



Review Article

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Clinical Management of COVID-19: Pharmacotherapeutic Options

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To Cite This Article: Yiran E. Li, Yuqi Luo, and Jun Ren*. Clinical Management of COVID-19: Pharmacotherapeutic Options. Am J Biomed Sci & Res. 2025 26(1) AJBSR.MS.ID.003391, DOI: 10.34297/AJBSR.2025.26.003391

Received: 📅 February 19, 2025; **Published:** 📅 February 25, 2025

Abstract

First reported and identified in Wuhan, China, the SARS-CoV-2 infection immediately spread throughout the world, claiming more than 580 million infections and over 6.42 million deaths. Given the severity of this pandemic, scientists and physicians are strived to develop antiviral strategies to combat this disease. Vaccines, such as inactivated vaccines, nucleic acid-based vaccines, and vector vaccines, have already entered clinical trials. Although vaccines serve as a vital public health tool to lower the COVID-19 burden, management of this disease will still heavily depend on pharmacotherapy. Several specific FDA-approved therapeutics have already been repurposed for COVID-19 treatment, including antiviral drugs, immunotherapy, and traditional Chinese medicine. This review will systemically discuss on the efficacy of these medications drugs comprising clinical trials, combination therapies, other treatment strategy and future drug development. Currently, the efficacy and safety of COVID-19 drugs must be closely monitored, as their long-term efficacy can only be recognized after several years of clinical trials.

Introduction

SARS-CoV-2, classified as a beta coronavirus, is an enveloped, sizable virus with a single-stranded RNA genome, exhibiting genomic plasticity owing to its high mutation rate, genetic diversity, and adaptability to multiple hosts [1]. It is estimated that the main route of transmission of SARS-CoV-2 is infection by respiratory droplets via aerosol contact, Contaminated surfaces are also a route of infection because all three structural proteins (E, M and S) play a vital role in the replication cycle of SARS-CoV-2, with infection initiated when the spiked glycoprotein binds to human angiotensin-converting enzyme 2 [2].

Featuring variable clinical severity, the clinical image of SARS-CoV-2 infection ranges from asymptomatic to acute respiratory distress syndrome (ARDS), even death [3]. Propelled by clinical evidence, dysregulated and excessive proinflammatory cytokines result in ARDS, which is common in severe cases in health deterioration [4].

For therapeutics and management of SARS-CoV-2 infection, three vaccines are used in the clinics including two mRNA vaccines and the Janssen viral vector vaccine. In the meantime, pharmacotherapy constitutes a significant component to alleviate disease burden. Therefore, this review is aimed to offer some insights to

wards the pharmacotherapy being evaluated, repurposed or newly developed in the management of COVID-19.

Antiviral Drugs for the Fight against COVID-19

Reverse Transcriptase Inhibitors: Targeting RNA-Dependent RNA Polymerase

SARS-CoV-2 is an RNA-positive-sense virus to translate its genome upon entrance into cells using the host ribosomes [5]. Therefore, reverse transcriptase inhibitors are drawn great attention in the combat against COVID-19 infection, including remdesivir, favipiravir, ribavirin, tenofovir, molnupiravir and galidesivir. These drugs are summarized in Table 1 to distinguish their feature and mechanism.

Lemdecivir, also known as GS-5734, is an adenosine analogue with wide-ranging antiviral capabilities targeting RNA viruses [6]. It is a prodrug necessitating metabolic conversion within host cells to its active form, GS-441524, disrupting viral RNA-dependent RNA polymerase, delays strand termination and inhibits RNA synthesis and viral replication [5]. Remdesivir is known to lower viral load, restrain SAR-CoV-associated pulmonary pathology and slow down deteriorated pulmonary function [7]. Since remdesivir may restrain viral replication in SARS-CoV, remdesivir treatment is suggested to inhibit viral replication, and prevent pulmonary pathology [6]. Limitations of clinical application of remdesivir are mainly due to the inability of animal models to fully mimic human pharmacokinetics and metabolic toxicity due to excessive hydrolysis or impaired hepatic function. Given the mechanism of remdesivir as an antiviral agent to stop viral replication, it can be assumed that remdesivir plays an important role in the early active phase of viral replication in PCR-positive patients with COVID-19 [8].

