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Review Article

Advances in treatment strategies for COVID-19: Insights from other coronavirus diseases and prospects

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ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic is the third human disease outbreak caused by an emerging coronavirus in the 21st century. Caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the COVID-19 pandemic has been the most devastating, with millions of deaths. Medical countermeasures are needed to limit the number of infections and fatalities. Here, we discuss advances in clinical and research-based treatment methods for SARS-CoV-2 that were initially derived from treatments for other coronaviruses. Recent advances in SARS-CoV-2 treatments, from traditional drugs and immunotherapies to artificial intelligence to predict potential future treatment methods, are summarized and discussed.

1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiological agent of coronavirus disease 2019 (COVID-19), has spread globally since late 2019, causing hundreds of millions of human infections and deaths. Due to the nature of the viral genome, SARS-CoV-2 mutates rapidly, and numerous variants of concern (V.O.C.) and variants of interest (V.O.I.) have emerged. As of April 2023, the predominant V.O.C. worldwide is the Omicron strain, first reported in late 2021 (Table 1) [1].

The life cycle of SARS-CoV-2 is similar to that of many well-characterized pathogens that have been extensively studied (Fig. 1). However, investigators have not yet fully elucidated the mechanisms of pathogenesis for SARS-CoV-2. On a molecular level, it is known that coronavirus infections generally start from virus entry into the host cell. To facilitate entry, the spike (S) protein of SARS-CoV-2 binds to receptors on the target cell's surface. The receptors and co-receptors that are involved in this process include ACE2 [2], NRP1[3], CD147 [4], and A.X.L. [5]. When the S protein binds to the receptor, proteases such as TMPRSS2 [6] and furin [7] promote viral entry. The persistent transmission of the SARS-CoV-2 within the human population, as well as susceptible animal species, has allowed the virus to gain mutations that allow for immune escape, rendering the host susceptible to a new V.O.C. or V.O.I., even if immunity was previously established with prior natural infection or vaccination with another variant. During the early stages of SARS-CoV-2 infection, immunosuppression of host immune responses by the virus plays a role in delaying antiviral immunity, and as such, the virus can replicate efficiently during this period [8]. Although the deployment of various vaccine candidates against SARS-CoV-2 has resulted in the immunization of billions of people, studies have shown that the adaptive immunity induced by natural infection or vaccines cannot wholly prevent future infections with the newly emerging SARS-CoV-2 V.O.C. or V.O.I. [9,10].

Various treatment methods developed during previous coronavirus outbreaks, such as monoclonal antibodies, glucocorticoids, and antiviral small molecule drugs, are promising avenues for exploring new medical countermeasures. Over 5,000 clinical trials related to SARS-CoV-2 are being conducted globally, and new drugs are constantly being developed and launched [11]. However, because the mechanisms of SARS-CoV-2 entry and subsequent infection are not fully understood, especially in the context of mutations from viral variants, it is essential to derive lessons from past experiences regarding the treatment of other coronaviruses in order to select the most promising drugs to be used against current and future coronavirus outbreaks. Here, we present the current research progress in treating and

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Table 1
Treatment methods for different courses of infection with SARS and MERS.

Pathogen/ Severity	SARS-CoV	MERS-CoV
Non-severe	Hospitalization Prevent fever	Hospitalization Prevent fever
Severe	IL-6 receptor/Dexamethasone/ ribavirin/lopinavir Mechanical ventilation/Oxygen therapy	Hormonotherpy Ribavirin /IL-6 receptor Mechanical ventilation/ Oxygen therapy
Critical	E.M.C.O./Mechanical ventilation Dexamethasone/Antibody cocktail	E.M.C.O./Mechanical ventilation Dexamethasone/Antibody cocktail

Abbreviations: SARS-CoV, severe acute respiratory syndrome coronavirus; MERS-CoV, Middle East Respiratory Syndrome; IL-6, interleukin 6; EMCO, extracorporeal membrane oxygenation.

potentially preventing SARS-CoV-2 and highlight their utility against infections with other coronaviruses.

