



Advances in the treatment of novel coronavirus disease (COVID-19) with Western medicine and traditional Chinese medicine: a narrative review

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Abstract: In December 2019, the coronavirus disease 2019 (COVID-19) caused by the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was discovered. Since its emergence, COVID-19 has been outbreaking rapidly worldwide, where the virus has so far caused the death of hundreds of thousands and infected more than a million, what has been called a pandemic by the World Health Organization (WHO). According to the WHO-Coronavirus disease 2019 Situation Report-142, by June 10, 2020, there are 7,145,539 confirmed cases and 408,025 deaths. There is an urgent need to develop a suitable specific medicine against this novel coronavirus; therefore, scientists and researchers around the world are making great efforts endeavoring to discover an efficient specific medication for COVID-19 treatment. Given the similarity of the novel coronavirus with previous epidemic viruses, namely, the acute respiratory syndrome coronavirus (SARS-CoV) and the Middle East respiratory syndrome coronavirus (MERS-CoV), previously tested drugs could potentially work against the novel coronavirus. In this narrative review, we aim to summarize and discuss the effectiveness of current Western medicine and traditional Chinese medicine options for COVID-19 treatment based on the overview of the scientific literature. Some Western medicines including remdesivir, chloroquine, hydroxychloroquine, favipiravir, lopinavir/ritonavir, and arbidol, as well as some traditional Chinese medicine (TCM) such as Qingfei Paidu decoction, Yupingfeng, Lianhua Qingwen, and TCM injections have revealed a relative activity against SARS-CoV-2 *in vitro*, in observational studies, and in clinical trials. However, further extensive studies and clinical trials including double-blind and randomized clinical trials, with a higher number of patients, are necessary to confirm the activity of these medicines. There are several ongoing trials conducted on the drugs of COVID-19, and the results are urgently needed to make a suitable treatment recommendation.

Keywords: Coronavirus disease 2019 (COVID-19); coronavirus; treatment; traditional Chinese medicine (TCM)

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Coronaviruses (CoVs) are large, enveloped, positive-stranded RNA viruses of zoonotic origin that belong to the Coronaviridae family of the Nidovirales order, and can be divided into four types: α , β , δ , and γ CoVs (1,2). α

and β CoVs chiefly infect mammals, while δ and γ CoVs predominantly infect birds (3). Human CoVs include α -CoVs, β -CoVs, MERS-CoV, SARS-CoV, and 2019 novel coronavirus (1,3). SARS-CoV, MERS-CoV, and SARS-

CoV-2 are β -coronaviruses that infect the respiratory tract and cause pneumonia in humans (4).

SARS-CoV-2 is found responsible for the COVID-19 disease, which has rapidly spread around the world. The rapid growth in the number of patients caused widespread panic and commotion among the population. Furthermore, the rapid growth in the number of patients caused widespread panic and commotion among the population. Individuals of any age are predisposed to SARS-CoV-2, particularly the elderly and those with underlying chronic diseases (heart disease, diabetes, or lung disease) that are easy to become severe cases (5). By January 30, 2020, the WHO declared the epidemic to be a public health emergency of international alarm in the second meeting of the Emergency Committee (6). It was recommended that the corresponding vaccine and specific antiviral drug should be obtained as soon as possible (6). Nevertheless, the development of these drugs will take months or even years. The situation of COVID-19 is progressing quickly, with the cases count currently growing into the hundreds of thousands, what has been called a pandemic by the WHO (7). By June 10, 2020, based on the WHO-COVID-19 Situation Report, more than seven million are confirmed cases and more than four hundred thousand are deaths (8).

The sequencing of the entire genome of SARS-CoV-2 was discovered and discharged to open databases, exhibiting rapid data sharing during the outbreak response. Initial analyses revealed that SARS-CoV-2 has some amino acid similarity to SARS-CoV and can utilize the angiotensin-converting enzyme 2 (ACE2) as a receptor (2). This has huge ramifications for foreseeing pandemic possible pushing forward (2). Most Coronaviruses share comparable viral structure, comparable infection pathway, and a similar S protein structure, which suggests that research strategies already developed for other coronaviruses ought to be appropriate for the COVID-19 (9).

Like SARS and MERS, the SARS-CoV-2 genome encodes non-structural proteins, structural proteins, and accessory proteins. The non-structural proteins include RNA-dependent RNA polymerase (RdRp), papain-like protease, 3-chymotrypsin-like protease, and helicase, which are key enzymes in the life cycle of viruses. In contrast, structural proteins include the spike glycoprotein that is crucial for the interactions of the virus-cell receptor during viral entry MERS (10,11). Therefore, these proteins were perceived as appealing to create antiviral agents against SARS and MERS2 (10). Preliminary analyses of genomic sequences from SARS-CoV-2 demonstrated that the

catalytic sites of its enzymes that could be antiviral targets are exceptionally conserved, and share an elevated level of arrangement comparability with the related SARS and MERS enzymes (11). Besides, analyses of protein structure suggest that critical drug-binding pockets in viral enzymes are presumably preserved across SARS-CoV-2, SARS, and MERS (12,13). Therefore, it is rational to consider repurposing present MERS and SARS inhibitors for COVID-19 treatment.