Favipiravir is a drug with mechanism of action reminiscent of remdesivir [9]. Common side effects shown in clinical trials include: increased blood uric acid, diarrhoea, neutropenia. However, Favipiravir exhibits advantageous profile over remdesivir such as oral administration [10], making it a choice for hospital treatment for symptomatic patients who are not critically ill [11]. Given that a large portion of COVID-19 cases suffer from mild to moderate accompanying diseases, this medication can be used for home care in multiple cases [8]. In the meantime, Favipiravir is an investigative drug functioning as a RNA polymerase inhibitor to hinder viral replication [12]. Its effectiveness and safety profile have predominantly been established through preclinical studies involving influenza and Ebola virus disease [13]. Based on available clinical profile, favipiravir did not overtly promote the clinical cure rate on day 7 [14]. Recovery of viable virus was related to age, male sex, and viral load, but not to favipiravir treatment [13]. Moreover, there was no significant difference in the need for supplemental oxygen or non-invasive mechanical ventilation. However, the duration of fever and cough was significantly shorter in patients treated with favipiravir [15].

Ribavirin has broad-spectrum RNA antiviral properties and is a guanosine analogue used to treat viral diseases, including respiratory syncytial virus, hepatitis C virus and some haemorrhagic viruses [16]. Despite its proven clinical benefit, ribavirin-evoked reduction in hemoglobin is an undesirable detrimental side effect for patients suffering from respiratory failure. In the most extreme cases, ribavirin may cause reproductive toxicity and hemolytic anemia [17]. Other than the dose of 500 mg 2 to 3 times daily by intravenous delivery in adults, it is recommended that ribavirin be used together with interferon with ritonavir/lopinavir [18].

Molnupiravir is the first direct-acting oral antiviral agent that is highly effective in reducing infectious nasopharyngeal viruses and SARS-CoV-2 viral RNA, with favorable safety and tolerability [19]. Molnupiravir can reduce the time required to clear SARS-CoV-2 in nasopharyngeal swabs and is well tolerated in adults with symptomatic SARS-CoV-2 [20]. Furthermore, molnupiravir displayed little rises in serious or treatment-related side effects [21].

Showing a great spectrum of antiviral activities, Galidesivir excels at inhibiting SARS-CoV-2 infection to decrease viral load and improve pulmonary function [22]. It is a unique structure capable of interacting with viral RNA polymerase, resulting in premature termination of the elongated RNA chain [23]. Results from antiviral studies have shown its ability to combine multiple lethal mutations via viral RNA rather than host RNA, resulting in a strong suppression of drug resistance [24].

Protease Inhibitors

Major protease of SARS-CoV-2 has been considered a promising target. Much attention has been given for antiretroviral protease inhibitors with clinical indications, which are concluded in Table 1. Among which, Paxlovid is a combination of nirmatrelvir and ritonavir for emergency use in COVID-19 treatment [25]. It has the advantages of two drugs, with paxlovid proving more effective and reducing the number of hospitalisations or deaths by 89% among patients with mild to severe COVID-19 [26]. Moreover, Paxlovid is able to be taken at home to treat mild illness instead of being used in hospital, which adds hope of preventing progression to more acute disease [27]. However, the use of Paxlovid could be limited because it might interact with a wide range of commonly used medications [28]. Therefore, additional cautions should be taken for COVID-19 patients on multitherapy for comorbidities [29]. Although the efficacy of Paxlovid has been proven, the safety profile of this combination needs to be confirmed in the long term.

