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Recent progress of antiviral therapy for coronavirus disease 2019

Mengmeng Zhao [a,b,c,1], Jishou Zhang [a,b,c,1], Hanli Li [d,1], Zhen Luo [a,b,c,1], Jing Ye [a,b,c], Yao Xu [a,b,c], Zhen Wang [a,b,c], Di Ye [a,b,c], Jianfang Liu [a,b,c], Dan Li [e], Menglong Wang [a,b,c,**], Jun Wan [a,b,c,*]

[a] Department of Cardiology, Renmin Hospital of Wuhan University, Wuhan, 430060, China
[b] Cardiovascular Research Institute, Wuhan University, Wuhan, China
[c] Hubei Key Laboratory of Cardiology, Wuhan, China
[d] Department of Neurology, The First Affiliated Hospital of Anhui Medical University, China
[e] Department of Pediatrics, Renmin Hospital of Wuhan University, Wuhan, China

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic has become a global public health crisis, for which antiviral treatments are considered mainstream therapeutic approaches. With the development of this pandemic, the number of clinical studies on antiviral therapy, including remdesivir, chloroquine and hydroxychloroquine, lopinavir/ritonavir, ribavirin, arbidol, interferon, favipiravir, oseltamivir, nitazoxanide, nelfinavir, and camostat mesylate, has been increasing. However, the efficacy of these antiviral drugs for COVID-19 remains controversial. In this review, we summarize the recent progress and findings on antiviral therapies, aiming to provide clinical support for the management of COVID-19. In addition, we analyze the causes of controversy in antiviral drug research and discuss the quality of current studies on antiviral treatments. High-quality randomized clinical trials are required to demonstrate the efficacy and safety of antiviral drugs for the treatment of COVID-19.

1. Introduction

Coronavirus disease 2019 (COVID-19) has spread all over the world and become a global pandemic (Velavan and Meyer, 2020; Zhu et al., 2020a). According to data from the World Health Organization, as of June 16, 2020, 7, 941, 791 cases have been diagnosed with COVID-19 globally, of which 434, 796 died (Organization, 2020). The estimated fatality of COVID-19 is 6.9%. Compared to severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), COVID-19 appears to be relatively mild with lower mortality, but more contagious (CI et al., 2020).

The clinical manifestations of patients infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) range from mild nonspecific symptoms to severe pneumonia and impaired organ function. Most patients present with fever, cough, and shortness of breath (Wang et al., 2020a). Some patients with COVID-19 presented with diarrhea (Zhang et al., 2020). Furthermore, many patients may be asymptomatic (Guan et al., 2020). Elderly COVID-19 patients and patients with comorbidities, such as hypertension, diabetes, and other diseases, are more likely to develop into severe conditions and have higher mortality rates (CDC, 2020; Lippi et al., 2020). Severe SARS-CoV-2 infection can rapidly develop into organ dysfunction, such as acute kidney injury, shock, and acute heart injury, which eventually causes death (Wang et al., 2020a).

SARS-CoV-2 is an enveloped, positive-sense, single-stranded RNA virus (Zhu et al., 2020a). Similar to SARS-CoV, SARS-CoV-2 targets the cell via the combination of viral structural spike protein and the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell (Hoffmann et al., 2020a). ACE2 is abundantly distributed in the lung and small intestine epithelial cells, which suggests a possible entry route for SARS-CoV-2 (Hamming et al., 2004). Another protease on the host cell membrane, TMPRSS2, can promote cell entry through the spike protein (Hoffmann et al., 2020a). The SARS-CoV-2 genome encodes nonstructural proteins for viral replication, such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RNA-dependent RNA polymerase (RdRp) (Li and De Clercq, 2020). These four nonstructural proteins play

* Corresponding author. Department of Cardiology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, China.
** Corresponding author. Department of Cardiology, Renmin Hospital of Wuhan University, 238 Jiefang Road, Wuhan 430060, China.
E-mail addresses: whuwangmenglong@163.com (M. Wang), wanjun@whu.edu.cn (J. Wan).
[1] These authors contributed equally.

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key roles in the viral life cycle, and together with the spike protein are considered as potential pharmacological targets of anti-SARS-CoV-2 therapy (Zumla et al., 2016). The life cycle of SARS-CoV-2 from attachment to reproduction and the therapeutic targets of antiviral drugs are shown in Fig. 1 and Table 1. The mechanisms of anti-SARS-CoV-2 therapy include acting on the genetic material of the virus to prevent the synthesis of viral RNA, inhibiting virus replication by acting on key enzymes of SARS-CoV-2, blocking the binding of SARS-CoV-2 to human cell receptors, or inhibiting the self-assembly process of SARS-CoV-2 via acting on some structural proteins (Wu et al., 2020b).

With the development of this pandemic, the number of clinical studies on antiviral therapy, including remdesivir, chloroquine (CQ) and hydroxychloroquine (HCQ), lopinavir/ritonavir (LPV/r), ribavirin, arbidol, interferon (IFN), favipiravir, oseltamivir, nitazoxanide, nelfinavir, and camostat mesylate, has been increasing. In this review, the recent progress and findings on antiviral therapy are summarized, aiming to provide clinical support for the management of COVID-19.

2. Antiviral therapy

2.1. Preclinical screening of anti-SARS-CoV-2 drugs

In the past fight against the coronavirus, scientists have proposed three strategies for developing new drugs (Zumla et al., 2016). The first strategy is to test the role of existing broad-spectrum antiviral drugs in the treatment of coronavirus pneumonia, such as interferon and ribavirin (Chan et al., 2013). The advantage of these therapies is that their metabolic characteristics, dosages used, potential efficacy and side effects are clear, as they have been approved for the treatment of other viral infections. But the disadvantage is that these therapies are too broad-spectrum to kill the coronavirus in a targeted manner, so their side effects should not be underestimated. The second strategy is to develop new targeted drugs directly based on the different genome information and pathological characteristics of coronavirus. New discovered drugs will show better antivirus effects theoretically, but the development of new drugs may take huge time and economic costs. The third strategy is to use existing molecular databases to screen for molecules that may have therapeutic effects on the coronavirus (Dyall et al., 2014). Virtual screening makes this strategy possible, and through this strategy, new functions of many drugs can be discovered, for example, the anti-HIV drugs lopinavir/ritonavir (Baldelli et al., 2020).