Since the emerging COVID-19, many scientific studies and clinical trials about therapy strategies have been published, but knowledge about COVID-19 therapy is still limited. Currently, there is an urgent necessity for an efficient treatment strategy to control the clinical deterioration of COVID-19 patients. In this article, we aim to summarize, analyze and discuss the effectiveness of current Western medicine and traditional Chinese medicine options for the treatment of COVID-19 based on an overview of the current scientific literature. Moreover, we discuss selected approved medicines that have already been verified in research studies or clinical trials for other viral diseases.

We present the following review in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/jtd-20-1810>).

Methods

We searched the bibliographic databases and search engines including PubMed, Science Direct, Springer, and Google Scholar for English-language sources, while, Chinese National Knowledge Infrastructure (CNKI) was searched for Chinese-language sources. We also searched the official websites of the following organizations: the WHO (www.who.int/), Centers for Disease Control and Prevention (CDC, www.cdc.gov/), National Institute for Health and Clinical Excellence (NICE, www.nice.org.uk/), National Administration of Traditional Chinese Medicine (www.satcm.gov.cn/), National Health Commission of the People's Republic of China (NHC, www.nhc.gov.cn/), and Chinese government website (<https://www.gov.cn/>). The search terms included coronavirus, pneumonia, severe acute respiratory syndrome coronavirus 2, SARS-CoV-2, 2019-nCoV, SARS-CoV, MERS-CoV, and COVID-19 in combination with antiviral agents, drugs, medicines, treatment, therapy, and traditional Chinese medicine (TCM). We searched the current literature conducted on the drugs of COVID-19 from virus emergence time

until May 2020. Additionally, we searched for literature that conducted on the therapeutic drugs of SARS-CoV (From 2003 to 2019) and MERS (From 2012 to 2019), and we included only the literature related to drugs that declared activity against these two previous viruses and have repurposed for COVID-19 treatment.

Search strategy

We searched the databases and engines mentioned above. The literature in English and Chinese languages were included, and the literature in other languages were excluded. All types of studies were evaluated including clinical trials, *in vitro* study, case-studies, systematic reviews, expert committees, and clinical guidelines. The combination of the following key words was used for electronic search: (“COVID-19” OR “2019 novel coronavirus disease” OR “COVID19” OR “COVID-19 pandemic” OR “SARS-CoV-2 infection” OR “COVID-19 virus disease” OR “2019 novel coronavirus infection” OR “2019-nCoV infection” OR “coronavirus disease 2019” OR “coronavirus disease-19” OR “2019-nCoV disease” OR “COVID-19 virus infection”) AND (“SARS Virus” OR “Severe Acute Respiratory Syndrome Virus” OR “SARS-Related Coronavirus” OR “SARS Related Coronavirus” OR “SARS-CoV” OR “SARS Coronavirus” OR “Severe acute respiratory” OR “syndrome-related coronavirus” OR “Severe acute respiratory syndrome related coronavirus” OR “SARS-Associated Coronavirus” OR “SARS Associated Coronavirus”) AND (“Coronavirus Infections” OR “Coronavirus Infection” OR “Middle East Respiratory Syndrome” OR “MERS (Middle East Respiratory Syndrome)”) AND (“Antiviral Agents” OR “Agents, Antiviral” OR “Antivirals” OR “Antiviral Drugs” OR “Drugs, Antiviral”) AND (“Drug Therapy” OR “Therapy, Drug” OR “Drug Therapies” OR “Therapies, Drug” OR “Chemotherapy” OR “Chemotherapies” OR “Pharmacotherapy” OR “Pharmacotherapies”) AND (“Medicine, Chinese Traditional” OR “Traditional Chinese Medicine” OR “Traditional Medicine, Chinese” OR “Chinese Traditional Medicine” OR “Chinese Medicine, Traditional”). The initial literature search identified 1530 articles, of which 95 articles were included in this narrative review.

Results and discussion

Western medicines

Remdesivir

Remdesivir is an investigational nucleotide analogue

inhibitor of the RdRp enzyme (14) that integrates into budding viral RNA chains and causes premature termination (15). Remdesivir displays a broad spectrum of antiviral action against many RNA viruses (16,17), including SARS-CoV and MERS-CoV (18), which are structurally similar to SARS-CoV-2. It has proved effective on EBOV infections in a human clinical trial (19). It has demonstrated that remdesivir inhibits the activity of SARS-CoV and MERS-CoV which can replicate in human epithelial cells and mediate entry via human CoV receptors, and resistance mutations have not been identified (18,20). In preclinical trials, remdesivir has shown essential activity against coronavirus and a great genetic barrier to resistance (21).

Recently, an *in vitro* study established that remdesivir inhibited SARS-CoV-2 with a half-maximal effective concentration (EC_{50}) = 0.77 μ M and a half-cytotoxic concentration (CC_{50}) greater than 100 μ M in Vero E6 cells (22). In the United States, the first COVID-19-confirmed case has recovered after treatment with remdesivir intravenously in January 2020 (23). A recent study on a cohort of patients hospitalized with severe complications related to SARS-CoV-2 infection revealed clinical improvement in most patients after the compassionate use of remdesivir (24). A clinical trial (NCT04252664) in China is ongoing to evaluate the activity of remdesivir in COVID-19-infected; the data from this trial will be reported by May 2020 (25). By April 29, 2020, Gilead Sciences Company reported the preliminary results of Phase 3 SIMPLE trial to evaluate 5- and 10-day dosing durations of the antiviral remdesivir in hospitalized patients with severe COVID-19 disease, in which preliminary results revealed that at least 50% of patients treated with a 5-day dosage of remdesivir improved and more than half were discharged from the hospital within 14 days. The company said that the study also showed that patients receiving the remdesivir for 10 days achieved similar improvement in clinical status compared with those taking the drug for 5 days (26). The recommended dose of remdesivir is shown in *Table 1*.