Atazanavir stably interferes with the active site of the SARS-CoV-2 central protease and inhibits the enzymatic activity of the SARS-CoV-2 central protease [30]. Furthermore, atazanavir reduces production of proinflammatory cytokine and cell death in SARS-CoV-2-infected monocytes [26]. With documented bioavailability in respiratory tract, atazanavir owns the proposed ability against pulmonary fibrosis [31]. It is revealed that cytokine storm-associated mediators and cellular mortality were decreased following treat-

ment with atazanavir [32]. In clinical applications, Atazanavir is highly regarded for its excellent antiviral activity profile. In cellular findings, it shows greater efficacy in respiratory cells and its ability to reduce the levels of inflammatory mediators in monocytes [33].

Lopinavir treatment failed to robustly accelerate clinical improvement, diminish throat viral RNA detectability, or reduce mortality in hospitalized adult patients with severe COVID-19 [34]. Although there was no significant difference in clinical improvement with lopinavir compared to standard treatment, serious adverse events were less common for lopinavir therapy [35]. Meanwhile, the combination of lopinavir and ribavirin was linked to a lower incidence of ARDS or mortality in patients with SARS [36]. In animal experiments and case reports, lopinavir has been shown to be effective in the treatment of coronavirus caused by Middle East respiratory syndrome [37].

Darunavir was well tolerated in COVID-19 patients with subtle adverse events [38]. It's auspicious anti-proliferative impact against SARS-CoV-2 has been shown in silico studies [39]. Unfortunately, although the SARS-CoV-2 main protease was among the potential targets for darunavir, darunavir failed to be the best docked drug [35]. It is reported that 5 days of darunavir therapy could not

decrease the COVID-19 positive proportion on day 7. It is consistent with preliminary in vitro data showing that darunavir is active at concentrations as low as 300 μ M, which is significantly higher than the level achievable with oral darunavir [40].

Fusion Inhibitors: Targeting Spike Protein

In the presence of fusion inhibitors summarized in Table 1, SARS-CoV-2 spike protein is reduced to prevent the virus from entering the cell, thus inhibiting surface fusion [41]. In vitro studies, Arbidol hydrochloride is a non-nucleoside antiviral drug which not only inhibits a variety of drug targets, but also activates immune system [42]. Through activation of antiviral protein in the host, arbidol specifically reduces contact, adhesion and fusion of viral lipid envelope within host cell membrane, thereby suppressing viral replication in host cells [43]. It was reported that patients exhibited a shorter duration of positive RNA test without detectable viral load during the therapy, validating its potent antiviral effect [44]. With regards to the safety of arbidol, the overall adverse effect is trivial with little discernable side effect in the treatment. Moreover, a retrospective study with 69 enrolled COVID-19 patients revealed that arbidol tended to decrease mortality rate and improve discharging rate [45].

Table 1: Pharmacotherapeutic options that could be used to combat COVID-19.

	Classification	Drug	Feature	Mechanism of action
Antiviral drugs for the fight against COVID-19	Reverse transcriptase inhibitors	Remdesivir	A viral replication inhibitor used in the early viral replication phase	Lower viral load, slow down deteriorated pulmonary function
		Favipiravir	A RNA polymerase inhibitor to hinder viral replication	Oral administration for home care in multiple cases
		Ribavirin	An analog of guanosine with a wide range of RNA antiviral property	Ribavirin-evoked reduction in hemoglobin
		Molnupiravir	An oral and direct-acting antiviral medication	Reduce nasopharyngeal SARS-CoV-2 infectious virus and viral RNA
		Galidesivir	An inhibitor of SARS-CoV-2 infection	Decrease viral load, improve pulmonary function
	Protease inhibitors	Paxlovid	A combination of nirmatrelvir and ritonavir for emergency use	Prevent progression to more acute disease
		Atazanavir	An inhibitor of the SARS-CoV-2 major protease	Own the proposed ability against pulmonary fibrosis
		Lopinavir	An anti-retroviral protease inhibitor	Reduce frequency of acute respiratory distress syndrome or mortality
		Darunavir	An anti-proliferative protease inhibitor	subtle adverse events
	Fusion inhibitors	Arbidol	A non-nucleoside antiviral drug	Inhibit a variety of drug targets, activate immune system
		Camostat mesylate	An inhibitor of serine protease	Block the entry of SARS-CoV-2 into epithelial bronchial cells
The role of immunotherapy in the treatment of COVID-19	Monoclonal antibodies in monotherapy	P2C-1F11	An antibody which mimics binding of receptor angiotensin	Own the highest binding affinity to receptor binding domain