Table 1
Therapeutic targets of antiviral drugs for SARS-CoV-2.

Therapeutic Targets	Function	Potential Antiviral Drugs
3-chymotrypsin-like protease	A protease that cleaves multiple proteins to produce non-structural proteins	Lopinavir
Papain-like protease	A protease that cleaves multiple proteins to produce non-structural proteins	Lopinavir, Remdesivir.
RNA-dependent RNA polymerase	An RNA-dependent RNA polymerase for replicating coronavirus genome	Remdesivir, ribavirin, favipiravir, oseltamivir
Spike protein	A viral surface protein for binding to host cell receptor ACE2	Arbidol, nelfinavir
TMPRSS2	A host type 2 transmembrane serine protease, promotes cell entry through the S protein	Camostat mesylate
ACE2	A viral receptor protein on the host cells which binds to viral S protein	Chloroquine, hydroxychloroquine.
Antiviral protein	Decompose viral mRNA, inhibit the synthesis of viral polypeptide chains, and stop viral replication.	Interferon

Abbreviation: 3CLpro, 3-chymotrypsin-like protease; Plpro, papain-like protease; RdRp, RNA-dependent RNA polymerase.

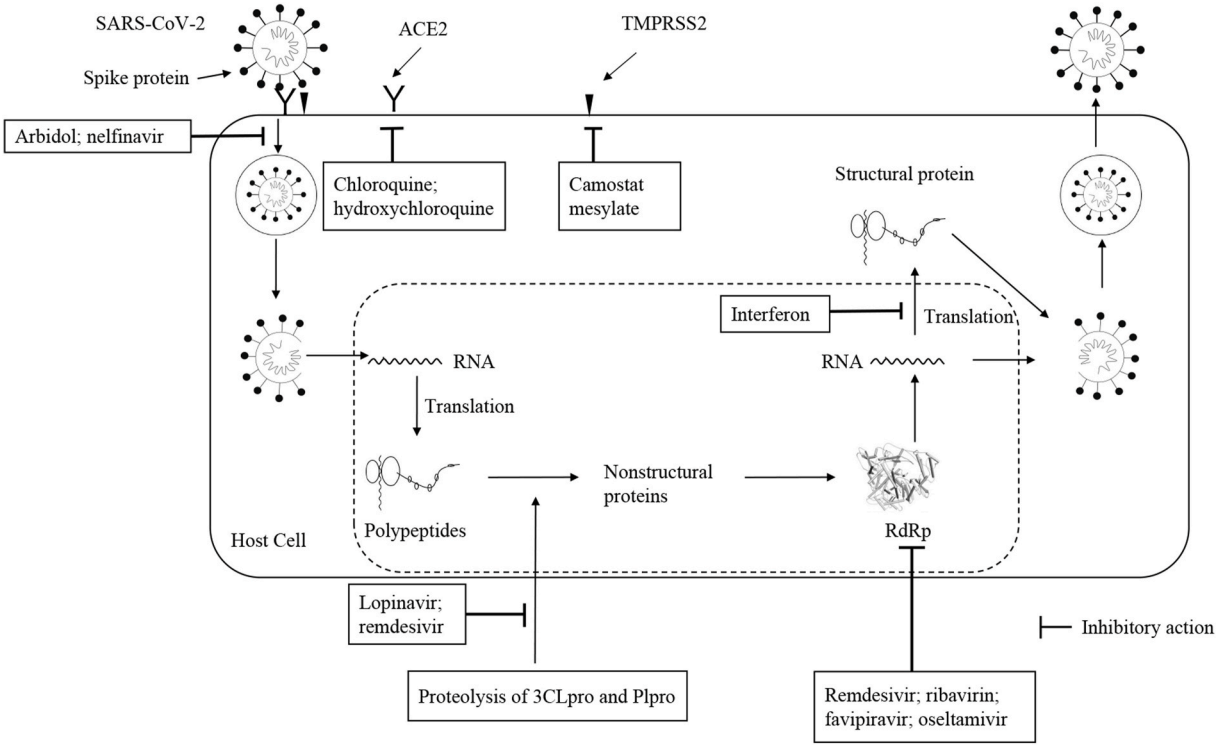

Fig. 1. Schematic diagram shows the replication and synthesis of SARS-CoV-2 in the host cell and the potential targets of antiviral drugs. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; ACE2, angiotensin-converting enzyme 2; 3CLpro, 3-chymotrypsin-like protease; Plpro, papain-like protease; RdRp, RNA-dependent RNA polymerase.

Virtual screening technology is widely used in the search for effective anti-SARS-CoV-2 drugs. With the help of computer-aided drug discovery technology, virtual screening can efficiently develop drugs and minimize the cost and time of the drug development process (Leelananda and Lindert, 2016). It is one of the most promising computer-aided drug design technologies. Scientists' early analysis of SARS-CoV-2 structural and non-structural proteins provided the basis for virtual screening, which is an indispensable condition for virtual screening. Researchers constructed all the protein structures related to SARS-CoV-2 through homology modeling, including 3-chymotrypsin-like protease, papain-like protease, helicase, RNA-dependent RNA polymerase and spike protein (Wu et al., 2020b). Then they used these proteins and human ACE2, TMPRSS2 as targets, screened ZINC US Food and Drug Administration (FDA)-approved drug database (ZINC drug database, ZDD), the database of traditional Chinese medicine and natural products, and the database of commonly used anti-viral drugs (78 compounds) by virtual ligand screening method. Researchers have discovered many compounds that may have antiviral activity from the drug database, including antiviral drugs, antibacterial drugs, anti-asthma drugs and liver protection drugs. Remdesivir, chloroquine, lopinavir and ritonavir have been found to have anti-SARS-CoV-2 activity among the existing antiviral drugs (Wu et al., 2020b). In another study, the researchers screened a large database of more than 606 million compounds and discovered twelve novel inhibitors of SARS-CoV-2 3-chymotrypsin-like protease, including natural substances like rhamnetin, and existing protease inhibitors such as nelfinavir and so on (Fischer et al., 2020). Another study used virtual screening technology in silico models to find molecules that may inhibit both SARS-CoV-2 Nsp13 helicase and Nsp14 proteins from the FDA-approved drug library (Gurung, 2020).