Lopinavir/ritonavir (LPV/r)

Lopinavir and ritonavir are protease inhibitors antiviral agents that can inhibit the replication of viruses and are used for acquired immunodeficiency syndrome (AIDS) treatment. They are currently formulated as a combination, in which ritonavir inhibits the metabolism of CYP3A-mediated of lopinavir. This results in extending exposure to this drug, as well as enhanced patient compliance

Table 1 Dosage, duration of treatment, mechanism of action, and level of recommendation of COVID-19 drugs

Drug	Dosage and duration of treatment	Route of administration	Mechanism of action	Comments	Ref.
Remdesivir	200 mg as loading dose on first day, followed by 100 mg once-daily as maintenance dose for 9 days	Intravenous injection	RNA dependent RNA polymerase (RdRp) inhibitor	One of the most promising agents, but clinical data still insufficient	(22-24)
Lopinavir/ritonavir (LPV/r)	400 mg/100 mg per time, twice daily for no more than 10 days	Oral	Inhibits 3-chymotrypsin like protease (3CL Protease)	Its activity is reported from a case study. It is recommended to prescribe with ribavirin or interferon. A clinical trial revealed that no benefit to use it alone	(27-29)
Ribavirin	500 mg/time, three times daily in combination with LPV/r or interferon- α for no more than 10 days	Intravenous infusion	RNA polymerase inhibitor	Its activity is limited and required high doses (but hemolytic anemia side effect) or combination with another drug (LPV/r or interferon)	(28,30,31)
Favipiravir	1,600 mg/time as a loading dose twice, followed by 600mg/time, twice daily for 7 days	Oral	RNA polymerase inhibitor	It showed activity better than arbidol and LPV/r, but less preclinical support has been established compared to remdesivir	(32,33)
Arbidol	200 mg/time, three times daily for no more than 10 days	Oral	Viral fusion inhibitor by targeting S protein/ACE2 interaction	It is recommended to prescribe in combination with LPV/r	(28,29,34)
Interferon- α	5 million U/time, twice daily for no more than 10 days	Vapor inhalation	Immunomodulatory effect and interferes with virus replication	It is recommended by experts, and it is suggested to be prescribed in combination with ribavirin or LPV/r	(28,35,36)
Interferon beta-1b	8 million IU (0.25 mg) on alternate days, one to three doses for 14 days	Subcutaneous injection	As interferon- α	It is recommended to be prescribed in triple combination with ribavirin and LPV/r	(37)
Chloroquine phosphate	500 mg/time, twice daily for no more than 10 days	Oral	Blockade of viral entry by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification. Immunomodulatory effect	Its activity is confirmed by <i>in vitro</i> study and clinical trial, but should monitor the patient for prolonged QTc interval	(22,28)
Hydroxy-chloroquine	200 mg/time, three times daily for 10 days, or 400 mg twice daily as loading dose, followed by 200 mg/time twice daily as maintenance dose for 4 days	Oral	It shares the same mechanism of action as chloroquine	One of the most promising agents. It reveals better results in combination with azithromycin, but may increase its prolonged QTc interval side effect. But 3 recent clinical trials results revealed that it is not recommend to use it	(38-42)

due to diminished pill burden; LPV/r is generally well tolerated (43). Recently, it was found that Lopinavir can inhibit 3CL protease of SARS-CoV-2 (44).

Many previous studies declared that receiving LPV/r either alone or in combination with antiviral helped in the SARS and MERS treatment, leading to a decrease in the incidence or mortality of acute respiratory distress syndrome (ARDS) (45-48). Furthermore, a recent systematic review indicated that the early use of LPV/r regimen could diminish the mortality of SARS and MERS, and reduce the dose steroids. Consequently, it was concluded that LPV/r could be used as a component of the experimental regimen to treat COVID-19 pneumonia. However, if the early treatment window is missed, there will be no important activity in their late administration (49). Thus, it is strongly suggested that preliminary real-world trials should be carried out to explore the true clinical effects of LPV/r in COVID-19 patients. In Korea, a new case study demonstrated that patients with COVID-19 pneumonia treated with LPV/r, the viral load was reduced, and the clinical symptoms improved during the treatment, no virus at all were reported to the extent that very small viral titers or no virus at all were reported (27). In China, LPV/r combination is recommended for novel coronavirus treatment, and it is included in the guidelines on the diagnosis and treatment of COVID-19 issued by NHC (Trial 7th edition) (28). On the contrary, a recent randomized controlled trial of LPV/r in adults hospitalized with severe COVID-19 has carried out, and the results revealed that no benefit was observed with LPV/r treatment further than standard care (50). The dose of LPV/r that can be considered for COVID-19 treatment is shown in *Table 1*.