The role of immunotherapy in the treatment of COVID-19	Monoclonal antibodies in monotherapy	CR3022	An antibody derived from a SARS-CoV-infected individual	Confer eradication of infected cells even in the setting of high ACE2 secretion
		LY-CoV555	An anti-spike antibody, potentially neutralizing SARS-CoV-2	Recognize neutralizing human mAbs
	Monoclonal antibodies used in combination	Bamlanivimab and etesevimab	A combination for emergency use	Accelerate decline in SARS-CoV-2 viral load
		Casirvimab and imdevimab	A combination with	Can be administered subcutaneously
			great tolerance in pregnant women	
		BR11-196 and BR11-198	Long-lasting noncompetitive antiviral monoclonal antibodies	Reduce virus binding to the receptor, safe and well tolerated
		AZD7442	A combination of AZD8895 and AZD1061	Form a complex with the receptor binding domain
	Immuno-regulator	Tocilizumab	A recombinant humanized monoclonal antibody	Suppress IL-6 signal transduction
		Corticosteroid	A drug to promote respiratory function	Decrease the immune response
		Anakinra	A recombinant IL-1 receptor antagonist	Reduce CRP levels and overall mortality
Traditional Chinese medicine		Lianhua Qingwen	A capsule composed of 13 Chinese herbs	Improve the symptoms of cough, fever and fatigue
		Xue Bijing	A patented medicinal compound composed of 5 herbal extracts	Improve pneumonia-severity index, shorten the duration of mechanical ventilation
		Huoxiang Zhengqi	A Chinese medicine to improve gastrointestinal function	Remove cold and dampness, enhance cellular immunity
		Jinhua Qinggan	A Chinese medicine to improve inflammatory symptoms	Reduce serum CRP and IFN- γ levels in patients with viral pneumonia
Discovery for potential anti-COVID-19 drugs		Baricitinib	A potential drug with a short half-life	Reduce inflammation while minimize biologic redundancy
		Imatinib	A immunomodulator capable of reducing pro-inflammatory cytokines	Exhibit antiviral properties against other β -coronaviruses in vitro
		Quinadoline B	The most promising metabolite	Dynamic stable binding affinities to SARS-CoV-2 protease
		Cordycepin	A secondary metabolite with a broad range of biological activities	Indicate an additional role in preventing the poly(A)
		Quercetin	An anti-inflammatory agent	High affinity for the active site of 3CLpro
		Pyranonigrin A	A potent inhibitor of the Main protease	Depend on docking and molecular dynamics
Peculiarities of the use of anti-COVID-19 drugs in pregnant women and children		Hydroxychloroquine	An antimalarial agent with anti-inflammatory activities	Improve lung imaging findings, promote a virus-negative conversion
		Tocilizumab	A drug valid for pregnant women	Confined to acute COVID-19 infection cases

Another drug that targets viral synthesis is the serine protease inhibitor camostat mesylate, which has been used to treat patients [46]. Since SARS-CoV-2 reaches the TMPRSS2 receptor on target

cells, camostat mesylate acts as a TMPRSS2 inhibitor, blocking the entry of SARS-CoV-2 into human bronchial epithelial cells [47].

The Role of Immunotherapy in the Treatment of COVID-19

Convalescent Plasma

Case reports show that the use of convalescent plasma is useful and effective in the treatment of COVID-19 [48]. In the case of convalescent plasma therapy, plasma collected from a convalescent patient is transfused to a symptomatic patient [49]. This type of convalescent plasma provides passive immunity in actively infected patients [50]. It was reported that convalescent plasma may execute a novel role in the inhibition of progression to noninvasive or high-flow oxygen, invasive mechanical ventilation or ECMO, ultimately mortality [51].

