-2, has recovered and discharged with the ritonavir/lopinavir therapy. The therapeutic effect may be due to their inhibitory effect on coronavirus endopeptidase C30 (Lin et al. 2020). Lopinavir and ritonavir were initially hypothesized to inhibit the 3-chymotrypsin-like protease of SARS and MERS, and appeared to be associated with improved clinical outcomes of patients with SARS in a non-randomized open-label trial (Zumla et al. 2016).

Lopinavir/ritonavir was subsequently recommended in the “Guideline on diagnosis and treatment of COVID-19 (Trial 7th edition)” issued by National Health Commission of China (2020b; in Chinese), and was also the first anti-HIV drugs to be recommended. In a multicentre randomised open-label phase II trial in patients with COVID-19 showed that early treatment with the triple combination of antiviral therapy with interferon beta-1b, lopinavir-ritonavir, and ribavirin is safe and highly effective in shortening the duration of virus shedding, decreasing cytokine responses, alleviating symptoms, and facilitating the discharge of patients with mild to moderate COVID-19. Furthermore, the triple antiviral therapy rapidly rendered viral load negative in all specimens, thereby reducing infectiousness of the patient (Hung et al. 2020).

**Arbidol**

Arbidol is a broad-spectrum antiviral drug mainly used for respiratory diseases caused by influenza A and B viruses (Boriskin et al. 2008). Regarding coronaviruses, the potential therapeutic benefits of arbidol were firstly reported in 2008, when the concentration of arbidol was 50 μmol/L, it had a significant inhibitory effect on SARS-CoV infection *in vitro* (Khamitov et al. 2008). Recent research showed that arbidol can significantly inhibit SARS-CoV-2 infection at 10 ~ 30 μmol/L (Zhang C et al. 2020). Further verification of the anti SARS-CoV-2 efficacy *in vivo* is in need.

**Teicoplanin**

Teicoplanin, a glycopeptide antibiotic which has routinely been used in the clinic to treat bacterial infection with low toxicity, significantly inhibits the invasion of cells by Ebola virus, SARS-CoV and MERS-CoV, via specifically inhibiting the activity of cathepsin L (Zhou et al. 2016). A study tested the efficacy of teicoplanin against SARS-CoV-2 infection and found that teicoplanin potently prevented the entrance of SARS-CoV-2-Spike-pseudoviruses into the cytoplasm, with an IC₅₀ of 1.66 μmol/L (Zhang J et al. 2020). Although the inhibitory effect upon the replication of wildtype viruses *ex vivo* and *in vivo* remains to be determined, preliminary results indicated that the potential antiviral activity of teicoplanin could be applied for the treatment of SARS-CoV-2 infection.

**Glycyrrhizic Acid**

Glycyrrhizic Acid is an extract of liquorice roots. Liquorice, *Glycyrrhiza glabra*, has long been employed against coughs and colds as well as to settle disturbed digestion. The diammonium glycyrrhizinate has anti-inflammatory activity and is used to treat liver damage caused by hepatitis B (Redeploying plant defences 2020). Glycyrrhizin has been used as an effective drug for the treatment of SARS, it can regulate immune function and exert antiviral effect, and it has a clear anti-inflammatory mechanism (Hoever et al. 2005). ACE2 is the cell surface receptor of the SARS-CoV and SARS-CoV-2. Recent studies have shown that Glycyrrhizic Acid can bind to ACE2 and thus has potential resistance to SARS-CoV-2 (Chai et al. 2020). Glycyrrhizin is the main
active ingredient in licorice. Among the traditional Chinese medicine prescriptions used to treat COVID-19 in this epidemic, licorice is the most frequently used in all prevention and treatment programs, accounting for 6.7% (Wang YF et al. 2020).

**Bismuth Salts**

A study imply that the gastrointestinal tract is also the target of SARS-CoV-2 and the risk of further dissemination of this virus to healthy population through fecal–oral route cannot be omitted (Shu et al. 2020). Since bismuth potassium citrate (BPC) and ranitidine bismuth citrate (RBC) are already used to treat disorders in gastrointestinal tract, they may have the potential to be further developed for the prevention and treatment of COVID-19 (Shu et al. 2020). Future study should evaluate the inhibitory effect of BPC or RBC on SARS-CoV-2 replication in cells and in vivo.