Ribavirin

Ribavirin is a guanosine analogue antiviral drug that is phosphorylated intracellularly by host cell enzymes. It interferes with guanosine triphosphate synthesis to block the capping of viral messenger RNA and to inhibit the viral RdRp enzyme of certain viruses (43). In a previous study, the activity of ribavirin on replication of SARS-CoV was systematically tested in a panel of SARS-CoV permissive cell lines, in which ribavirin was shown to inhibit SARS-CoV replication in five different cell types of animal or human origin at therapeutically realizable concentrations (51,52). Ribavirin can function synergistically in combination with lopinavir/ritonavir, and the combination of these three agents has been used against SARS and MERS (53). A recent study on LPV/r alone

was not mainly remarkable, suggesting that triple therapy of LPV/r with ribavirin may be needed (53). In a virtual screening study for repurposing many drugs against SARS-CoV-2 main protease (Mpro), ribavirin revealed a potent binding to SARS-CoV-2 Mpro (30). A recent molecular docking study showed that ribavirin was able to bind tightly with the SARS-CoV-2 RdRp, with a binding energy of -7.8 kcal/mol. Consequently, it can oppose the polymerase function, and it is proposed to contribute as a potent drug against SARS-CoV-2 (31). Ribavirin is included in the guideline issued by NHC (7th edition) in a dose, as shown in *Table 1*, and it was suggested to be used in combination with lopinavir/ritonavir or interferon (28).

Favipiravir

Favipiravir is a guanine analog antiviral drug that can efficiently inhibit the RdRp enzyme of RNA viruses such as Ebola, yellow fever, and influenza (12). Thus, favipiravir might have a likely antiviral effect on SARS-CoV-2, which is an RNA virus. A recent study stated that favipiravir has efficacy against SARS-CoV-2 ($EC_{50} = 61.88$ μ M in Vero E6 cells) (22). On February 14, a clinical trial introduced by the Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen on favipiravir for COVID-19 treatment accomplished promising preliminary results, in which a total of 80 patients showed that favipiravir has more strong antiviral activity than that of LPV/r (32). In March 2020, a clinical trial in Wuhan demonstrated that favipiravir could be considered as a preferred drug for COVID-19 treatment compared with arbidol due to its higher seven day's clinical recovery rate and more efficiently diminished the cough and fever incidence (33). According to the expected synergistic effect of viral inhibition and immune enhancement, a clinical trial (ChiCTR2000029600) has recruited patients to evaluate the efficacy of favipiravir plus interferon- α against SARS-CoV-2. Currently, Russia's Ministry of Health has approved favipiravir for treatment of COVID-19 but the clinical trial results weren't shown (54).

Arbidol

Arbidol is a broad-spectrum antiviral agent that inhibits viral fusion and can be used to treat influenza viruses. Arbidol was shown to have a direct antiviral effect against SARS-CoV in early viral replication *in vitro* (55). Recently, a retrospective cohort study demonstrated that the combination of arbidol with LPV/r might delay the lung lesions progression and reduce the probability of respiratory

and gastrointestinal transmission for declining the viral load of COVID-19. Besides, this combination treatment led to a considerable improvement of chest CT scans in 7 days (29). In Wuhan, China, a current study analyzed the clinical features of 69 cases with COVID-19 infection. In this study, the efficacy of arbidol was evaluated. The results showed that 33% of patients had been discharged in the arbidol-treated group, whereas 19% of patients have been discharged in the arbidol-untreated group. Besides, there were no deaths in the arbidol-treated group. Therefore, it appeared that arbidol treatment could improve the discharging rate and decrease the mortality rate (34). Arbidol has been included in the guideline issued by NHC (Trial 7th edition) as a recommended agent for COVID-19 treatment in a standard dose as shown in *Table 1* (46).

Interferons

Interferons are host cytokines that can exert complicated immunomodulatory, antiviral, and anti-proliferative effects. Interferon- α seems to work by intracellular signal stimulation following binding to specific cell membrane receptors, causing in inhibition of viral entry, translation, transcription, protein processing, maturation, and release. Besides, interferons increase expression of major histocompatibility complex antigens, enhance the phagocytic activity of macrophages, and augment cytotoxic T cells proliferation and survival (43).

Many previous studies demonstrated the activity of interferon with ribavirin combination. Since the clinical activity of type I interferon or ribavirin alone as anti-SARS-CoV is limited, a combination of these two drugs was investigated, and the consequent determination of the virus yield showed a significant synergistic anti-SARS-CoV effect of the combination, suggesting the consideration of interferon- β together with ribavirin for SARS treatment (52). The interferon- β with ribavirin combination inhibits the replication of SARS-CoV in significantly reduced concentrations compared with either single treatment. This might enable reaching sufficient therapeutic plasma levels sufficient to inhibit the replication of SARS-CoV throughout the early phase of SARS and consequently prevent immunopathological damages (51). Therefore, interferon- α 2b and ribavirin combination was used effectively as a primary treatment and prophylaxis in SARS (51). Furthermore, interferon- α 2b and ribavirin combination was shown to have some *in vitro* synergistic activities against MERS-CoV (56). This combination was given to patients with severe MERS-CoV infection, and the

patient's survival was increased (57). Additionally, a study case described the successful use of this combination in human MERS-CoVs (58). Thus, interferon plus ribavirin combination is included in the guideline issued by NHC (7th edition) (28).