2. Progress in the treatment of SARS-CoV-2

2.1. From effective treatment for other coronavirus infections to clinical treatment for COVID-19

Treatments tested during past epidemics of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) are repurposed to treat SARS-CoV-2 infections. For severe SARS and MERS infections, glucocorticoids, extracorporeal membrane oxygenation (ECMO), and plasma from convalescent patients are used to alleviate disease symptoms. Treatment with monoclonal antibodies and screening compounds from drug libraries against the major receptors ACE2 and DPP4 or other targets, such as protein cleavage sites or co-receptors, were also studied after the SARS and MERS outbreaks. Based on the experience gained from the development of treatment methods against the first two outbreaks of coronaviruses causing severe respiratory disease in humans, several types of treatments for COVID-19 were rapidly developed.

Currently, COVID-19 cases are classified into four categories based on the severity of the patient's condition: mild, moderate, severe, and critical. First, for mild and moderate infections, multiple studies have shown that Remdesivir, a broad-spectrum antiviral drug, can inhibit the replication of the virus, shortening the hospitalization time and reducing the viral load of COVID-19 patients [12]. The WHO recommends that patients with mild and moderate symptoms can also use Paxlovid [13]. In addition, nirmatrelvir plus ritonavir, developed initially as an anti-HIV drug, can inhibit virus replication during early-stage SARS-CoV-2 infections, alleviate the development and deterioration of symptoms, and reduce the mortality or hospitalization rate by approximately 67% [14].

Proactive antiviral and anti-inflammatory treatments must be implemented for patients with moderate infection and possibly progressing to severe illness. For severe or critical patients, glucocorticoids such as Dexamethasone can be used because glucocorticoids can alleviate inflammation and respiratory distress in COVID-19 patients and significantly reduce mortality when survival is assessed at 28 days [15]. The WHO currently lists Dexamethasone as one of the first-line drugs for treating severe COVID-19 infections. For severe patients who need respiratory support, mechanical ventilation, and ECMO can effectively support their breathing and increase their chances of survival [16,17]. The use of convalescent plasma collected from recovered patients has been investigated, and studies have shown that convalescent plasma can reduce the relative risk of severe cases by 48%, shorten hospitalization time, and improve symptoms in 24% of severe cases [18,19]. However, the antibody levels of convalescent patients are variable and can easily trigger unwanted immune reactions, and the logistics of plasma transport are relatively challenging. Especially with virus mutations, previously collected plasma may no longer be effective against newly emerging virus variants. Therefore, the safety of convalescent plasma treatment still requires further research and verification before large-scale deployment.