The application of virtual screening technology has greatly improved the efficiency of anti-SARS-CoV-2 drug development. On the one hand, it saves a lot of time, and on the other hand, it helps to discover many potential drugs for the treatment of COVID-19. These studies will provide new lead compounds and targets for further in vitro and in vivo studies of SARS-CoV-2, new insights for those drugs currently ongoing clinical studies, and also possible new strategies for drug repositioning to treat SARS-CoV-2 infections (Wu et al., 2020b). The relevant clinical studies of some potential effective anti-SARS-CoV-2 drugs are discussed below.

2.2. Remdesivir

Remdesivir is a phosphoramidate prodrug of 1′-cyano-substituted adenosine nucleotide analogs, which can be integrated into the nascent viral RNA chain and inhibit viral RNA synthesis via delaying chain termination (Tchesnokov et al., 2019; Warren et al., 2016). Remdesivir has broad-spectrum antiviral activity against a variety of viruses, including SRAS-CoV and MERS-CoV (Sheahan et al., 2017). Study in vitro showed that remdesivir can effectively control SARS-CoV-2 infection (Wang et al., 2020b). Moreover, remdesivir significantly improved the lung function of mice infected with SRAS-CoV-2 (Pruijssers et al., 2020). A similar therapeutic effect was observed in the rhesus monkey model infected with SARS-CoV-2 (Williamson et al., 2020). Remdesivir was first applied compassionately to COVID-19 patients in the United States (Team, 2020). Clinical improvement was observed in patients who were hospitalized for severe COVID-19 and received compassionate use of remdesivir (Grein et al., 2020). These early reports were only retrospective descriptive studies, which are not sufficient to support the clinical use of remdesivir, but have aroused the interest of researchers.

A terminated clinical trial (NCT04257656) suggests that remdesivir usage cannot reduce the time to clinical improvement (Wang et al., 2020c). Patients who received remdesivir within 10 days after onset achieved clinical improvement earlier than patients who received placebo, although the difference was not statistically significant (Wang et al., 2020c). There was no difference in mortality between remdesivir recipients and placebo recipients (Wang et al., 2020c). However, remdesivir treatment reduced the time of ventilator application (Wang et al., 2020c). Previous reports have suggested that the survival rate of patients using a ventilator is notably lower than that of patients who do not use it (Grasselli et al., 2020; Richardson et al., 2020). From this perspective, investigating the potential applications of remdesivir might be helpful.

Recently, two additional clinical trials were completed and they reported on the results of remdesivir use. One study (NCT04280705) suggested that the time to recovery for remdesivir recipients was significantly shorter than placebo recipients (11 versus 15 days) (Beigel et al., 2020). Remdesivir treatment reduced the mortality of COVID-19 numerically (8.0% versus 11.6%), suggesting a survival benefit, although no statistical difference was observed (Beigel et al., 2020). Another study (NCT04292899) showed that compared with patients with standard care, 65% of patients with 5-day remdesivir treatment achieved clinical improvement. But patients receiving 5-day or 10-day remdesivir treatment had similar clinical improvements, which helped to explore safer and more effective remdesivir use strategies (Goldman et al., 2020). In a randomized, open-label, multinational, phase III SIMPLE moderate trial (NCT04292730), patients with moderate COVID-19 pneumonia receiving remdesivir for 5 days were more likely to have clinical improvement at day 11 than those receiving standard of care (Spinner et al., 2020). (Table 2)

All four clinical trials above showed that remdesivir cannot significantly reduce the mortality of COVID-19, but have a positive effect on clinical improvement of mild COVID-19. Therefore, remdesivir was permitted to be applied in severe COVID-19 patients by the U.S. Food and Drug Administration (2020). In June and July 2020, remdesivir was approved conditionally in several other countries/regions around the world. On August 10, 2020, a new drug application for remdesivir for the treatment of COVID-19 was submitted to the US FDA (Lamb, 2020). Remdesivir has become one of the most promising drugs for the treatment of COVID-19. But the side effects of remdesivir need to be noted. The most common adverse events in 10% of patients taking remdesivir are nausea and liver damage (Grein et al., 2020; Wang et al., 2020c). However, it is not clear whether these effects are due to the drug itself or the virus. At present, there are too few data on the adverse reactions of remdesivir used in humans, and more phase 3 clinical trials are needed to further explore the effectiveness and safety of remdesivir.

2.3. Chloroquine and hydroxychloroquine

CQ and HCQ have closely related chemical structures and are used in the prevention and treatment of malaria and autoimmune disorders such as rheumatoid arthritis and systemic lupus erythematosus (Ben-Zvi et al., 2012; Zhou et al., 2020). CQ interferes with the virus life cycle, inhibiting the virus at different stages (entry, uncoating, assembly, and release) (Romanelli et al., 2004; Savarino et al., 2003, 2006; Yan et al., 2013). CQ and HCQ can also effectively control the life activities of viruses by interfering with ACE2 glycosylation, increasing endosomal pH, and preventing degradation of lysosomal proteins (Hashem et al., 2020; Zhou et al., 2020). And CQ was reported to inhibit SARS-CoV-2 infection effectively in vitro (Wang et al., 2020b).

Owing to the antiviral effects of CQ and HCQ mentioned above, they have garnered considerable attention for their potential to treat COVID-19 (Zhou et al., 2020). An early clinical study in China reported that clinical improvement was observed in more than 100 COVID-19 cases with CQ treatment, manifested in improving radiological performance, enhancing virus clearance, and shortening the clinical course (Gao et al., 2020). However, the summary report did not publish data supporting these findings, provide clinical information including the severity and prognosis of the disease, or provide statistical analysis (Gao et al., 2020). Another study from China showed that HCQ did not improve the virus clearance rate of mild COVID-19 patients, nor did it improve clinical manifestations, including fever time and lung imaging changes (Chen

Table 2
Clinical studies of remdesivir for COVID-19.