A recent study demonstrated that interferon- α could decrease the viral load in the early stage of infection which leads to relieving symptoms and reduces the progression of disease in COVID-19 patients (35). Moreover, an *in vitro* study described the sensitivity of SARS-CoV-2 and SARS-CoV to type I interferon (IFN-I) in Vero cells. The results demonstrated that both viruses maintain a similar replication in untreated Vero E6 cells, but SARS-CoV-2 has a significant decrease in viral replication following IFN-I pretreatment, thus suggesting that IFN-I may be used as prophylactic against SARS-CoV-2 (36). Moving forward, these data could provide valuable insights for both the treatment of COVID-19 and the development of novel animal models of disease (36). Recently, an open-label randomized trial revealed that early triple combination antiviral therapy with interferon beta-1b, LPV/r, and ribavirin was safe and more effective than LPV/r alone in alleviating symptoms and shortening the duration of viral shedding and hospital stay in patients with mild to moderate COVID-19 (37).

Chloroquine and hydroxychloroquine

Chloroquine is a widely used antimalarial and immunomodulatory medicine that has recently been described as an effective broad-spectrum antiviral agent (59,60). It blocks viral infection by elevating the endosomal pH that is necessary for the virus-cell interaction, as well as interfering with the glycosylation of SARS-CoV cellular receptors (61). Moreover, chloroquine is efficient in precluding the spread of SARS-CoV in cell culture. An advantageous inhibition of virus spread was seen when the cells were either treated with chloroquine previously or after SARS-CoV infection (60). Therefore, the antiviral and anti-inflammatory effects of chloroquine may explain its strong activity in treating of COVID-19 pneumonia patients (62).

Recent study results revealed that chloroquine worked at both entry, and post-entry stages of the SARS-CoV-2 in Vero E6 cells and that it can block the virus infection at low-micromolar concentration with $EC_{50} = 1.13 \mu\text{M}$ and CC_{50} greater than $100 \mu\text{M}$. Chloroquine showed efficiency in inhibiting the replication of SARS-CoV-2 and can block the growth of this virus *in vitro* (22). In addition to its

antiviral effect, chloroquine has an immune-modulating activity, which can augment its antiviral effect *in vivo*. After oral administration, chloroquine can be found in the entire body, including the lungs (22). On February 15, 2020, a conference was held, and participants, including regulatory authorities, specialists from government, and coordinators of clinical trials, agreed that chloroquine phosphate has strong activity against SARS-CoV-2. Two days after, the State Council of China held a news briefing demonstrating that chloroquine phosphate had revealed obvious efficacy and satisfactory safety in treating COVID-19 associated pneumonia in multicenter clinical trials conducted in China (62,63). Several consequent clinical trials have been rapidly accompanied in China to test the efficiency and safety of chloroquine in the treatment of SARS-CoV-2 associated pneumonia in many hospitals in different cities. The results from over 100 patients have revealed that chloroquine phosphate is superior to the control treatment in preventing the exacerbation of pneumonia, improving lung imaging findings, inducing a virus-negative conversion, and diminishing the infection course. Severe side effects of chloroquine phosphate were not observed in the patients mentioned above (62). Moreover, chloroquine phosphate is included in the guideline issued by NHC (7th edition) to treat COVID-19 patients in a recommended dose, as shown in *Table 1* (28).

Hydroxychloroquine, an analog of chloroquine, was reported to have activity against coronavirus *in vitro* in the previous SARS outbreak (64). The clinical safety of hydroxychloroquine during prolonged use is better than that of chloroquine, and there are fewer concerns about drug-drug interactions, which allows a higher daily dose. Hydroxychloroquine may be an ideal drug to treat the SARS-CoV-2 infection as it can inhibit the virus and help mediate the cytokine storm via its immunomodulatory effects (38). A recent *in vitro* study demonstrated that hydroxychloroquine is more potent than chloroquine at inhibiting SARS-CoV-2 *in vitro* (38). In this study the pharmacological activity of chloroquine and hydroxychloroquine was verified using SARS-CoV-2 infected Vero cells, and the results showed that hydroxychloroquine ($EC_{50} = 0.72 \mu\text{M}$) had a more potent *in vitro* anti-SARS-CoV-2 activity than chloroquine ($EC_{50} = 5.47 \mu\text{M}$) (36). In France, confirmed COVID-19 patients were included in a clinical trial from the beginning of March to March 16, to take hydroxychloroquine in a dose of 600 mg daily. The results revealed a considerable decline of the viral carriage at D6-post inclusion compared

with controls and much lower average carrying duration than that of untreated patients (39). Viral clearance at day 6 was 70% (14/20) for the hydroxychloroquine group versus 12.5% (2/16) for the control group. It was also reported that the addition of azithromycin to hydroxychloroquine in six patients led to numerically higher viral clearance (6/6, 100%) compared with hydroxychloroquine monotherapy (8/14, 57%), thus suggesting that this combination has more activity than hydroxychloroquine alone (39). The recommended dose of hydroxychloroquine for COVID-19 treatment is shown in *Table 1*.

On the contrary, a retrospective cohort study of patients from a random sample of admitted patients with laboratory-confirmed COVID-19 in 25 hospitals in New York State indicated that treatment with hydroxychloroquine, azithromycin, or both, compared with no treatment, was not significantly associated with differences in in-hospital mortality (40). Furthermore, recent open-label randomized controlled trial in patients admitted to hospital with mild to moderate COVID-19 has revealed that adding hydroxychloroquine to the current standard of care in patients with mainly persistent mild to moderate COVID-19 did not show additional benefits of virus elimination (41). Another randomized control trial, to investigate whether hydroxychloroquine can prevent symptomatic infection after SARS-CoV-2 exposure, has demonstrated that after high-risk exposure to COVID-19, hydroxychloroquine did not prevent illness compatible with COVID-19 or confirmed infection when used as post-exposure prophylaxis within 4 days after exposure (42).