Compared with other therapeutics for COVID-19, convalescent plasma was well tolerated, making it a potential therapy without serious transfusion-related adverse effects [52]. Moreover, convalescent plasma administered with favipiravir improved clinical outcomes and patients were typically discharged two weeks [53].

Although convalescent plasma may provide clinical benefits in the treatment of COVID-19, the efficacy of recovery plasma for all patients has not been demonstrated, resulting in largely inconclusive consensus [54]. Furthermore, due to varying donor titer amount and dosing, standardization is warranted to arouse great practical awareness [55]. Since convalescent plasma is often used in combination with other therapies, it is hard to attribute efficacy solely to convalescent plasma [56].

Monoclonal Antibodies in Monotherapy

Ample evidence has suggested the utility of antibody neutralization of SARS-CoV-2 for effective therapeutics and vaccine development. Many monoclonal antibodies concluded in Table 1, were isolated from SARS-CoV-2-infected individuals, with a number of promising antibodies. According to a corresponding enzyme study, P2C-1F11, P2B-2F6 and P2C-1A3 were the most potent live SARS-CoV-2 inhibitors [53]. Among them, P2C-1F11, an antibody which mimics binding of receptor angiotensin converting enzyme 2 in cellular models, is highlighted [57] and displays potent neutralizing activity in vitro to confer protection against SARS-CoV-2 infection [58]. Meanwhile, it occupies the largest binding surface, demonstrating the highest binding affinity to receptor binding domain. Distinct from other antibodies, P2C-1F11 possesses unique ability to trigger immediate and robust shedding of S1 from cell-surface expressed spike glycoprotein in cellular models [59].

To investigate the potential immunoprotective and immunopathological role of antibodies, the CR3022 antibody derived from a human infected with SARS-CoV has attracted considerable attention [60]. CR3022, which targets a conserved epitope in the receptor binding domain, was evaluated for its functional potential as a SARS-responsive antibody to investigate the role of Fc activity in immunity against SARS-CoV-2 [61]. This allowed us to secure the broadly active effector function of the antibody for critical immune clearance [62]. Moreover, CR3022 has the potential to ensure eradication of infected cells even in the presence of high ACE2 secretion [63].

Although the ability of antibodies to target infected cells through Fc interaction is crucial for virus elimination, antibody competence is affected by different functional profiles of Fc, suggesting mechanisms of antibody action that may not be acceptable in the development of antiviral antibody therapeutics [64].

LY-CoV555 is derived from a convalescent COVID-19 patient to treat other patients and acts as an anti-spirate antibody that potentially neutralizes SARS-CoV-2 [65]. It is able to protect the upper and lower respiratory tract of non-human primates against SARS-CoV-2 infection, reinforcing the promise of LY-CoV555 in the clinical assessment for the treatment and prevention of COVID-19 [66]. Courtesy of its identification and characterization, LY-CoV555 has the ability to rapidly recognize neutralizing human mAbs [67]. Therefore, it could play a role in the early stages of addressing an evolving pandemic, supplementing widespread vaccination efforts by offering immediate passive immunity and safeguarding vulnerable populations [68].

Monoclonal Antibodies Used in Combination

The recent boost in monoclonal antibodies revealed the benefit of combination therapy, in addition to monotherapy. The following drugs have been summarized in Table 1. For example, combination of bamlanivimab and etesevimab is indicated for emergency use because the combination not only resulted in a reduced incidence of COVID-19-related hospitalizations and deaths, but also accelerated the decline in SARS-CoV-2 viral load [69]. Bamlanivimab and etesevimab should be administered immediately after a positive SARS-CoV-2 test and within 10 days of the onset of COVID-19 symptoms [70]. It is recommended that patients be treated in a center with staff and equipment for the treatment of anaphylaxis [71]. It is also recommended to monitor patients for hypersensitivity reactions during drug administration for at least 1 hour after infusion [72].