Source	Study design	Results	Adverse Events	Prognosis	Time to recovery
Grein et al.	Remdesivir was administered to 61 confirmed COVID-19 patients; 200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days.	53 cases were available for analysis. During the 18-day median follow-up, 36 patients (68%) had improved oxygen support levels. 25 patients (47%) were discharged and 7 patients (13%) died. Among patients receiving invasive ventilation, the mortality rate was 18% (6/34), and 5% of patients not receiving invasive ventilation (1/19)	32 patients (60%) reported adverse events during follow-up. The most common adverse events were increased hepatic enzymes, diarrhea, rash, renal impairment, and hypotension.	Improved	No report
Wang et al.	A randomized, double-blind, placebo-controlled, multicentre trial; 237 patients were enrolled and randomly assigned to a treatment group (158 to remdesivir and 79 to placebo)	Remdesivir use was not associated with a difference in time to clinical improvement (HR 1.23 [95% CI 0.87–1.75]). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (HR 1.52 [0.95–2.43]).	The most common adverse events in the remdesivir group were constipation, hypoalbuminemia, hypokalemia, anemia, thrombocytopenia, and increased total bilirubin.	No improvement	Improved
Beigel et al.	A double-blind, randomized, placebo-controlled trial; 1059 patients were randomly assigned to a treatment group (538 assigned to remdesivir and 521 to placebo).	Patients who received remdesivir had a median recovery time of 11 days (95% CI, 9–12), as compared with 15 days (95% CI, 13–19) in those who received placebo (rate ratio for recovery, 1.32, [95% CI, 1.12–1.55] $P < 0.001$). The mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (HR for death, 0.70, [95% CI, 0.47–1.04]).	Serious respiratory failure (5.2% in remdesivir group vs 8.0% in placebo group); anemia or decreased hemoglobin (79% vs 9.0%) in the placebo group); acute kidney injury (7.4% vs 7.3%); pyrexia (5.0% vs3.3%); hyperglycemia or increased blood glucose level (4.1% vs 3.3%); and increased aminotransferase levels (4.1% vs5.9%).	No improvement	Improved
Gilead	An open-label, Phase 3 SIMPLE trial; The study randomized 397 patients in a 1:1 ratio to receive remdesivir 200 mg on the first day, followed by remdesivir 100 mg each day until day 5 or 10, administered intravenously, in addition to standard of care.	Patients receiving a 10-day treatment course of remdesivir achieved similar improvement in clinical status compared with those taking a 5-day treatment course (Odds Ratio, 0.75 [95% CI 0.51–1.12] on Day 14).	Nausea (9.3%), acute respiratory failure (8.3%), and elevated liver enzymes (ALT) (7.3%)	No report	No report

Abbreviation: HR, hazard ratio; CI, confidence interval; ALT, alanine aminotransferase.

et al., 2020). Compared with lopinavir/ritonavir, CQ can more effectively shorten the time of virus clearance, accelerate the improvement of lung function, and cause early recovery and discharge (Huang et al., 2020b). Another nonrandomized, open-label study from France indicated that HCQ treatment is significantly associated with viral load reduction or elimination of COVID-19 patients (Gautret et al., 2020). Although these three studies have limitations in research methods, they provide early support for the clinical application of CQ and HCQ for COVID-19.

However, the completion of three recent clinical studies has helped clarify the relationship between HCQ and COVID-19. In a retrospective study, Rosenberg et al. suggested that among patients hospitalized for COVID-19 in New York, treatment with HCQ, azithromycin, or both was not significantly associated with differences in in-hospital mortality rates when compared with cases subjected to neither treatment (Rosenberg et al., 2020). A clinical trial (ChiCTR2000029868) from China showed that compared with standard care, HCQ treatment did not improve the rate of negative conversion in mild and moderate COVID-19 patients (Tang et al., 2020). Another clinical trial from France suggested that HCQ cannot improve the rate of survival without transfer to intensive care unit to improve the oxygen demand on day 21 (Mahévas et al., 2020). This study did not provide support for the application of HCQ in COVID-19 patients who were admitted to the hospital and in need of oxygen (Mahévas et al., 2020). In another observational study involving hospitalized COVID-19 patients, the administration of HCQ was not associated with a greatly reduced or increased risk of the composite end point of intubation or death (Geleris et al., 2020). These four studies reach a common conclusion that HCQ does not improve the prognosis of COVID-19 patients (Table 3).

However, a recent multicenter prospective observational study from China suggested that patients treated with CQ had a shorter time of virus clearance than patients without CQ (Huang et al., 2020a). No serious adverse events were observed in the CQ group (Huang et al., 2020a). Researchers believe that this study provides evidence for the safety and efficacy of CQ in COVID-19, but randomized controlled trials (RCTs) are needed for further evaluation. Therefore, the conclusion of this study was contrary to previous reports and triggered the controversy over the effectiveness of CQ and HCQ once again. To determine the reason for the different outcomes of CQ and HCQ, we compared the above two clinical trials completed in China, and found that the different experimental designs of the two studies may have led to the different conclusions (Huang et al., 2020a; Tang et al., 2020). First, the two studies enrolled different participants. Tang included patients with severe COVID-19, while Huang included mainly patients with mild and moderate COVID-19. Second, the outcome measures of the two experiments were different. Tang defined the proportion of SARS-CoV-2 negative conversion by 28 days as the outcome measure, while Huang defined the virus removal time as the main end event and the proportion of patients with undetectable viral RNA by day 10 and 14 as the secondary end event. We cannot evaluate which trial design is more reasonable; however, currently the clinical application of CQ and HCQ remains controversial. In addition, the number of patients included in previous studies was relatively small. Large-scale clinical trials are needed for further research (Table 3).

Although there are still controversies in CQ-related clinical studies, the latest published cell experiment results suggested that CQ cannot effectively protect against the spread of SARS-CoV-2 in and between patients (Hoffmann et al., 2020b). The conclusion of this study is diametrically opposed to the results of previous study in vitro, which are the theoretical basis for subsequent clinical studies of CQ or HCQ (Wang

Table 3
Clinical studies of CQ and HCQ for COVID-19.