**Clofazimine**

In an artificial intelligence approach fighting COVID-19 with repurposing drugs, AI system identified 80 marketed drugs with potential. Among them, 8 drugs (bedaquiline, brequina, celecoxib, clofazimine, convivaptan, gemcitabine, tolcapone, and vismodegib) showed in vitro activities against the proliferation of a feline infectious peritonitis (FIP) virus in Fcwf-4 cells (Ke et al. 2020). The infection by FIP virus in cats presented similar features to the SARS infection such as pulmonary lesions in humans (Paltrinieri 2004). Clofazimine is an old hydrophobic riminophenazine, has a wide range of antimycobacterial activity ranging from leprosy to nontuberculous mycobacterial diseases (Riccardi et al. 2020). Taking the advantages of low price and long half-life and high drug concentration in the lungs, clofazimine with minimum adverse effects might be potential for treating COVID-19 (Ke et al. 2020).

**Network-Based Pharmacology Research**

Drug repurposing, represented as an effective drug discovery strategy from existing drugs, could significantly shorten the time and reduce the cost compared to de novo drug discovery and randomized clinical trials. However, experimental approaches for drug repurposing is costly and time-consuming. Computational approaches offer novel testable hypotheses for systematic drug repositioning before in vitro and in vivo verification (Zhou Y et al. 2020).

Network pharmacology is a research strategy for multi-target and multi-channel interactions of drugs. Starting from the integrity and systematicness of interactions between drug targets and diseases, it uses computer methods to model multi-target activities on the basis of multi-level networks of diseases, genes and drugs. At the same time, it studies the biological basis of drugs acting on the body, which is a powerful tool for medicine research (Yu et al. 2020).

Molecular docking is a computational tool for predicting the binding ability and binding mode of proteins and ligands (Ou et al. 2020). It is based on the “lock key model” of the interaction between proteins and small ligands, calculating and predicting the conformation and orientation of ligands at protein active sites, so as to judge the binding degree. It plays an important role in the target prediction of drug organisms (Duan et al. 2019).

Similar to SARS and MERS, SARS-COV-2 genome encodes non-structural proteins (such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase), structural proteins (such as spike glycoprotein) and accessory proteins. The four non-structural proteins are key enzymes in the viral life cycle, and the spike glycoprotein is indispensable for virus–cell receptor interactions during viral entry. These five proteins were therefore recognized as attractive targets to develop antiviral agents (Zumla et al. 2016; Li and De Clercq 2020).

**3CLpro Inhibitor**

3CLpro is a cysteine protease responsible for the proteolysis of replicase polyproteins resulting in the formation of various functional proteins. Six approved anti-HIV-1 drugs were chosen to investigate their binding interactions with 3CLpro, and to evaluate their potential to become clinical drugs for SARS-CoV-2 infection. The results show that darunavir has the best binding affinity with SARS-CoV-2 3CLpro among all inhibitors, indicating it has the potential to become an anti-COVID-19 clinical drug (Sang et al. 2020).

Another computational analysis screened SARS-CoV-2 3CLpro compounds against an in-house library of 123 antiviral drugs. The results proposed that raltegravir, paritaprevir, bictegravir and Dolutegravir are excellent lead candidates for 3CLpro and they could become potential therapeutic drugs against SARS-CoV-2 (Rameez Jabeer et al. 2020).

**PLpro Inhibitor**

A study screened the FDA approved drugs targeting the papain-like protease (PLpro) in silico. In the docking studies, the homology model of the protease was built based on the SARS-CoV PLpro structure, and sixteen FDA approved drugs, including chloroquine and formoterol, was
found to bind the target enzyme with significant affinity and good geometry, suggesting their potential to be utilized against the virus (Rimanshee et al. 2020). This also indicated that chloroquine may act as papain-like protease inhibitor.