Casirvimab and imdevimab, administered intravenously or subcutaneously, are approved for the combination treatment of mild-to-moderate COVID-19 in individuals over 12 years of age and weighing no more than 40 kg [10]. If intravenous infusion is not available or there is a delay in treatment, this combination may be administered subcutaneously [73]. Conversely, casirvimab and imdevimab may worsen outcomes if administered to COVID-19 patients who are hospitalised or require high flow oxygen or mechanical ventilation [13]. Although anaphylaxis reactions are very rare, they have occasionally been reported with this combination. Moreover, casirvimab and imdevimab have shown great tolerance in pregnant women [74].

BRII-196 and BRII-198 are non-competitive, long-acting monoclonal antibodies against SARS-CoV-2 that reduce the binding of the virus to the receptor [75]. This combination has been shown to be safe and well tolerated, with a significant reduction in the risk of hospitalization and death among adults with mild to moderate COVID-19 and at high risk of progression to severe disease [76]. Meanwhile, adverse events are rarely observed among patients on BRII-196 and BRII-198.

AZD7442 is a combination of two monoclonal antibodies, the long-acting AZD8895 (zigagevimab) and AZD1061 (zilgavimab), which bind simultaneously to different non-translocated epitopes [77]. Both have potent neutralising activity against SARS-CoV-2 and antigenic variants, forming a complex with receptor binding domains. AZD7442 did not improve SARS-CoV-2 post-exposure prophylaxis [78]. However, in pre-exposure prophylaxis, AZD7442 plays a significant role in reducing the risk of developing symptomatic COVID-19, maintaining for up to 12 months [79].

Immuno-Regulator

Clinical benefits were observed with different immuno-regulators, among which the following drugs concluded in table 1 carry the most prominent efficacy.

Tocilizumab is a recombinant humanized monoclonal antibody bound to IL-6 receptor to suppress IL-6 signal transduction [80]. It is clinically used for the treatment of certain forms of juvenile arthritis because it can result in a significant reduction of invasive mechanical ventilation and death [81]. Although tocilizumab is not effective in preventing intubation or death in moderately ill hospitalised patients with COVID-19, patients treated with tocilizumab had fewer serious infection compared with other drugs [82]. Comparable effects were observed with intravenous and subcutaneous administration of tocilizumab.

The ability of corticosteroid to decrease the immune response offers advantage in COVID-19 therapy. Although the effect of corticosteroid varied significantly according to respiratory support, patients treated with corticosteroid exhibited a distinct recovery of respiratory function [83]. Furthermore, a lower clinical outcome score, a trend towards decreased mortality, shorter hospital stay and a reduced need for respiratory support were observed in patients after treatment [84]. When corticosteroid is used in combination with tocilizumab, an additive effect was noted, contributing to mortality reduction by one-third up to 50% depending on the severity of oxygen support [85].

Since SARS-CoV-2 induces a pro-inflammatory syndrome, the recombinant IL-1 receptor antagonist anakinra exhibited benefit in reducing CRP levels and overall mortality [86]. Moreover, anakinra treatment was accompanied with improvements in respiratory function and a rapid reduction of serum CRP level. These results suggest that anakinra may be beneficial in patients with very high serum CRP levels [87]. It is noteworthy that anakinra should be administered early, as its use in patients with mechanical ventilation has not been effective [88].

Traditional Chinese Medicine

As an ancient system of alternative medicine, traditional Chinese medicine plays an active role in the prevention of COVID-19 and the following drugs are summarized in Table 1. It improves the clinical symptoms of patients, effectively relieving the operating pressure on the national medical system during critical conditions [89].