Source	Study design and participants	Results	Adverse Events	Prognosis	Time to recovery
Chen et al.	A randomized controlled trial; 30 patients were randomly divided into HCQ group (HCQ 400 mg for 5 days and received conventional treatment) and control (conventional treatment) according to 1: 1 ratio.	Nucleic acid of throat swabs was negative in 13 (86.7%) cases in the HCQ group and 14 (93.3%) cases in the control group on day 7 ($P > 0.05$). The median duration from hospitalization to virus nucleic acid negative conservation was 4 (1–9) days in HCQ group, which is comparable to that in the control group [2 (1–4) days, $P > 0.05$].	Four cases (26.7%) of the HCQ group and 3 cases (20%) of the control group had transient diarrhea and abnormal liver function	No improvement	No improvement
Huang et al.	A randomized controlled trial; 22 patients were randomly divided into CQ group (CQ 500 mg for 10 days) and LPV/r group (LPV/r 400 mg for 10 days)	Compared with LPV/r, CQ can more effectively shorten the time of virus clearance, accelerate the improvement of lung function, and recover and discharge earlier	Vomiting, abdominal pain, nausea, diarrhea, rash or itchy, cough, and shortness of breath	Improved	Improved
Gautret et al.	an open-label non-randomized clinical trial; 36 patients (20 HCQ-treated patients and 16 control patients) were enrolled.	A significant reduction of the viral carriage was found in HCQ group at D6-post inclusion compared to control group. HCQ group had much lower average carrying duration than control group.	No report	Improved	Improved
Rosenberg at al.	a retrospective multicenter cohort study; 1438 confirmed patients were divided into four groups, receipt of both HCQ and azithromycin, HCQ alone, azithromycin alone, or neither.	Compared with patients receiving neither drug, there were no significant differences in mortality for patients receiving HCQ + azithromycin [HR, 1.35 (0.76–2.40)], HCQ alone [HR, 1.08 (0.63–1.85)], or azithromycin alone [HR, 0.56 (0.26–1.21)].	Cardiac arrest; abnormal electrocardiogram findings	No improvement	No improvement
Tang et al.	A multicenter, open label, randomized controlled trial.150 confirmed patients were included in the intention to treat analysis (75 patients assigned to HCQ plus standard of care, 75 to standard of care alone).	The probability of negative conversion by 28 days in the standard of care plus HCQ group was 85.4% (73.8%–93.8%), similar to that in the standard of care group [81.3% (71.2%–89.6%)].	Adverse events were recorded in 7/80 (9%) HCQ non-recipients and in 21/70 (30%) HCQ recipients. The most common adverse event in the HCQ recipients was diarrhea, reported in 7/70 (10%) patients.	No improvement	No improvement
Mahévas et al.	Comparative observational study; 181 patients aged 18–80 years with SARS-CoV-2 pneumonia who required oxygen but not intensive care.	The survival rate without transfer to the intensive care unit at day 21 was 76% in the treatment group and 75% in the control group [HR 0.9 (0.4–2.1)]. Overall survival at day 21 was 89% in the treatment group and 91% in the control group [1.2 (0.4–3.3)]. Survival without acute respiratory distress syndrome at day 21 was 69% in the treatment group compared with 74% in the control group [1.3 (0.7–2.6)].	Electrocardiographic modifications; QT interval prolongation	No improvement	No improvement
Geleris et al.	Comparative observational study; 1446 patients hospitalized with Covid-19.	Hydroxychloroquine-treated patients were more severely ill at baseline than those who did not receive hydroxychloroquine. In the main analysis, there was no significant association between hydroxychloroquine use and intubation or death [HR 1.04, (0.82–1.32)]. Results were similar in multiple sensitivity analyses.	No report	No improvement	No report
Huang et al.	A multicenter prospective observational study; 197 patients completed CQ treatment, and 176 patients were included as historical controls.	The median time to achieve an undetectable viral RNA was shorter in CQ than in non-CQ [absolute difference in medians −6 (−6 to −4) days]. The duration of fever is shorter in CQ [geometric mean ratio 0.6 (0.5–0.8)].	No report	No report	Improved

Abbreviation: CQ, chloroquine; HCQ, hydroxychloroquine; LPV/r, lopinavir/ritonavir; HR, hazard ratio; CI, confidence interval.

et al., 2020b). The cell type used in two cell experiments may be one of the reasons for the difference. The cells used in the previous study were the African green monkey kidney cell line (Vero E6 Cells). There must be some differences between these cells and human lung epithelial cells. In recent study, German scientists discovered that the TMPRSS2 protease, which is essential for SARS-CoV-2 infection, exists in human lung epithelial cells instead of Vero cells (Hoffmann et al., 2020b). Previously, they discovered that the activation of SARS-CoV-2 spike protein by TMPRSS2 protease is the prerequisite for SARS-CoV-2 to bind to ACE2 and invade human cells (Hoffmann et al., 2020a). Researchers found that if Vero cells express TMPRSS2 protease, the effect of CQ on inhibiting SARS-CoV-2 from invading cells almost disappears. They also verified in the human Calu-3 lung cell line that highly expresses TMPRSS2 and found that CQ cannot protect lung cells against SARS-CoV-2 infection (Hoffmann et al., 2020b). Further experiments have shown that cathepsin L (CatL) in Vero cells can process spike protein, which is similar to TMPRSS2. CQ affects the intracellular pH, inhibits the function of CatL, and indirectly prevents the invasion of SARS-CoV-2, which can explain the protective effect of CQ on Vero cells in the previous study (Hoffmann et al., 2020b; Rolain et al., 2007). These results suggested that CQ does not exert anti-SARS-CoV-2 effects in the lung. The research team also pointed out that it is very important to

select cell lines that are closer to respiratory epithelial cells in cell experiments.

In another study, French scientists also found that the antiviral effect of HCQ in Vero cells cannot be transformed into reconstructed human respiratory epithelial cells that are closer to the real situation of the human body (Maisonnasse et al., 2020). They used primate experimental animals to further explore the effectiveness of HCQ against SARS-CoV-2 infection. In order to comprehensively evaluate the effects of HCQ, the researchers designed five different medication regimens, including high-dose/low-dose medication of HCQ started one day after SARS-CoV-2 exposure, low-dose medication started 5 days after exposure, and simultaneous use of HCQ + azithromycin started 1 day after exposure, and preventive medication before exposure. However, regardless of the medication regimen and timing of use, HCQ failed to reduce the viral load in the cynomolgus monkeys, nor did it improve clinical symptoms or prevent viral infections (Maisonnasse et al., 2020). These results indicate that CQ and HCQ cannot effectively treat and prevent COVID-19.