**ACE2 Inhibitor**

Tennessee University used the world’s most powerful supercomputer to conduct a virtual high-throughput screening of the ensemble docking. 77 ligands were calculated to bind strongly to either the S-protein: ACE2 interface-ligand binding complex or the binding-interface of the isolated S-protein, of which 24 had regulatory approval from the FDA or similar agencies. The identified small-molecules may be repurposed to limit viral recognition of host cells or disrupt host-virus interactions (Smith M and Smith JC 2020). Another study using molecule docking showed that Mongolian medicine active ingredients forsythin and chlorogenic acid can be effectively combined with ACE2 and may be a potential candidate drug (Yu et al. 2020).

**TMPRSS2 Inhibitor**

Host cell entry of SARS-CoV-2 depends on the SARS-CoV receptor ACE2 and can be blocked by a clinically proven inhibitor of the cellular serine protease TMPRSS2, which is employed by SARS-CoV-2 for S protein priming (Hoffmann et al. 2020). The finding highlights TMPRSS2 as a host cell factor that is critical for spread of several clinically relevant viruses, including influenza A viruses and coronaviruses. A serine protease inhibitor camostat mesylate, which blocks TMPRSS2 activity, has been approved in Japan for pancreatitis (Uno 2020). This compound or related ones with potentially increased antiviral activity could thus be considered for off-label treatment of SARS-CoV-2-infected patients.

**RdRp Inhibitor**

The viral RdRp is a promising target with polymerase inhibitors successfully used for the treatment of several viral diseases. A promising class of RdRp inhibitors are nucleoside analogues (NAs), small molecule drugs that are metabolized intracellularly into their active ribonucleotide 5′-triphosphate (RTP) forms and incorporated into the nascent viral RNA by error-prone viral RdRps. Several NAs currently being used for the treatment of other viral infections have been identified as potential anti-Cov candidates (Pruijssers and Denison 2019). Among these is the purine base analogue favipiravir that has broad spectrum activity against a number of RNA viruses and is currently licensed in Japan for use in the treatment of influenza virus (Du and Chen 2020). A recent study showed that favipiravir exerted an antiviral effect as a nucleotide analogue through a combination of chain termination, slowed RNA synthesis and lethal mutagenesis (Shannon et al. 2020). Clinical trials are currently ongoing in China, Italy, and the UK for the treatment of COVID-19 (Shannon et al. 2020).

**Antibody Drugs**

Antibody drugs have the advantages of high specificity, good safety, and long half-life in serum. It has shown good application prospects in the field of antivirals. Several candidate monoclonal antibody drugs are currently in the preclinical or clinical development stage for the treatment of chronic viral infections (AIDS) and acute viral infections (Ebola hemorrhagic fever) (Qiu et al. 2014; Caskey et al. 2015).

The analysis of the antigenic similarity of S protein between the SARS-CoV-2 and SARS-CoV by computer algorithms showed that both proteins had a cross-protected epitope (Qiu et al. 2020). Neutralizing antibodies targeting this cross-protected epitope may become broad-spectrum antiviral drugs for SARS-CoV-2 and SARS-CoV. SARS-CoV S protein mouse polyclonal serum can effectively inhibit the entry of SARS-CoV-2 virus into target cells (Zhou et al. 2020) and the mouse polyclonal antibodies can effectively inhibit SARS-CoV-2 S protein-mediated cell entry (Walls et al. 2020). Furthermore, German scientists have found that serum from SARS-infected patients during recovery can prevent SARS-CoV-2 from infecting cells (Hoffmann et al. 2020). This indicates that there is indeed a cross-protected epitope between SARS-CoV and SARS-CoV-2, and the antibodies previously developed to treat SARS do have the potential to treat COVID-19.

Recent study has identified a SARS-CoV specific human monoclonal antibody CR3022, which could effectively bind to the receptor binding domain (RBD) of SARS-CoV-2 spike protein (Tian et al. 2020). Therefore, CR3022 has the potential to be developed as candidate therapeutic antibodies for SARS-CoV-2 infection.