Corticosteroids

The use of corticosteroids for COVID-19 treatment is controversial. Reasonable utilization of glucocorticoids can considerably improve the clinical symptoms of SARS patients, decline the degree of disease progression, and accelerate the absorption of lung lesions; but it cannot reduce the length of the hospital stay (65,66). Early constrained utilization of corticosteroids in CoV pneumonia might be efficient in decreasing the pulmonary lesions and viral replication (67); however, many previous studies revealed that the corticosteroids use in SARS patients caused significant side effects, including secondary severe viral, bacterial, or fungal infections because of the immunosuppressive effects, myopathy, and finally an increased risk of either mortality or intensive care support requiring mechanical ventilation (68-70).

Methylprednisolone is suitable for COVID-19 patients

with rapid disease progression or severe ailments (71). Additionally, short-term moderate-dose corticosteroid plus immunoglobulin is useful for reversing the continued deterioration of COVID-19 patients who failed to respond to low-dose therapy (72). In China, systemic glucocorticosteroid is recommended by the guideline issued by NHC (7th edition) as a short-term use (1–2 mg/kg/d, 3–5 d) of methylprednisolone, but it should be taken with caution (28,73). It is recommended to avoid corticosteroid utilization with a prolonged high-dose (67,71).

Antibiotics

Antibiotics are not prescribed to treat COVID-19 itself. However, bacterial pneumonia occurs during hospital treatment (especially in intubated ventilator-associated pneumonia in COVID-19 patients) (74), and the secondary infection reached 16% (11/68) among patients who died from SARS-CoV-2 in one series, which may require the use of antibiotics (75). Therefore, the WHO recommended that empiric antimicrobial therapy should be based on clinical diagnosis (community-acquired pneumonia, hospital-acquired pneumonia) (76). Recently, the guidelines on diagnosis and treatment of COVID-19 (7th edition) emphasized that COVID-19 patients should avoid blind or unsuitable utilization of antibiotics, especially the combination of broad-spectrum antibiotics (28). Therefore, it is necessary to evaluate the use of antibiotics appropriately. According to the patient's clinical condition, if secondary bacterial infections cannot be excluded, mild patients should be provided antibiotics for community-acquired pneumonia, such as azithromycin, amoxicillin, or fluoroquinolones; and severe patients should be given empiric antibiotic treatment covering all of the possible pathogens, reducing therapy until the pathogenic bacteria are clarified (71).

Azithromycin, a macrolide antibiotic, was demonstrated to be effective *in vitro* against Ebola and Zika viruses (77,78). Besides, azithromycin is supposed to have good activity in preventing severe respiratory tract infections when it is administered to patients with viral infection (79). A recent study proved the synergistic effect of azithromycin plus hydroxychloroquine, in which this combination revealed more efficiency in eliminating viruses for treating COVID-19 infection compared with hydroxychloroquine alone (39). Another antibiotic that has revealed some activity against coronavirus is teicoplanin. It is a glycopeptide antibiotic that used in the treatment of Gram-positive bacteria, especially staphylococcal infections. It

has shown efficiency against many viruses including SARS-CoV and MERS (80,81). A recent study has revealed that teicoplanin effectively blocks the cell entry of 2019 novel coronavirus (82). Thus, teicoplanin is suggested to be a possible alternative for the treatment of SARS-CoV-2.

Traditional Chinese medicine (TCM)

TCM has a long history and has played a crucial role in the prevention and treatment of various epidemic ailments. In 2003, the intervention of TCM in the treatment of SARS patients achieved a noteworthy therapeutic activity (83). Throughout the SARS-CoV-2 therapy, over 4,900 medical staff of TCM were sent out to Hubei Province, and a TCM scheme was included in the guidelines on the diagnosis and treatment of COVID-19 issued by NHC (84,85).

TCM specialists actively contributed to the entire rescue process and participated in treatment collectively. Thousands of COVID-19 patients were successfully treated by TCM (86). However, the Chinese government is counseling physicians to consider combining Western antiviral medicines with TCM in combating COVID-19 pneumonia. Based on the clinical trials and current results, we describe here the most effective prescribed TCM remedies in the treatment of COVID-19.

Qingfei Paidu decoction (QFPDD)

QFPDD, composed of Rhizoma Dioscoreae, Fructus aurantii immaturus, Asarum, Wrinkled giant hyssop, and other 17 TC compounds *Table 2* (87), is officially recommended as a SARS-CoV-2 medicine suitable for the treatment of light, medium, heavy, and critical patients as mentioned in the guideline issued by NHC (Trial 7th edition) (28). The total survey effective rate was higher than 90% and verified by a clinical trial (85,88).