At the beginning of the pandemic, CQ and HCQ were used to prevent SARS-CoV-2 infection by some people. However, recent evidence showed that HCQ cannot reduce the rate of confirmed infection after exposure to Covid-19, suggesting that there is no effective preventive effect of HCQ (Boulware et al., 2020). In the current COVID-19 pandemic, isolation, quarantine, social distancing, and community containment appear to be the only preventive measures that have proven to be effective (Wilder-Smith and Freedman, 2020). Furthermore, the use of CQ and HCQ will cause some patients to suffer from rare but potential side effects, including severe skin reactions (Murphy and Carmichael, 2001), fulminant liver failure (Makin et al., 1994), and ventricular arrhythmias (especially when prescribed with azithromycin) (Mercuro et al., 2020; Saleh et al., 2020). Moreover, an overdose is dangerous and difficult to treat (Gunja et al., 2009). The clinical efficacy of CQ and HCQ in the treatment of COVID-19 still remains controversial. The results of cell and animal experiments further indicate that CQ cannot effectively treat and prevent COVID-19. Recently, FDA revoked the emergency use authorization for CQ and HCQ in COVID-19 due to lack of evidence to prove the efficacy, and the serious adverse reactions (Fischer et al., 2020). In addition, the WHO and other authoritative organizations have stopped clinical researches on CQ/HCQ in the treatment of COVID-19. The clinical usage of CQ and HCQ in COVID-19 is now not suggested.

2.4. Lopinavir/ritonavir

Lopinavir is a human immunodeficiency virus 1 (HIV-1) protease inhibitor approved by FDA. Lopinavir is mainly eliminated in the intestine and liver through CYP3A4 (the main enzyme involved in the metabolism of most protease inhibitors) (Kappelhoff et al., 2004). Ritonavir is an effective CYP3A4 inhibitor, which forms the basis for the enhancement of lopinavir administered at the same time (Hsu et al., 1998). Ritonavir can increase the plasma concentration of lopinavir by improving its bioavailability or increasing its elimination half-life in plasma (Hill et al., 2009). Therefore, lopinavir is recommended to be used in combination with ritonavir (Hammer et al., 2008). Early reports had different opinions on LPV/r for COVID-19 treatment. Ye et al. reported that compared with the control group, LPV/r can effectively reduce body temperature and restore normal physiological function, with no obvious toxicity and side effects (Ye et al., 2020). However, another study showed that LPV/r did not promote the negative conversion or clinical improvement of COVID-19 patients (Wen et al., 2020). A recent randomized, controlled, open-label trial showed that the time to clinical improvement, 28-day mortality rates, and virus negative conversion of patients with LPV/r treatment was not different from that with the standard treatment (Cao et al., 2020). This study suggested that LPV/r treatment cannot improve the clinical condition and prognosis of COVID-19 (Table 4).

Table 4
Clinical Studies of LPV/r, arbidol, IFN, ribavirin and FPV for COVID-19.

Source	Study design and participants	Interventions	Findings
Ye et al.	A retrospective single-center cohort study; 47 confirmed patients were divided into the test group and the control group according to whether they had been treated with LPV/r or not during hospitalization.	LPV/r	Compared with the treatment of pneumonia-associated adjuvant drugs alone, the combination treatment with LPV/r and adjuvant drugs has a more evident therapeutic effect in lowering the body temperature and restoring normal physiological mechanisms with no evident toxic and side effects.
Wen et al.	A retrospective single-center cohort study; 178 patients were divided into 4 groups including LPV/r group (59 patients), arbidol group (36 patients), combination therapy with LPV/r plus arbidol group (25 patients) and the conventional treatment group without any antiviral drugs (58 patients).	LPV/r, arbidol	No evidences could prove that LPV/r and arbidol could shorten the negative conversion time of novel coronavirus nucleic acid in pharyngeal swab nor improve the symptoms of patients.
Cao et al.	A randomized, controlled, open-label trial; 199 confirmed cases; 99 were assigned to the LPV/r group, and 100 to the standard-care group.	LPV/r	Treatment with LPV/r was not associated with a difference from standard care in the time to clinical improvement (HR 1.31, 95% CI [0.95–1.80]), Mortality at 28 days, and the percentages of patients with detectable viral RNA at various time points.
Yuan et al.	A retrospective single-center study; 94 discharged patients with COVID-19 infection	IFN-α, LPV/r, ribavirin	Therapeutic regimens of IFN-α + LPV/r and IFN-α + LPV/r + ribavirin might be beneficial for treatment of COVID-19.
Hung et al.	An open-label, randomized, phase 2 trial; 127 patients were randomly assigned (2:1) to a 14-day combination of lopinavir/ritonavir, ribavirin, IFN-β1b (combination group) or to 14 days of lopinavir/ritonavir (control group).	IFN-β1b, LPV/r, and ribavirin	The combination group had a significantly shorter median time from start of study treatment to negative nasopharyngeal swab (median 7 [5–11] d) vs control group (12 [8–15] d; HR 4.37, 95% CI [1.86–10.24], p = 0.001).
Zhu et al.	A retrospective single-center cohort study; 50 confirmed cases were divided into two groups: LPV/r group (34 cases) and arbidol group (16 cases).	LPV/r , arbidol	On day 14 after the admission, more patients treated with LPV/r had viral load than patients in arbidol group. Patients in the arbidol group had a shorter duration of positive RNA test compared to those in the LPV/r group (P < 0.01)
Deng et al.	A retrospective cohort study; 16 patients given oral arbidol and LPV/r in the combination group and 17 LPV/r only in the monotherapy group for 5–21 days.	LPV/r , arbidol	Combination of LPV/r and abidol can shorten the time to achieve an undetectable viral RNA and improve pneumonia imaging performance.

(*continued on next page*)

Table 4 (*continued*)

Source	Study design and participants	Interventions	Findings
Xu et al.	A multicenter retrospective cohort study; 141 adults were included. Combined group patients were given Arbidol and IFN-α2b, monotherapy group patients inhaled IFN-α2b for 10–14 days.	Arbidol, IFN-α2b	The duration of viral RNA of respiratory tract in the monotherapy group was not longer than that in the combined therapy group. The absorption of pneumonia in the combined group was faster than that in the monotherapy group.
Lian et al.	A retrospective study; 81 COVID-19 patients were included, with 45 in the umifenovir group and 36 in the control group.	umifenovir	The median time from onset of symptoms to SARS-CoV-2 turning negative was 18 ([IQR] 12–21) d in the umifenovir group and 16 (11–21) d in the control group. Patients in the umifenovir group had a longer hospital stay than patients in the control group (13 [9–17] vs 11 [9–14] d).
Cai et al.	An open-label control study; 35 patients enrolled in the favipiravir arm and the 45 patients in the LPV/r arm.	FPV, LPV/r	A shorter viral clearance time was found for the FPV arm versus the control arm (median [IQR], 4 [2.5–9] vs 11 [8–13] d, $P < 0.001$). The FPV arm also showed significant improvement in chest imaging compared with the control arm, with an improvement rate of 91.43% vs 62.22% ($P = 0.004$).