There are 16 related drugs in the field of human coronavirus antibodies worldwide, mainly located in the United States (10) and China (3) (Li D et al. 2020). U.S. agencies have deployed related antibody and drug research in the fields of SARS-CoV and MERS-CoV. Among them, SAB-301, an anti-MERS immunotherapy candidate drug developed by SAB Biotherapeutics, has entered the phase II clinical trial in 2019; The REGN-3048, REGN-3051, and REGN-3048-3051, which were developed by Regeneron Pharmaceuticals, are all candidates for anti-MERS immunotherapy, and entered the phase I clinical trial in
2018. Drug development in Chinese institutions primarily targeted at SARS-CoV and is still in the discovery/explo-ration stage. Related products include hyperimmune glob-ulins (Shenchen Weiguang Biological Products Co., Ltd.), immune globulin (Beijing Tiantan Biological Products Co., Ltd.) and human SARS immunoglobulin (Wuhan Biological Products Research Institute Co., Ltd.) (Li D et al. 2020).

In addition to artificial polyclonal or monoclonal anti-bodies, specific antibodies can also be obtained by direct infusion of plasma from COVID-19 patients during recovery. This method has achieved well effects in the treatment of SARS and highly pathogenic influenza viruses (Cheng et al. 2005; Zhou et al. 2007; Hung et al. 2011). But the resource of plasma during the recovery is limited, and the level of neutralizing antibody titer in the extracted plasma cannot be guaranteed, so its clinical application is also limited.

Recent study reports the isolation of two specific human monoclonal antibodies (MAbs) CA1 and CB6 from a convalescent COVID-19 patient. The study demonstrated CA1 and CB6 have potent SARS-CoV-2-specific neutralization activity in vitro against SARS-CoV-2. In addition, CB6 inhibited SARS-CoV-2 infection in rhesus monkeys at both prophylactic and treatment settings. Further structural studies revealed that CB6 recognizes an epitope that overlaps with angiotensin converting enzyme 2 (ACE2)-binding sites in SARS-CoV-2 receptor binding domain (RBD), thereby interfering with the virus/receptor inter-actions by both steric hindrance and direct interface-residue competition (Shi et al. 2020). The results suggest CB6 deserves further clinical translation.

Researchers at Utrecht University, Erasmus Medical Center and Harbour BioMed (HBM) reported that they have identified a fully human monoclonal antibody that prevents the SARS-CoV-2 virus from infecting cultured cells. The discovery, published in Nature Communications, is an initial step towards developing a fully human anti-body to treat or prevent the respiratory disease COVID-19 caused by the novel coronavirus SARS-CoV-2. The 47D11 antibody was found to potently inhibit infection of Vero E6 cells with SARS-S and SARS2-S pseudotyped VSV with IC50 values of 0.061 and 0.061 μg/mL, respectively (Wang and Li 2020). This discovery provides a strong foundation for additional research to characterize this antibody and begin development as a potential COVID-19 treatment. Conventional therapeutic antibodies are first developed in other species and then must undergo additional work to ‘humanize’ them. The antibody was generated using Harbour BioMed’s H2L2 transgenic mouse technology, which is “fully human source”, allowing development to proceed more rapidly and reducing the potential for immune-related side effects.

The use of intravenous immunoglobulin to block FcR activation may be a viable option for the urgent treatment of pulmonary inflammation to prevent severe lung injury. Such treatment may also be combined with systemic anti-inflammator drugs or corticosteroids (Fu Y et al. 2020).

In patients with COVID-19, a large number of T lymphocytes and mononuclear macrophages are activated, producing cytokines such as interleukin-6 (IL-6), which bind to the IL-6 receptor on the target cells, causing the cytokine storm and severe inflammatory responses in lungs and other tissues and organs (Xu and Han 2020). Tocilizumab, as a recombinant humanized anti-human IL-6 receptor monoclonal antibody, can bind to the IL-6 receptor with high affinity, thus preventing IL-6 itself from binding to its receptor, rendering it incapable of immune damage to target cells, and alleviating the inflammatory responses (Xu and Han 2020).