Composed of 13 Chinese herbs, Lianhua Qingwen capsules are able to improve the symptoms of cough, fever and fatigue, leading to the shorter median time to symptom recovery [90]. Besides, it is reported that Lianhua Qingwen could not only affect the viral morphology in vivo, but also suppress the replication of SARS-CoV-2 [91]. Therefore, Lianhua Qingwen prevented mild to moderate cases of COVID-19 from deteriorating into severe forms [92]. Meanwhile, it reliably delivers the desired efficacy in the treatment of COVID-19 due to its ability to clear the lungs, clear away heat, and have functionality in treating viral infection and inflammatory response [93].

Developed and marketed for SARS treatment in China, Xue Bijing injection is a patented Chinese medicinal compound composed of 5 herbal extracts, including Saffron, *Paeonia lactiflora*, *Rhizoma Ligustici Chuanxiong*, *Salvia miltiorrhiza* *Angelica Sinensis* [94]. Combination of Xuebijing injection and a classical anti-infective drug is proved to improve their pneumonia-severity index, shortening the duration of mechanical ventilation and length of ICU stay reduce the mortality in patients with severe pneumonia and [95].

Based on dispelling cold and dampness, Huoxiang Zhengqi enhances cellular immunity and improves gastrointestinal function, composed of *Rhizoma Atractylodis Macrocephalae*, *Pericarpium Citri Reticulatae*, Ginger, *Angelica Dahurica* and *Poria* [96]. It is recommended that Huoxiang Zhengqi can be given to COVID-19 patients in case of fatigue and diarrhea under medical supervision [97]. Furthermore, it is used to relieve abdominal distention and pain, vomiting and diarrhea caused by exogenous wind-cold and endogenous moisture stagnation [98].

Mainly composed of Golden Honeysuckle, Gypsum, *Scutellaria Baicalensis* and *Forsythia*, Jinhua Qinggang granules can reduce serum CRP and IFN- γ levels, improve inflammatory symptoms and regulate immunity in patients with viral pneumonia [99]. Therefore, due to its thermoremediation and detoxification functions, it may not only improve patients' general clinical symptoms but also alleviate their psychological distress. It is reported that Jinhua Qinggang granules have good efficacy and clinical safety in the wind-heat invasion syndrome of influenza lung invasion [100]. Additionally, it effectively shortens the detection time of nucleic acids and promotes the absorption of inflammatory exudate in pneumonia without obvious side effects [101].

Discovery for Potential anti-COVID-19 Drugs

To fight against COVID-19, it is pertinent to identify potential therapies with antiviral and/or anti-inflammatory properties.

With a short half-life, Baricitinib reduces inflammation while minimizing biologic redundancy with antiviral and less immunosuppressive properties [102]. Despite concerns for immunosuppression and secondary infections, addition of baricitinib was not associated with an overtly higher incidence of adverse or thromboembolic events [103]. Moreover, among patients receiving high oxygen flow or non-invasive ventilation, baricitinib in combination

with remdesivir is more effective than remdesivir alone in terms of recovery time and clinical improvement in patients with COVID-19 [104].

In vitro investigations, has antiviral properties against other β -coronaviruses in vitro and inhibits the early stages of the viral life cycle [105]. Unfortunately, owing to conflicting results from pre-clinical studies, the exact efficacy of imatinib against SARS-CoV-2 viability remains controversial [106]. Additionally, according to preclinical models, it is suggested that Imatinib serves as a potential immunomodulator that can reduce pro-inflammatory cytokines and vascular adhesion molecules [107]. However, the molecular mechanisms are not completely understood and warrants further elucidation. Meanwhile, observed in some inflammatory conditions, imatinib is associated with the prevention of pulmonary endothelial barrier dysfunction, leading to a reduction in pulmonary capillary leakage [108].

Reviewing the history, fungal metabolites have served as a boon for the mankind from antibiotics to food preservatives [109]. Recently, as antiviral agents in fighting against COVID-19, the potentials of fungal metabolites are explored, and the success is promising.

Screening of fungal metabolites with antiviral activity has shown that quinadoline B is the most promising metabolite with dynamic stable binding to SARS-CoV-2 protease, RNA-directed RNA polymerase, non-structural protein 15 and S-protein [110]. Moreover, quinadoline B possesses an outstanding pharmacokinetic profile such as oral bioavailability, high drug likeness and lack of toxicity [111].