Abbreviation: LPV/r, lopinavir/ritonavir; HR, hazard ratio; CI, confidence interval; IFN, interferon; FPV, favipiravir.

Although there was no clear evidence supporting the treatment with LPV/r for COVID-19, abandoning the use of LPV/r is considered a premature action. We cannot ignore the significantly reduced time to clinical improvement in patient with LPV/r, although no statistical difference was found (Dalerba, 2020). LPV/r is still the current recommended antiviral treatment in countries such as China (2020). However, when using LPV/r, adverse effects including nausea, diarrhea, and hepatotoxicity should be considered (Cao et al., 2020; Young et al., 2020). Liver dysfunction was also reported in patients treated with LPV/r (Wu et al., 2020a). The application conditions and methods of LPV/r require more researches and guidance.

2.5. Ribavirin

Ribavirin is usually used to treat virus infection like hepatitis C virus via inhibition of the replication viruses (Crotty et al., 2002). Ribavirin can also enhance the antiviral response of the immune system to indirectly exert antiviral properties (Hultgren et al., 1998). Its activity against other coronaviruses showed its potential in treating COVID-19 (Ferron et al., 2018). A retrospective study suggested that treatment with IFN-α + LPV/r + ribavirin might be beneficial for COVID-19 patients (Yuan et al., 2020). A recently terminated clinical trial (NCT04276688) reported that the group treated with combined IFN-1b, LPV/r, and ribavirin had a significantly shorter time to negative conversion than the control group treated with LPV/r (Hung et al., 2020). The efficacy and safety of early triple antiviral therapy were significantly better than LPV/r alone. Ribavirin is recommended in the latest diagnosis and treatment plan for COVID-19 in China (Authority, 2020). Clinical data on the therapeutic role of ribavirin in SARS-CoV-2 need to be studied further. However, adverse effects, including hemolytic anemia (Stockman et al., 2006), hypocalcemia (Knowles et al., 2003), hypomagnesemia (Knowles et al., 2003) and transaminase elevations (Stockman et al., 2006)should be taken seriously (Table 4).

2.6. Arbidol

Arbidol, also known as umifenovir, is another antiviral agent that exerts antiviral effect by inhibiting spike protein/ACE2 binding and inhibiting viral envelope fusion (Blaising et al., 2014; Kadam and Wilson, 2017). Early studies reported that arbidol treatment showed a tendency to improve the discharge rate and decrease the mortality rate of COVID-19 patients (Wang et al., 2020d; Wang et al., 2020e). But they cannot support the effectiveness of arbidol. Recently, a retrospective study showed that arbidol administration may be superior to LPV/r in COVID-19 treatment (Zhu et al., 2020b). Another retrospective study suggested that combination therapy with LPV/r and arbidol may be more helpful (Deng et al., 2020). In addition, arbidol/IFN-2b therapy was suggested to be an effective method to improve COVID-19 pneumonia in mild patients, although it does not accelerate virus clearance (Xu et al., 2020). However, there is a different opinion about treatment with arbidol. Arbidol was reported to have nothing to do with the prognosis or virus clearance of COVID-19 patients (Lian et al., 2020; Wen et al., 2020). The different results may be because the above studies were all retrospective studies, the inclusion and exclusion criteria of patients were different, the number of patients was small, and the observation indicators were different. Currently, the improvement by arbidol still has no clear proof, and further study is warranted (Table 4).

2.7. Interferon

Interferons are cytokines with spectral antiviral properties (de Weerd et al., 2007). Early retrospective studies found that IFN-α + LPV/r + ribavirin might be beneficial for the treatment of COVID-19 (Yuan et al., 2020). A recent clinical trial reported that COVID-19 patients receiving treatment of combined IFN-1b, LPV/r, and ribavirin had a shorter time to clinical improvement and negative conversion than patients with LPV/r treatment alone (Hung et al., 2020). This report may support the recommendation of IFN as an alternative to combination therapy in Chinese guidelines (Authority, 2020). Multiple antiviral therapy based on IFN is worthy of further study to find a more appropriate treatment strategy. In addition, when applying interferon, it is also important to consider adverse reactions, including flu-like symptoms, leukopenia, lymphopenia, autoimmune hepatitis, and thyroid disease (Sulkowski et al., 2011). (Table 4)

2.8. Favipiravir

Favipiravir (FPV), is an antiviral compound that selectively and potently inhibits the RdRP of influenza and many other RNA viruses (Furuta et al., 2013). Clinical data to support the use of FPV for COVID-19 are limited. In an open-label controlled study, enrolled patients were divided into the FPV arm and LPV/r arm. A short time to viral clearance and more clinical improvement were achieved in FPV arm versus the LPV/r arm (Cai et al., 2020). This study showed an improved prognosis in COVID-19 patients treated with FPV. These data support further investigation with RCTs on the efficacy and safety of FPV for the treatment of COVID-19. In addition, adverse effects of FPV, including diarrhea and liver injury should be given more attention (Cai et al., 2020). (Table 4)

2.9. Other potential antiviral drugs

Oseltamivir, a neuraminidase inhibitor used for the treatment of influenza, is also being studied for the treatment of COVID-19 (Ding

et al., 2020). It has been reported to have the putative inhibitory potential for SARS-CoV-2 (Adeoye et al., 2020). Case reports showed an improved prognosis in COVID-19 patients treated with oseltamivir (Ghiasvand et al., 2020; Xiong et al., 2020). However, the efficacy of oseltamivir for the treatment of COVID-19 needs further investigation in RCTs.

Nitazoxanide is a broad-spectrum antiviral agent used for the treatment of influenza and other viral respiratory infections (Rossignol, 2014). It is currently recommended as a treatment for COVID-19 (Kelleni, 2020). However, the efficacy and safety of nitazoxanide for SARS-CoV-2 are yet to be proven by further studies.