In March 2020, a retrospective evaluation of the COVID-19 clinical experience in China reported that, in the subset of patients who progressed to acute respiratory distress syndrome (ARDS), objectively sicker patients who received methylprednisolone had lower mortality rates than patients not receiving methylprednisolone (Wu et al. 2020). On 16 June, investigators on the COVID-19 RECOVERY trial revealed in a press release that participants with severe COVID-19 (2104) given 6 mg dexamethasone once daily had an 8%–26% lower mortality than the subset of patients who progressed to acute respiratory distress syndrome (ARDS), objectively sicker patients who received methylprednisolone (Wu et al. 2020). On 16 June, investigators on the COVID-19 RECOVERY trial revealed in a press release that participants with severe COVID-19 (2104) given 6 mg dexamethasone once daily had an 8%–26% lower mortality than 4321 participants given standard care. The findings support use of dexamethasone only for patients with hypoxaemia, not those with milder disease (Mahase 2020). Regarding potential side effects, the harm that has been noted in the past with steroids have been related to high doses. The known side effect profile of these drugs at high doses is well known. What was critical is getting the dose right with the right patients. The doses should be either a low or moderate dose, minimising the side effects while max-imising the benefits. Despite concerns about the possibility of sterio associated complications, it would not be rea-sable to delay use of a widely available treatment with a demonstrated mortality benefit.

**Traditional Chinese Medicine**

Traditional Chinese medicine (TCM), which mainly treat disease based on syndrome differentiation, has a long his-tory in China and other Asian countries and plays an indispensible role in the prevention and treatment of severe epidemic diseases. During the SARS epidemic in 2003, the intervention of TCM has achieved remarkable therapeutic effect. A number of clinical practice results showed that traditional Chinese medicine plays significant role in the
treatment of COVID-19, bringing new hope for the prevention and control of COVID-19 (Ren et al. 2020).

Qingfei Paidu Decoction

Qingfei Paidu Decoction (QPD) is an optimized combination of several classic recipes for treating exogenous fever caused by cold in Zhang Zhongjing’s Treatise on Febrile and Miscellaneous Diseases in the Han Dynasty. QPD has been promoted as a general prescription in the diagnosis and treatment plan of COVID-19 in the 7th Version of Diagnosis and Treatment Protocol for COVID-19 in China (National Health Commission of the People’s Republic of China 2020b). It was used to treat COVID-19 patients with mild, moderate and severe cases, and was also used reasonably with the consideration of the actual conditions of critically ill patients (National Health Commission of the People’s Republic of China 2020a).

The network pharmacology analysis showed that QPD has an overall regulatory effect via multi-component and multi-target. The primary site of pharmacological action is the lung, as 16 herbs to lung meridian, which indicated that the decoction is mainly specific for lung diseases (Zhao et al. 2020). Through comprehensive analysis by liquid chromatography coupled with high resolution mass spectrometry (MS), a total of 129 compounds of QPD were putatively identified. Through constructing molecular networking of mass spectrometry data, 14 main clusters compounds were classified, in which exhibited specific patterns of flavonoids (45%), glycosides (15%), carboxylic acids (10%), and saponins (5%) (Yang et al. 2020). Among the 701 confirmed cases treated by QPD, 130 cases were cured and discharged, clinical symptoms of 51 cases disappeared, 268 cases of symptoms improved, and 212 cases with stable symptoms without aggravation (Ren et al. 2020). Although the effective cure rate of QPD against COVID-19 is over 90%, as indicated by the authors, the control group without QPD treatment is absent and more data are needed to validate the high efficiency.

Toujie Quwen Granules

The prescription is developed by Tan Xinghua, a doctor of Guangzhou Eighth People’s Hospital, based on his more than ten years of experience in clinical treatment of pneumonia, and adjusted according to the characteristics of COVID-19. The main ingredients include forsythia, honeysuckle, scutellaria, fritillaria, bupleurum, Artemisia annua, tangerine peel, poria, cardamom, etc. (Fu X et al. 2020). A statistical analysis of 121 patients was carried out, among whom the body temperature of 72 patients before taking the drug exceeded 37.3 °C, and 108 cases of cough, and 108 cases of chest CT had inflammation and exudation. Six days after taking the drug, 84.72% (61 cases) patients’ temperature returned to normal, 66.67% (72 cases) patients’ cough symptoms disappeared, and other symptoms such as fatigue, anorexia, sore throat, etc. also had obvious curative effects. 74.07% (80 cases) patients had chest CT improved significantly. The results of the study suggest that the overall clinical symptoms of the patients have improved significantly, with a total effective rate of 94.21%, while the total effective rate of the western medicine control group was 69.7% (Fu X et al. 2020).