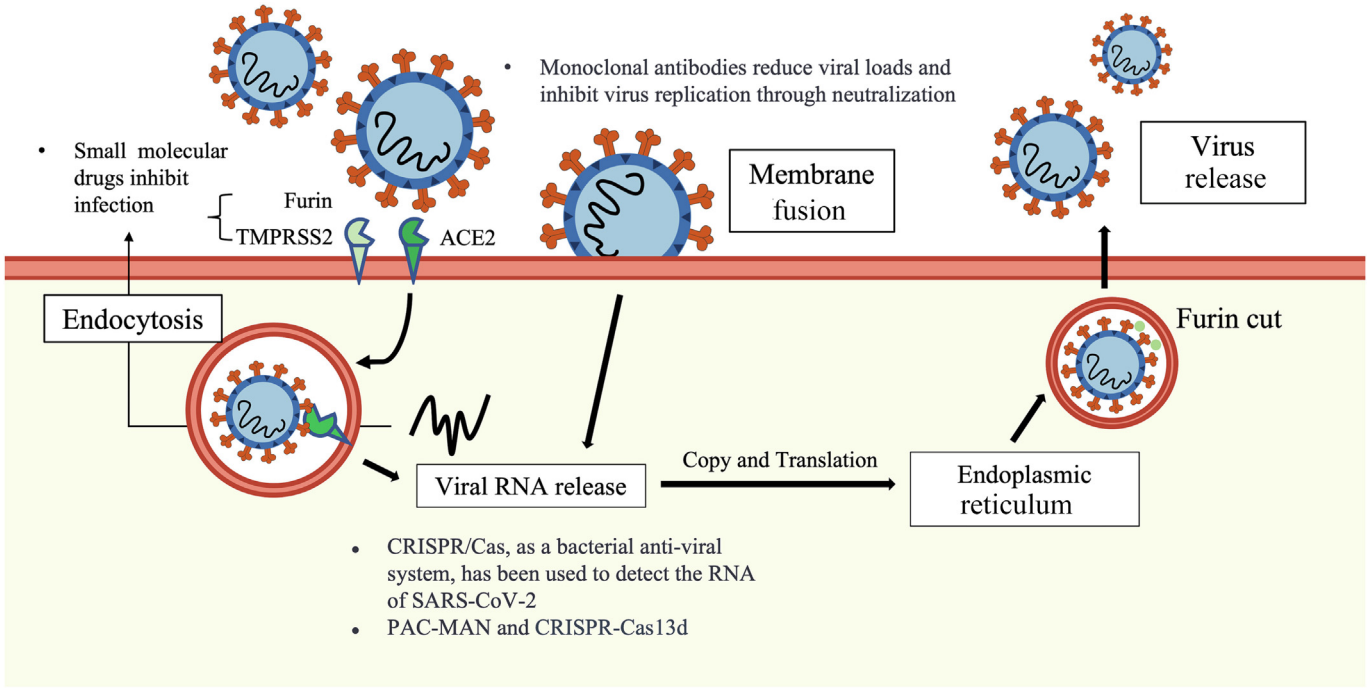

Fig. 1. The infection and viral replication cycle of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), in which potential treatment strategies can be developed targeting various stages of the cycle.

2.2. Repurposed monoclonal antibodies and related proteins from other viral indications to the treatment of COVID-19

Monoclonal antibodies are artificially synthesized immunoglobulins with high specificity and affinity towards their viral target antigen and have been used to treat and prevent various diseases, including SARS-CoV-2 infections. For example, ZMapp, a combination of monoclonal antibodies (components: c1H3, c2G4, and c4G7), can neutralize the Ebola virus. Studies have shown that the optimized ZMapp cocktail, derived from two previous antibody cocktails, could rescue 100% of rhesus macaques within five days after the challenge, and the results justify further development of this cocktail for clinical use [20]. In addition, the monoclonal antibody CR3022, developed for treating SARS, also exhibits neutralizing effects on MERS and SARS-CoV-2 [21].

Neutralizing monoclonal antibodies against the SARS-CoV-2 glycoprotein has been investigated as a potential method for treating COVID-19 and is effective for early-stage infection and patients with mild symptoms [22]. These antibodies primarily reduce viral loads and inhibit virus replication through neutralization, thus shortening the course of the disease, relieving symptoms, and reducing hospitalization and mortality rates. Examples of monoclonal antibodies that have been studied include Casirivimab/Imdevimab [23] and Bamlanivimab/Etesevimab [24]. Casirivimab and Imdevimab are non-competing monoclonal antibodies that bind to two sites on the SARS-CoV-2 spike glycoprotein receptor binding domain, blocking viral entry into host cells. Combining Casirivimab and Imdevimab can reduce the mortality rate of infected seronegative patients [23]. Since these two antibodies have similar binding affinities, the effect of Bamlanivimab and Etesevimab is comparable. However, compared to using Bamlanivimab alone, a *meta*-analysis found that combining Bamlanivimab and Etesevimab is associated with better treatment outcomes[22]. In addition, for treating infections with SARS-CoV-2 V.O.C.s, a single antibody or a combination of antibodies with overlapping binding domains can easily lead to immune escape. Using non-competing antibody cocktails can minimize the adverse effects of escape mutants [25].