Nelfinavir is an anti-HIV protease inhibitor and has been reported to strongly inhibit SARS-CoV-1 replication and cell culture cytopathic effects in vitro (Pai and Nahata, 1999; Yamamoto et al., 2004). Owing to the performance of nelfinavir in SARS, researchers have considered exploring its effect on COVID-19. A recent study showed that nelfinavir inhibits SARS-CoV-2 spike-mediated cell fusion, which is projected to be an important determinant of SARS-CoV-2 infectivity, spread, and pathogenicity (Musarrat et al., 2020). There are no clinical data regarding the efficacy of nelfinavir treatment for SARS or COVID-19.

Camostat mesylate is a protease inhibitor used to treat pancreatitis in Japan (Ikeda et al., 1988). Camostat mesylate effectively protected mice from death after fatal SARS-CoV-1 infection with a survival rate of 60% (Zhou et al., 2015). Camostat mesylate was also reported to inhibit TMPRSS2-dependent host cell entry by MERS-CoV (Yamamoto et al., 2016). Recent studies show that camostat mesylate prevents SARS-CoV-2 spike protein-mediated entry into primary human lung cells (Hoffmann et al., 2020a). Camostat mesylate might block the activation of SARS-CoV-2, which could provide a new treatment option for COVID-19 (Hoffmann et al., 2020c).

3. Discussion

COVID-19 has become a huge global health threat, and hundreds of related clinical studies and drug experiments have been reported. Reviewing the investigation processes of anti-SARS-CoV-2 drugs, we found that most of the drugs currently in use are drugs that have proven to be effective or have potential therapeutic value in other viral infections such as SARS and MERS. On the one hand, SARS-CoV and SARS-CoV-2 have homology and have similar structures and life activities. Antiviral drugs that are effective against SARS-CoV may be the most potential drugs for the treatment of COVID-19, such as arbidol and nelfinavir that inhibit the combination of spike protein and the ACE2 receptor. On the other hand, some broad-spectrum antiviral drugs are also worthy of attention, such as remdesivir and IFN. And some drugs which have been approved to treat other viral infections have inhibitory effects on the non-structural proteins of SARS-CoV-2, such as 3-chymotrypsin-like protease, papain-like protease, helicase, and RdRp. Reseachers reconsidered them for the treatment of COVID-19, such as LPV and Ribavirin.

Although no effective drugs and vaccines have been found for COVID-19, some clinical studies have provided a reference for the clinical treatment of patients, which helps patients recover quickly, such as remdesivir (Beigel et al., 2020). A small number of antiviral treatments have been proven effective in rigorous clinical trials, such as the triple combination of IFN-1b, LPV/r, and ribavirin (Hung et al., 2020). There are also some controversies about the efficacy of some drugs, such as CQ and HCQ, as treatment for COVID-19 (Huang et al., 2020a; Rosenberg et al., 2020). More clinical researches are needed to further explore the effectiveness and safety of antiviral treatments for COVID-19.

Recalling the current reports related to antiviral treatments for COVID-19, several drug studies have reported controversial conclusions, such as remdesivir, CQ, and arbidol. Our further analysis of the research methods of these reports revealed that there were many reasons for the different research results. Considering the two currently published RCTs on remdesivir, there is no doubt that both clinical studies were well designed and the trials were performed well, but the difference in the number of patients, inclusion criteria, and evaluation indicators led to different results (Beigel et al., 2020; Wang et al., 2020c). First, due to the timely control of the pandemic in China, the number of patients enrolled in China's research was insufficient, and the research did not reach the preset sample size, resulting in insufficient statistical power. Second, the two studies are essentially different because of the differences in evaluation indicators. For example, the American study included hospitalization as one of the rehabilitation standards without oxygen inhalation, but this standard did not apply to China. Different outcome evaluations may lead to different conclusions. Third, in terms of enrollment criteria, the Chinese trial required enrolled patients to have symptoms within 12 days and not to have received other experimental drug treatments within 30 days, but the US trial did not require this. The research on CQ and HCQ suffers from the same problems (Huang et al., 2020a; Tang et al., 2020). At the same time, we noticed problems in the design of some studies. For example, in a retrospective study on arbidol (Zhu et al., 2020b), patients were divided into the arbidol and control groups based only on drug history, and there was no good exclusion. The standard ignores the influence of other factors on the results, and the accuracy of the results of such studies is questionable.

Considering the current global pandemic of COVID-19 and the shortage of drugs to effectively treat COVID-19, we believe that accelerated clinical trials should be conducted; however, this does not imply that low-quality clinical research is allowed. It is suggested that the overall methodological quality of COVID-19 research is very low (Alexander et al., 2020). For example, we examined the results of the HCQ clinical trial, and results showed that the quality of the test was very low (Alexander et al., 2020). In another article, Dr. West reported that low-quality papers related to COVID-19 have become a reference for government decision-makers (London and Kimmelman, 2020). Dr. West urged researchers around the world not to use the urgency of the current COVID-19 outbreak as a reason to lower their research standards in virus research and vaccine development (London and Kimmelman, 2020). Clinical decision-makers must obtain evidence that is reliable and of the highest quality. Defective methods and sub-optimal reports of research results may lead to biased estimates of effectiveness. This may result in treatment decisions with biased estimates that are not optimal and may even harm the patient. Therefore, clinical trials of COVID-19 should seek the best COVID-19 treatment with high-quality methods.

4. Conclusion

Remdesivir is currently the most potential antiviral drug for the treatment of COVID-19. Triple combination of IFN-1b, LPV/r, and ribavirin was confirmed to be more effective. CQ and HCQ are not recommended for the treatment of COVID-19. The efficacy and safety of other antiviral treatments still have controversy and require more high-quality clinical trials.

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CRediT authorship contribution statement

Mengmeng Zhao: Writing - original draft, participated in the design of the project. **Jishou Zhang:** Writing - original draft. **Hanli Li:** Writing - original draft. **Zhen Luo:** Writing - original draft. **Jing Ye:** helped collect relevant literature. **Yao Xu:** helped collect relevant literature. **Zhen Wang:** helped collect relevant literature. **Di Ye:** helped collect relevant literature. **Jianfang Liu:** helped collect relevant literature. **Dan Li:** helped collect relevant literature. **Menglong Wang:** participated in the design of the project. **Jun Wan:** participated in the design of the project.

Author contribution

JW, MLW and MMZ participated in the design of the project. JY, YX, ZW, DY, JFL and DL helped collect relevant literature. MMZ, JSZ, HLL and ZL were responsible for drafting of the manuscript.

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