The treatment mechanism of this prescription is speculated as follows. First, it can quickly improve clinical symptoms and quickly reduce fever. Second, it enhances the physical resistance. Third, it inhibits the release of inflammatory factors and reduces lung inflammation. The fourth, it adjusts the intestinal flora balance and keeps the stool flowing. However, this prescription is used only for mild and general pneumonia caused by SARS-CoV-2 infections, and there is no enough evidence to prove that it has a positive effect on severe patients. In addition, the drug is not suitable for prophylactic usage and should be taken under the guidance of doctor (State Council Information Office of the People’s Republic of China 2020).

Qingfei Dayuan Granules and Chaihu Daxiong Mixture

A prescription bupleurum chest bind decoction, named “Pneumonia 1” (later renamed Qingfei Dayuan Granules), was recommended by a traditional Chinese medicine doctor, Guoqiang Mei. Afterwards, another prescription “Potent Pneumonia 1” (later renamed Chaihu Daxiong Mixture) was recommended to patients with severe cough, sputum, and wheezing (Zhou S et al. 2020).

Hubei Provincial Hospital of Traditional Chinese Medicine treated 517 COVID-19 patients with combined western and Chinese medicine schemes such as “Pneumonia 1” and “Potent Pneumonia 1”. 158 patients have been cured and discharged. Most of the patients have adopted the symptoms improved, the total clinical effective rate of integrated traditional Chinese and western medicine was more than 90%, as declared by the hospital. On 23 February, Qingfei Dayuan Granules and Chaihu Daxiong Mixture were approved by the Hubei Provincial Drug Administration for prevention and treatment of COVID-19 (Hubei Daily 2020).

Molecular docking showed that the compounds with good binding power to SARS-CoV-2-RBD-ACE2 complex in Qingfei Dayuan granules were mainly come from Bupleuri Radix, Codonopsis Radix, Anemarrhenae Rhizoma, and Glycyrrhizae Radix et Rhizoma. Saikosaponin, glycyrrhizic acid, anemarsaponin had good binding power with SARS-CoV-2-S-RBD-ACE2, which may be potential
active components against SARS-CoV-2. Conclusion Qingfei Dayuan Granules has the characteristics of multi-components, multi-targets and multi-pathway regulation. Saikosaponin, glycyrrhizic acid, and anemarsaponin may be the potential active components against SARS-CoV-2. The mechanisms of its treatment against COVID-19 may be related to the regulation of the co-expressed genes with ACE2, inhibition of inflammation and immune related signaling pathways, and the destruction of the complex structure of SARS-CoV-2-S-RBD-ACE2 (Zhou S et al. 2020). Network pharmacology approach revealed that the main active ingredients of Chaihu Daxiong Mixture were \(\beta\)-sitosterol and 11 flavonoids. The core targets were CASP3, MAPK3, IL-6, MAPK8, IL-10, CXCL8, MAPK1 and IL-1B (Xiao et al. 2020).

Huashi Baidu Granules

Huashi Baidu Granules is based on actual experience of COVID-19 treatment in Jinyintan Hospital. Its functions may include eliminating inflammation and improving immunity, and may play an active role in the treatment of COVID-19 patients. Huashi Baidu Granules is the first approval drug of traditional Chinese medicine for the clinical treatment of COVID-19 (Chen et al. 2020).