Monoclonal antibodies can also be considered for rapidly establishing a transient immunity to prevent SARS-CoV-2 infections[26]. In high-risk populations, such as those who need to come into close contact with SARS-CoV-2-positive individuals or those who cannot receive vaccines due to safety concerns, monoclonal antibodies can be used to prevent infection [27]. However, it should be noted that the protective window of monoclonal antibodies via passive transfer is relatively short, generally ranging from several weeks to several months, and therefore cannot replace vaccination as a long-term preventive measure.

2.3. Diagnosis and treatment related to CRISPR/Cas systems

Rapid and accurate detection of samples and timely identification of the viral strain and related information are critical for epidemic prevention and control. The emergence of viral mutations has also raised demands for novel and convenient detection methods. In recent years, Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR/Cas) technology has demonstrated enormous potential in real-time diagnosis and sequence-based antiviral therapy [28].

CRISPR/Cas, discovered initially as a bacterial anti-viral system, has been used to detect the RNA. of SARS-CoV-2 with high sensitivity and specificity. Various CRISPR/Cas-based assays were rapid, accurate, and cost-effective in diagnosing COVID-19-positive patients. Using CRISPR-Cas12 technology, SARS-CoV-2 can be detected from respiratory swab RNA. extracts, with 95% positive predictive agreement and 100% negative predictive agreement in SARS-CoV-2 real-time RT-PCR detection [29]. Bio-SCAN is a simple, rapid, sensitive, and specific pathogen detection platform based on CRISPR/Cas9 lateral flow assay. It successfully detected clinically relevant levels (4 copies/μL) of synthetic SARS-CoV-2 RNA. genome with 100% negative and 96% positive predictive agreement with RT-qPCR results when using clinical samples and efficiently distinguished between different SARS-CoV-2 variants[30]. CRISPR/Cas-based assays can directly quantify the viral load in the sample without nucleic acid amplification and read the fluorescent results via mobile phone, achieving lower costs and more convenient detection [31].

The CRISPR/Cas system also has potential applications in preventing and treating COVID-19 [32]. Based on the CRISPR-Cas13 strategy, prophylactic antiviral CRISPR in human cells (PAC-MAN) can be used for viral inhibition. In one study, six CRISPR RNAs (crRNAs) targeting over 90% of all known coronaviruses were designed and shown to inhibit coronavirus fragment expression in human lung epithelial cells effectively. Targeted interference of coronavirus RNA. can effectively inhibit virus replication and transmission, providing a potential new treatment method for SARS-CoV-2 infection [33].

CRISPR-Cas13d (CasRx) has shown the potential to be used for both the prevention and treatment of COVID-19 infections. Using an improved lung-targeting lipid nanoparticle [34] to deliver CRISPR-Cas13d mRNA, precisely and safely knocking down the mRNA levels of the lung Cstl gene, has been found to significantly reduce lung tissue protease L (C.T.S.L.), thereby blocking COVID-19 infection [35]. This approach has therapeutic potential, successfully reducing lung viral loads in a severe COVID-19 mouse infection model, inhibiting the cytokine storm from SARS-CoV-2 infection, and significantly improving the survival rates of infected mice. Importantly, this method provides a new approach to preventing and treating COVID-19 and is effective against SARS-CoV-2 V.O.C.s, as this strategy does not rely on recognizing specific viral sequences [34,35].

2.4. Development of small molecule drugs

The SARS-CoV-2 life cycle is typical of many well-characterized pathogens in that the virus enters susceptible cells through known receptors and related auxiliary receptors. It activates specific signaling pathways for productive replication or uses furin-cleavage sites to enhance infection (Fig. 1). The critical role of small molecule drugs in COVID-19 treatment includes intervention strategies targeting different stages such as virus entry, replication processes and host immune responses [36]. The clinical evaluation of treatment methods and efficacy for some drugs has been conducted (Table 2 and Table 3).