Cordycepin is a secondary metabolite with a wide range of biological effects, including antiviral activity. Molecular interaction modeling has shown its high affinity for binding to both major protease and spike protein binding sites [112]. Furthermore, this molecule indicates an additional role in preventing the poly(A) which is important for SARS-CoV-2 [113]. Pharmacology network predictions also place great emphasis on the significant potential of cordyceps in various biological pathways linked to viral infections and point to it as a promising drug candidate for the treatment of COVID-19 [114].

Quercetin is another prospective candidate for drug development against COVID-19. It certified high affinity not only for the active site of 3CLpro, but also for the potential targets involved in viral inhibition [115]. Used for clinical applications, Quercetin offers significant advantages in drug development due to its pharmacokinetic and ADMET properties [116]. Attention has been drawn to the potential impact of quercetin as an anti-inflammatory agent to protect patients from severe inflammation caused by SARS-CoV-2 infection [117].

It is proposed that pyranonigrin A could interact with the Main protease, which is one of the significant target proteins of SARS-CoV-2 [118]. Identified as a potent inhibitor of the Main protease, pyranonigrin A depends on docking and molecular dynamics to block the function of the Main protease. Therefore, it served as a

promising drug candidate against COVID-19 [119].

The above-mentioned candidate metabolites cover a wide range of antiviral activities and are concluded in table 1, encouraging continuous endeavor to explore the potential of this chemical library in drug research programs [120].

Peculiarities of the use of anti-COVID-19 Drugs in Pregnant Women and Children

Since some drugs have been empirically used in pregnant women and children, obstetricians should consider whether the same therapies used in the general population are appropriate for pregnant women or children with serious illnesses, according to their safety profile [121].

The use of tocilizumab is confined to acute COVID-19 infection cases in which the patients experienced cytokine storm leading to multiorgan failure [122]. Fortunately, those pregnant women started or maintained the medications due to clinical necessity, delivered healthy newborns [122]. Moreover, direct association cannot be established between the use of tocilizumab and maternal and fetal complications [123]. Therefore, it is recommended that tocilizumab could be maintained along the pregnancy if its benefits exceed the potential risks [124].

Currently, inadequate evidence is readily available for the recommended routine use of monoclonal antibody medications in children with COVID-19, even for those at higher risk of disease severity or hospitalization [125]. At this time, neither bamlanivimab nor casirivimab combined with imdevimab should be considered as the standard care in any pediatric population, even in those meeting high-risk criteria [126].

The above peculiarities have been summarized in Table 1. It is worth noting that the significance of implementing recommended prevention strategies should be emphasized in order to reduce risk for severe acute respiratory syndrome and inform clinical care for pregnant women and children [127].

Conclusion

New evidence gradually emerges from ongoing clinical trials testing COVID-19 drugs and guidelines will be updated periodically. This review summarizes the efficacy and safety on repurposing medications towards treatment for SARS-CoV-2. Based on their mode of action, COVID-19 medications are grouped into antiviral drugs composed of different inhibitors, immunotherapy especially convalescent plasma, traditional Chinese medicine and novel anti-COVID-19 drugs with promises for SARS-CoV-2. Also, the peculiarities of anti-COVID-19 drugs in pregnant women and children are discussed. These findings should help to broaden the therapeutic arsenal against COVID-19, although they should still be interpreted with caution.

Many local and international research centers are strived to test potential drugs for COVID-19 disease in diverse stages of clinical research. With more intricate in vitro and in vivo examinations, these candidate drugs might become rational therapeutics against

SARS-CoV-2. The effectiveness and safety of existing COVID-19 therapeutics must be closely monitored, recognizing that the long-term effects of drugs can only be evaluated through several years of clinical practice.

Acknowledgement

(Yiran E. Li and Yuqi Luo contributed equally to this work).

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