Using Network Pharmacology, a study demonstrated that QFPDD's chief targeting organ is the lung. Among QFPDD's 790 putative targets, 232 are co-expressed with ACE2, which is the receptor of the novel coronavirus. By regulating a sequence of proteins co-expressed with ACE2 and a series of signaling pathways closely related to the occurrence and development of diseases, QFPDD plays a role in balancing immunity and eliminating inflammation. Furthermore, it may act as an antiviral agent by targeting ribosomal proteins that are necessary for viral replication, thus inhibiting both viral mRNA translation and a group of proteins that interact with viral proteins. Notably, the key targets were mainly enriched in two categories of

Table 2 The components of TCMs (for reference only)

TCM	Chinese medicine components	Reference
Qingfei Paidu Decotion	Ephedra (9 g), Radix Glycyrrhizae Preparata (6 g), Almond (9 g), Fried Gypsum (15–30 g), Cassia twig (9 g), Rhizoma alismatis (9 g), Polyporus umbellatus (9 g), Rhizoma Atractylodis Macrocephalae (9 g), Poria cocos (15 g), Radix bupleuri (16 g), Radix scutellariae (6 g), Pinellia (9 g), Ginger (9 g), Aster (9 g), Winter flower (9 g), Belamcanda chinensis (9 g), Asarum (6 g), Rhizoma Dioscoreae (12 g), Fructus aurantii immaturus (6 g), Dried tangerine or orange peel (6 g), Wrinkled giant hyssop (9 g)	(28,87-89)
Yupingfeng	Astragalus membranaceus (60 g), Fried Rhizoma Atractylodis Macrocephalae (60 g), Saposhnikovia divaricate (30 g)	(90,91)
Huoxiang Zhengqi	The shell of areca nut (5 g), Angelica dahurica (5 g), Purple perilla (5 g), Poria cocos (5 g), Pinellia rhizome fermented mass (10 g), Rhizoma Atractylodis Macrocephalae (10 g), Dried tangerine or orange peel (10 g), Magnolia officinalis (10 g), Ginger juice (10 g), Platycodon grandiflorum (10 g), Wrinkled giant hyssop (15 g), Radix Glycyrrhizae Preparata (12 g)	(91)
Lianhua Qingwen Capsule	Forsythia, Honeysuckle, Honey-fried herba ephedrae, Fried bitter almonds, Plaster, Isatis root, Thick wood-fern rhizome, Houltuyunia cordata, Pogostemon cablin, Rheum officinale, Rhodiola root, Menthol crystal, Liquorice	(28,87,92,93)
Xuebijing injection	Carthamus tinctorious, Radix paeoniae rubrae (unpeeled) root of common peony, Ligusticum wallichii, The root of red-rooted salvia, Angelica sinensis	(87,94)
Shenfu injection, Reduning injection	Red ginseng, Root of Aconite; Artemisia apiacea, Honeysuckle, Cape jasmine	(91)
Tanreqing injection	Radix scutellariae, Bear gall powder, Cornu gorais, Honeysuckle, Forsythia	(87)
Xingnaojing injection	Musk, Radix curcumae, Borneol	(91)

diseases: viral infections and lung damage, indicating that its therapeutic effect on SARS-CoV-2 may be based on the anti-virus and repair of lung injury properties (89). Besides, a recent study has proven that QFPDD can inhibit the arachidonic acid (AA) metabolic pathway which is principally used to synthesize inflammatory cytokines, and consequently, it has a benefit for inhibiting the release of inflammatory factors in the body alleviating the cytokine storm (95).

Yupingfeng (YPF)

YPF, which consists of Astragalus membranaceus, Fried Rhizoma Atractylodis Macrocephalae, and Saposhnikovia divaricate, has been used in the prevention of SARS-CoV-2 as recommended by the Multi-province Chinese Medicine Prevention Program (90). Recently, a pharmacologic study found that YPF can exert immune regulation and anti-inflammatory effects through a variety of action mechanisms (96). Furthermore, the results of the KEGG pathway analysis revealed that YPF might be useful for treating lung injury and virus infection. The enriched pathways indicated that the effect of YPF regulating

immunity and eliminating inflammation might work through immune response and inflammatory response pathways, such as the PI3K/Akt, Ras, HIF-1, and MAPK signaling pathways. According to the prediction of molecular docking, YPF plays a prevention role, probably by inhibiting the binding of SARS-CoV-2 to ACE2 receptors (97).

Huoxiang Zhengqi (HXZQ)

The ingredients of HXZQ include Agastache rugosus, Licorice, Perilla leaf, Angelica dahurica, and six other TCM compounds *Table 2* (91). HXZQ was recommended for SARS-CoV-2 prevention due to its antiviral, anti-inflammatory, and immunomodulatory activities, as well as its ability to alleviate gastrointestinal discomfort (98). These properties of HXZQ have been shown by TCM theory and modern pharmacological studies (99-101). Moreover, clinical and pharmacological studies have also demonstrated that HXZQ has therapeutic effects on fever, nausea or vomiting, abdominal pain, and diarrhea related to viral infection, suggesting that HXZQ may also improve similar symptoms of COVID-19 (102-104).