Molnupiravir is a small molecule ribonucleoside prodrug of N-hydroxycytidine (NHC). After entering systemic circulation, NHC infiltrates viral RNA. Molnupiravir mimics some components of the genetic material RNA. in SARS-CoV-2, causing the virus to replicate incorrectly, ultimately rendering the virion non-infectious and unable to replicate. Molnupiravir is active against SARS-CoV-2 and other RNA. viruses and has a high barrier to developing viral resistance [37–39]. Studies have shown that Molnupiravir can reduce 61% of the viral load in COVID-19 patients within three days, decrease hospitalization and mortality rates by 31% within 28 days, and suppress viral spread within the host [40].

Baricitinib is an orally administered, selective inhibitor of Janus kinase (J.A.K.) 1 and 2. Baricitinib inhibits intracellular signaling pathways of cytokines known to be elevated in severe COVID-19 cases [41,42], including IL-2, IL-6, IL-10, IFN-γ, and granulocyte–macrophage colony-stimulating factor, and by disrupting AP2-associated protein kinase 1 and blocking SARS-CoV-2 cell entry and infection, thus suppressing excessive host inflammation [41,43]. Studies have shown 30% higher odds of improvement in clinical status at day 15 for using Baricitinib, and Baricitinib plus Remdesivir have a 5.1% mortality rate lower than the control group after 28 days [41]. Animals treated with baricitinib showed a rapid and remarkably potent suppression of cytokine production from lung macrophages responsible for inflammation and neutrophil recruitment [44].

Previous studies have shown that the spike protein (S) of SARS-CoV-2 uses host cell factors, angiotensin-converting enzyme 2

(ACE2) and transmembrane protease serine 2 (TMPRSS2), to enter host cells [6]. Camostat mesylate is a known protease inhibitor that can block TMPRSS2 activity, and Camostat and its metabolite G.B.P. A. (4-guanidinobenzoyloxy phenylacetic acid) have been shown to inhibit the spread of SARS-CoV-2 in human lung tissues *in vitro* [45]. However, further research is needed to validate the effectiveness of Camostat *in vivo* [45,46].

2.5. Anti-inflammatory and antiviral combination therapy

Studies have found that excessive secretion of pro-inflammatory cytokines due to SARS-CoV-2 infection is a significant cause of severe pneumonia in COVID-19 patients[47]. After SARS-CoV-2 infection, the host immune system produces many inflammatory compounds, leading to local and systemic inflammatory reactions and severe complications such as ARDS (acute respiratory distress syndrome) [47,48]. Anti-inflammatory and immune therapies are required to treat critically ill patients with hyperactivated and dysregulated immune systems [48]. Anti-inflammatory drugs can inhibit the production and release of inflammatory mediators, thereby preventing cytokine storms in the host [15]. Choosing appropriate anti-inflammatory drugs and therapies has become an important research direction for reducing the severity and mortality of COVID-19. Antiviral drugs can directly interfere with the replication and proliferation of the virus in host cells, thereby reducing viral load and transmission [12,49]. Combination therapy with antiviral drugs, such as Remdesivir and Dexamethasone, was shown to be superior compared to using a single compound for treating severe infections [12]. Studies have shown that the continuous use of anti-inflammatory drugs can suppress the host specific immune response to SARS-CoV-2, reduce neutralizing antibody levels in the blood, and increase the virus loads in the main respiratory tract tissue, indicating the necessity of using a combination of antiviral and anti-inflammatory drugs to treat severe COVID-19 [50,51]. The rational use of anti-inflammatory drugs or metabolites in combination with antiviral drugs as a cocktail therapy to suppress cytokine storms can be an effective strategy to alleviate severe pneumonia caused by SARS-CoV-2 infections.

3. Potential therapeutic strategies

3.1. Cytokine release syndrome (C.R.S.) and immunometabolic reprogramming

Cytokine release syndrome (C.R.S.) from viral infections is caused by over-activated immune cells, leading to the release of large amounts of cytokines and resulting in symptoms such as fever, hypotension, tachycardia, dyspnea, coagulation disorders, and organ damage, such as the liver and lungs. The cytokine storm induced by SARS-CoV-2 is believed to be related to the severity of COVID-19 disease [52,53]. An imbalanced acquired immune response and uncontrolled innate inflammatory responses to SARS-CoV-2 may lead to a cytokine storm. Thus, severe lung damage in COVID-19 patients is considered a result of both direct viral infection and immune hyperactivation [54,55]. Therefore, immunotherapy targeting cytokines associated with C.R.S. suggests that blocking the release of proinflammatory cytokines can potentially treat COVID-19 [56–58].