Based on the efficacy of Huashi Baidu Recipe on 75 severe COVID-19 patients, significant improvement in symptoms and nucleic acid conversion to negative was reported. 452 cases of randomized control were performed in the cabin hospital, and the effect was also found. In an animal infection model, this recipe reduced the viral load of SARS-CoV-2 in the lungs by 30%. The significant effects on the improvement of lung inflammation was also reported (China 2020-03-23). It is predicted that the main core compounds are quercetin, luteolin, kaempferol, begonin, naringenin, \(\beta\)-sitosterol, baicalein, etc., which play a key role in the entire network. The results of molecular docking showed that quercetin, luteolin, kaempferol had a good combination with 3CL hydrolase and ACE2 (Lai et al. 2020).

Lianhuaqingwen

Lianhuaqingwen (LH), a Chinese patent medicine composed of 13 herbs, has been used to treat influenza and exerted broad-spectrum antiviral effects on a series of influenza viruses and immune regulatory effects (Ding et al. 2017). It could significantly inhibit SARS-CoV-2 replication, alter the viral morphology and reduce the cytokine release from host cells, conferring anti-inflammatory activity in vitro (Li R et al. 2020). A retrospective analysis of clinical records was conducted in the SARS-CoV-2 infected patients at Wuhan Ninth Hospital and CR & WISCO General Hospital, LH combination could significantly relieve cardinal symptoms and reduce the course of the COVID-19 (Cheng and Li 2020). Therefore, LH has been included in the Guideline for the Diagnosis and Treatment of COVID-19 (Trial 7th Edition) (National Health Commission of the People’s Republic of China 2020b) and also recommended by 20 provincial health commissions including Hubei, Beijing, and Shanghai as well as National Administration of Traditional Chinese Medicine for the treatment of COVID-19. A prospective multicenter open-label randomized controlled trial on LH capsule in 283 confirmed cases with COVID-19 was conducted from February 2nd through February 15th, 2020 (Hu et al. 2020). The recovery rate was significantly higher in treatment group as compared with control group. The rate of improvement in chest computed tomographic manifestations and clinical cure was also higher in treatment group. However, both groups did not differ in the rate of conversion to severe cases or viral assay findings (Hu et al. 2020).

Recent clinical research reveals that LH capsules confer therapeutic effects on COVID-19 by improving the recovery rate of symptoms, shortening the time to symptom recovery, and improving the recovery of chest radiologic abnormalities (Hu et al. 2020). In light of the efficacy and safety profiles, LH capsules could be considered for the treatment of COVID-19. Future double-blind, prospective, randomized controlled trials are needed to fully evaluate the efficacy of LH capsules in a larger patient population.

Perspective

Although the genomic sequences and cryo-electron microscopy structure of SARS-CoV-2 have been obtained (Zhu et al. 2020), and the transmission routes are understood, the virus has the special characteristics of long incubation period, strong infectivity and quick conversion of severe disease, which have brought great difficulties to the prevention and control of COVID-19. Because of no specific drugs and vaccines have been available for the time being, more powerful treatment plan should be explored.

According to the existing research data, a batch of anti-SARS-CoV/MERS-CoV/HIV clinical drugs have potential anti-SARS-CoV-2 activities, which brings hope for the treatment of COVID-19. Some drugs have been approved by clinical trials or already listed. The strategy of repurposing of existing drugs for the clinical management of COVID-19 plays an important role in the current fight against SARS-CoV-2. Most of the clinical effects of these potential anti-SARS-CoV-2 drugs have yet to be verified. Prediction and screening of possible drugs according to the
structure of the virus is a fast and efficient screening method. Although some chemical drugs have been tested in vitro and have obtained anti-SARS-CoV-2 effects, how is the antiviral activity in vivo remains to be confirmed. At the same time, it should give full play to the advantages of Traditional Chinese Medicine in syndrome differentiation, the whole therapeutic effect, as well as the complication and fatality rate reduction.

In conclusion, although the repurposing existing antiviral agents, network-based pharmacology research, antibody drugs and Traditional Chinese Medicine have showed obvious anti-SARS-CoV-2 efficacy in vitro and in vivo, clinical trials are indispensable to determine the safety and efficacy of all these antivirals in a large patient population with COVID-19. A lot of them have been on the way and clinical application prospect is expected (Table 1).

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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