Lianhua Qingwen (LHQW)

The Chinese prescription LHQW contains *Angelica dahurica*, Purple perilla, *Poria cocos*, *Pinellia rhizome* fermented mass, *Rhizoma Atractylodis Macrocephalae*, and seven other TCM compounds *Table 2*. The guideline issued by NHC (Trial 7th edition) advocates the use of LHQW on patients during medical observation (28). A previous report revealed the mechanism of action for LHQW by virtual screening technology, and the results showed that the LHQW has a potential inhibitory effect on the AA metabolism pathway that translates into inhibiting the release of inflammatory factors (95). The latest *in vitro* studies have illustrated that the LHQW capsule can significantly inhibit the activity of new coronavirus, reduce the virus content in cell membrane and cytoplasm, inhibit the excessive activation of cytokines (92), and noticeably improve the symptoms of fever, cough, and fatigue in patients with COVID-19 (105). Recently, a study by the academician of the Chinese Academy of Sciences Zhong Nanshan and his team demonstrated that LHQW significantly inhibited SARS-CoV-2 replication in Vero E6 cells and decreased the production of pro-inflammatory cytokines (IL-6, TNF- α , CXCL-10/IP-10, and CCL-2/MCP-1) at the mRNA levels. Moreover, this study revealed that treatment with LHQW caused abnormal particle morphology of virion in cells (93).

Since the immune system of a SARS-CoV-2 patient is deteriorated, and bacterial infections are a severe risk, the antibacterial effect of LHQW might be of value in controlling secondary pulmonary infections (105). LHQW can improve the immune function of SARS-CoV-2 patients, relieve acute symptoms, improve clinical efficacy, and accelerate disease recovery. For these reasons, the China National Medical Products Administration (NMPA) has approved LHQW for the treatment of light and medium COVID-19 (106).

TCM injections

The guideline issued by NHC (Trial 7th edition) pointed out that the TCM injections are more beneficial in patients with heavy and critical SARS-CoV-2. The recommended TCM injections include Xuebijing injection, Shenfu injection, Reduning injection, Tanreqing injection, and Xingnaojing injection (28). The Xuebijing injection contains *Carthamus tinctorius*, *Radix paeoniae rubra*, *Ligusticum wallichii*, the root of red-rooted salvia, and *Angelica sinensis*. Previous research showed that this injection has many pharmacological effects such as antagonizing endotoxin, inhibiting inflammatory response,

improving immune function, regulating blood coagulation balance, and protecting tissues and organs (94).

Recently, Xuebijing injection has been approved by NMPA for the treatment of heavy and critical COVID-19 (107), in which it can play crucial roles as an anti-inflammatory, regulating blood coagulation, vascular endothelial protection, and improving immunity (108-110). Network pharmacology indicated that the mechanism of Xuebijing injection might work through the combined action of multiple components, multiple targets, and multiple pathways (111). In addition to targeting the 3CL hydrolase of SARS-CoV-2, the Xuebijing injection boosts the host's immunity and anti-infection ability after virus invasion (111). For adult viral pneumonia, Tanreqing injection has benefits in terms of effective rate, chest radiograph change time, and the average length of hospital stay (112). It is recommended to use TCM injections combined with Western drugs and other treatment methods to control the disease progression, suppress the cytokine storm, and reduce the mortality of critically ill patients (113).

Other TCMs

In addition to the drugs mentioned above, many other TCM drugs can play critical roles in the treatment of COVID-19. Jinhua Qinggan Granule is suitable for the treatment of patients with mild pneumonia. It can significantly reduce the clinical symptoms of fever, cough, fatigue, and expectoration in patients with mild coronavirus pneumonia as well as relieve psychological anxiety (114). Besides, Jinhua Qinggan Granules have been approved for the treatment of COVID-19, which can well meet the needs of clinical treatment (115). Huashi Baidu Fang and Xuanfei Baidu Fang are effective prescriptions summarized by academician Huang Luqi and academician Zhang Boli. According to clinical observations in the frontline of Wuhan, both drugs can block the development of the disease and improve symptoms, thus shortening the course of the disease. Recently, Huashi Baidu granules and Qingfei Paidu granules have been approved by NMPA and obtained the approval for national clinical trials (115).

Conclusions

The novel coronavirus is spreading rapidly and is considered a global pandemic that is causing terror worldwide. Knowledge on how to treat COVID-19 is still limited, and there is an urgent need to find a potentially effective medicine. Thus, scientists around the world are

actively exploring drugs that can be significantly effective in combating COVID-19. Based on the literature we have overviewed, that there is no specific effective drug for COVID-19 treatment to date. Recent research studies and clinical trial results revealed relative activity of some drugs in the treatment of COVID-19, and they are suggested for use the time being to treat the COVID-19 until an efficient anti-SARS-CoV-2 drug has been proven and established. The western medicines that inhibit RdRp enzyme (as remdesivir) are promising drugs for future treatment of COVID-19. A combination of 3CLpro inhibitors (as LPV/r), immunomodulatory agents (as interferon), and RNA polymerase inhibitor (as Ribavirin) might be a promising combination prospect for future therapy. TCM, with the advantages of the multi-target effect, had exhibited good effects in improving patients' symptoms, reducing inflammation, and regulating body immunity. In the future, with the improvement of TCMs' quality, more accurate researches on the mechanism, and the disclosure of effective clinical evidence, more opportunities will be given to TCMs. Therefore, it should be taken into consideration the combination of western medicine and TCM, they may prospect to be one of the best a promising effective strategy in the treatment of COVID-19. Actually, it is challenging to base a treatment decision in the absence of a complete research cycle and a clear vision of drug efficacy and safety. Further extensive studies and clinical trials including double-blind and randomized control trials, with a higher number of patients, are urgently needed to confirm the activity of these medicines. There are many ongoing clinical trials that are investigating the efficiency of single or combination therapy with the medicines mentioned in this review and new drugs are under development. The results of these trials are urgently required to make clear recommendations for the treatment of COVID-19.

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