Table 3
Clinical classification of COVID-19 patients and corresponding recommended treatment methods.

Clinical grades	Clinical manifestation	Therapeutic method
Mild	Mainly presents with respiratory infection symptoms.	Alleviate symptoms such as fever and cough, isolated at home.
Moderate	Persistent fever and respiratory symptoms > 3 days with mild pneumonia manifestations observed on imaging.	Antiviral treatments include Remdesivir/Lopinavir, Azvudine, Nirmatrelvir-ritonavir (Paxlovid), etcetera. Anti-inflammatory treatment: Bamlanivimab, Etesevimab Mild hypoxemia can be treated by providing oxygen therapy
Severe	Clinical symptoms progressively worsen, with increased respiratory distress, decreased oxygen saturation, and significant pneumonia manifestations observed on imaging.	Anti-inflammatory treatment: Corticosteroids/IL-6 receptor/ Baricitinib/Dexamethasone Supportive care: Mechanical ventilation/Oxygen therapy and hospitalization Anticoagulant therapy: Therapeutic doses of low-molecular-weight heparin or unfractionated heparin. Monoclonal Antibodies
Critical	Shock occurs, along with respiratory and other organ failures, requiring mechanical ventilation.	Supportive care: E.M.C.O./ Mechanical ventilation Anticoagulant therapy: Therapeutic doses of low-molecular-weight heparin or unfractionated heparin. Dexamethasone/Drug combined Antibodies cocktail

Abbreviations: COVID-19, coronavirus disease 2019; E.M.C.O., extracorporeal membrane oxygenation.

Table 2
Small molecular drugs for the treatment of COVID-19.

Name	Therapy method	Treatment population	Treatment effect	Safety
Remdesivir	i.v.	Patients with symptoms or inpatients	Shorten hospitalization time, alleviate symptoms, and reduce mortality	Relatively safe with occasional side effects
Molunpiravir	Oral	Adult; Used after the early onset of symptom	Rapidly reduce viral load, alleviate symptoms, and lower hospitalization and mortality rates.	Relatively safe for short-term use with minimal side effects
Nirmatrelvir (plus ritonavir named Paxlovid)	Oral; It can be used in combination with Molnupiravir to enhance efficacy	Non-severe; Used after the early onset of symptom	Inhibit the protease activity of SARS-CoV-2, thereby reducing viral replication and transmission, effectively controlling the progression and symptoms of COVID-19.	Relatively safe for short-term use with minimal side effects
Dexamethasone	i.v.	Severe and critical; Inpatients requiring oxygen support	Significantly reduce mortality	The appropriate dosage is relatively safe, but long-term or excessive use may lead to side effects such as immunosuppression, hyperglycemia, and osteoporosis.
Baricitinib	Oral	Severe and critical, especially with a high inflammatory state and Inpatients requiring oxygen support; Not recommended for non-severe	Inhibit the production of cytokines, reduce inflammation response in severe COVID-19 patients, decrease mortality rate, and shorten hospitalization time.	The appropriate dosage is relatively safe, but long-term or excessive use may lead to side effects such as immunosuppression and increased risk of infections.

Abbreviations: SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; COVID-19, coronavirus disease 2019; i.v., Intravenous.

Past research has found that pathogenic T-cells and inflammatory monocytes that secrete large amounts of IL-6 may trigger a cytokine storm[59]. Tocilizumab, a monoclonal antibody targeting the IL-6 pathway, may inhibit the cytokine storm [60,61], representing a potentially therapeutic approach for severe and critical COVID-19. TNF-α is another possible target for anti-inflammatory therapy. Some TNF-α inhibitors, such as ribavirin and infliximab, have been used to treat cytokine storms in other diseases and have shown some potential for COVID-19 treatment [62]. IFN-γ is also considered a potential target for anti-inflammatory therapy. Baricitinib, an orally available, selective, and reversible Janus kinase (J.A.K.) 1 and JAK2 inhibitor, has been shown to inhibit the inflammatory immune response and alleviate lung injury caused by C.R.S. and mitigate immune dysregulation in severe COVID-19 patients [53].

Recent studies on immunometabolism have found that cell metabolic reprogramming plays an essential regulatory role in activating the immune system and inflammatory response (including cytokine secretion caused by viral infections) [53]. By integrating and analyzing the metabolic reshaping and inflammatory response in COVID-19 patients using targeted and untargeted metabolomics techniques, it was found that the two are closely related and mutually influential, especially in severe cases. That intervention in arginine, tryptophan, or purine metabolism can significantly improve excessive inflammatory responses[60]. Compounds such as tryptophan, which play crucial roles in immunity and homeostasis, undergo altered metabolic flux following SARS-CoV-2 infection, which could also serve as a research direction for drug targeting in COVID-19, gaining deeper insights into the viral mechanism of action within the human body [63]. This function provides new insights into the molecular mechanisms of C.R.S. caused by SARS-CoV-2 infection and suggests that metabolic interventions may be a potential new strategy for treating C.R.S. in COVID-19 patients.

3.2. The potential applications of gene editing technology

Since the outbreak of SARS-CoV-2 and the emergence of its ongoing mutations, there has been an urgent need for novel therapeutic technologies that are fast, accurate, stable, easy to manufacture, and target-specific for monitoring and treating the virus. Gene-editing methods based on CRISPR-Cas12/13 and RNA. interference (RNAi) offer incredible speed and precision compared to traditional diagnostic or treatment approaches. RNAi, such as microRNAs, siRNAs, and shRNAs, show potential for silencing genes related to cancer, viral infections, and autoimmune diseases, and siRNAs can be used to target and suppress specific genes of SARS-CoV-2, such as structural and nonstructural proteins, to inhibit viral replication and reduce symptoms [64]. Additionally, RNAi can be employed for rapid virus detection, enabling early diagnosis and swift measures to control viral spread and outbreaks.

CRISPR technology has shown tremendous potential in treating and diagnosing COVID-19 infections. As a highly flexible and precise gene-editing tool, CRISPR can target the viral genome, blocking viral replication and transmission. CRISPR can also be used for rapid virus detection, enabling early diagnosis and prompt action [65]. These applications offer new directions and methods for global efforts to combat the COVID-19 pandemic.

3.3. Artificial intelligence methodologies for target prediction and drugs screening

Studying viruses through algorithms, machine learning, extensive data analysis, simulations, and other methods can reveal more potential treatment methods. Researchers have developed an artificial intelligence algorithm tool called PrismNet, which predicts many host protein factors that bind to SARS-CoV-2 RNA, and accurately predicts the binding sites and changes of RNA. binding proteins (R.B.P.s) [66]. Some existing targeted drugs for host factors can be repurposed to inhibit SARS-CoV-2 infections [67]. Similarly, intelligent algorithms can simulate the secondary structure of RNA., thereby exploring potential genomic targets of interest [68]. Target prediction and virtual screening are important when discovering new drugs and optimizing lead compounds. Researchers have developed the D3AI-CoV platform for target prediction and virtual screening based on anti-COVID-19 drugs. This platform can quickly predict possible drug targets and simulate the interactions between the virus and the drug [69]. The open-source protein structure prediction tool AlphaFold also has some potential in guiding the study of protein–protein interactions related to SARS-CoV-2 infection. Furthermore, the cross-reactive B cell receptor network (XBCR-net), a deep learning framework developed based on artificial intelligence, can predict the specific receptors of SARS-CoV-2 variants and quickly generate broadly reactive antibodies against newly discovered variants of SARS-CoV-2 and other emerging virus variants [70]. Overall, intelligent systems and machine learning methods can help accelerate the screening and design targeted drugs for SARS-CoV-2, predict possible infection mechanisms, and develop potential treatment methods.

4. Discussion

The COVID-19 pandemic has been limited by the widespread administration of vaccines and immunity derived from natural infections, and the number of daily infections has dropped from a peak of over 3 million infections to approximately 100,000 worldwide. Progress on developing treatment candidates against SARS-CoV-2 is mainly based on the findings made in studying other coronavirus infections. There are many similarities in the biology and transmission mechanisms between SARS-CoV-2 and other coronaviruses, such as how the virus enters and infects cells, replicates, and transmits to new hosts.

Previous work on the binding of SARS-CoV-2 to the receptor of host cells has led to the development of drugs that mainly focus on preventing the virus from binding to the receptor. However, whether directly inhibiting the receptor's expression can reduce the binding of the virus to the receptor depends on whether the receptor plays a role in other physiological functions that may be affected by the drug inhibition. For ACE2, the primary receptor of SARS-CoV-2, inhibiting its expression may reduce the ability of the virus to enter host cells, thereby reducing viral infection and replication. However, ACE2 expression is not limited to respiratory epithelial cells but is also distributed in various cells and tissues, including the lungs, heart, kidneys, liver, and digestive system, which all play essential physiological functions. Therefore, inhibiting ACE2 expression may interfere with normal physiological functions, leading to a series of adverse reactions and side effects, such as adverse effects on lung and heart functions. Additionally, inhibiting ACE2 expression requires maintaining this effect over a certain period and necessitates using techniques such as gene editing or RNA. interference, which have technical difficulties and safety risks. Therefore, research on inhibitors and small molecules preventing the virus from binding to the ACE2 receptor is a better strategy.

In the search for drugs against COVID-19, while potentially promising compounds will exhibit antiviral activity against other coronaviruses and SARS-CoV-2 variants, there may be side effects, and as such, not all compounds are suitable for all patients. Precision medicine is a promising treatment method that could improve effectiveness and reduce adverse reactions through personalized treatment plans. For example, by analyzing the patient's genome sequence, individual genetic variations potentially associated with susceptibility to severe

disease can be detected and predicted, individual differences in immune status can be analyzed, and personalized treatment plans can be developed by detecting various cytokines in patient plasma and their sensitivity to different types of drugs, the most suitable drugs for the patient may be screened efficiently, reducing the risk of adverse reactions and treatment failures. In addition, extensive data analysis in precision medicine can help identify the biological phenotype corresponding to specific mutations to develop new targeted therapies, supporting a personalized approach for treating COVID-19 and other infectious diseases in the future.

Using computational systems such as artificial intelligence can assist researchers in rapidly and accurately studying SARS-CoV-2, conducting epidemiological analyses, simulating drug effects, and vaccine research. By simulating infection mechanisms, predicting possible mutation types, and screening large drug libraries using models and algorithms, effective targets can be identified to accelerate the modification of known effective drugs and develop broad-spectrum, specific drugs against coronaviruses.

Due to similarities in the mechanism of cell entry and viral life cycle, small compounds or monoclonal antibodies previously studied for SARS-CoV, MERS-CoV, and other coronaviruses may have therapeutic effects on COVID-19 patients. For example, the monoclonal antibody CR3022 used to treat SARS can also treat COVID-19. Nafamostat, which has shown promising results in *in vitro* cell experiments for MERS-CoV, can also be considered for COVID-19. Investigating small molecule compounds previously characterized for infections with other coronaviruses may result in the development of broadly-reactive compounds effective against novel coronaviruses or their variants in the future.

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Conflict of interest statement

The author declare that there are no conflicts of interest.

Author contributions

Yingwen Li: Writing – original draft, Conceptualization. **Jiaming Lan:** Resources. **Gary Wong:** Conceptualization, Writing – review & editing.

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