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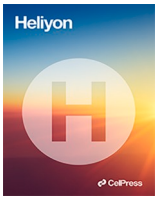

Review article

Repurposing existing drugs for the treatment ofCOVID-19/SARS-CoV-2: A review of pharmacological effects and mechanism of action

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ABSTRACT

Following the coronavirus disease-2019 outbreak caused by severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), there is an ongoing need to seek drugs that target COVID-19. First off, novel drugs have a long development cycle, high investment cost, and are high risk. Second, novel drugs must be evaluated for activity, efficacy, safety, and metabolic performance, contributing to the development cycle, investment cost, and risk. We searched the Cochrane COVID-19 Study Register (including PubMed, Embase, CENTRAL, ClinicalTrials.gov, WHO ICTRP, and medRxiv), Web of Science (Science Citation Index, Emerging Citation Index), and WHO COVID-19 Coronaviral Disease Global Literature to identify completed and ongoing studies as of February 20, 2024. We evaluated the pharmacological effects, *in vivo* and *in vitro* data of the 16 candidates in the paper. The difficulty of studying these candidates in clinical trials involving COVID-19 patients, dosage of repurposed drugs, etc. is discussed in detail. Ultimately, Metformin is more suitable for prophylactic administration or mildly ill patients; the combination of Oseltamivir, Tamoxifen, and Dexamethasone is suitable for moderately and severely ill patients; and more clinical trials are needed for Azvudine, Ribavirin, Colchicine, and Cepharanthine to demonstrate efficacy.

1. Introduction

In December 2019, the coronavirus disease-2019 (COVID-19) pandemic began, becoming the most urgent global public health emergency. Severe acute respiratory syndrome coronavirus type 2 (Sars-CoV-2) is the causative agent of COVID-19 and belongs to the coronavirus family of single-stranded RNA viruses, whose coronal structure depends on the spatial conformation of the "spike" protein [1]. The S protein is the most researched part of the Sars-CoV-2 viral genome. Because it recognizes angiotensin-converting enzyme 2 (ACE2) on the cell surface, it is directed by transmembrane serine 2 protease (cleavage of the spiked protein) as a part of fusion with the

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cell membrane and internalized, thereby infecting normal cells in the body [2]. ACE2 internalizes and activates the immune system triggering lung inflammation characterized by elevated levels of proinflammatory markers such as interleukin-6 (IL-6), interleukin-1β (IL-1β), tumor necrosis factor (TNF), and C-reactive protein (CRP) [3] (Fig. 1).

To date, few drugs have proven effective against SARS-CoV-2. Severe illness and death have been reported in patients with pre-existing diabetes mellitus [4], chronic obstructive pulmonary disease [5,6], hypertension, heart and kidney disease [7], cancer [8], and polycystic ovary syndrome [9]. Several studies [10,11]have shown that a few patients taking drugs for chronic diseases are not infected with SARS-CoV-2. James Black, the Scottish pharmacologist, suggested that the best method to discover a new drug is to begin with an old one [12]. This article will discuss how prior indications are related to the dosage of repurposed drugs used in COVID-19, or how the severity of the patient's condition affects the choice of repurposed drug or its dosing regimen, and also discusses in detail the difficulty of investigating these drug candidates in clinical trials involving patients with COVID-19.

2. Drug repositioning strategies and challenges

Currently, there are two main orientations—targeted and untargeted positioning. In targeted drug repositioning, the biological target is known for the original indication. However, it is for a different disease, and the known pharmacological mechanisms apply to the new indication. In untargeted drug repositioning, the pharmacological mechanisms remain unknown. Drugs and drug candidates act on new targets beyond the original range for new therapeutic indications. Therefore, the targets and indications are novel. Two different strategies [13] were explored to identify Mpro inhibitors based on structures within a mega-chemical library by docking. Two separate focused screens were implemented; the first-screened molecules that matched the active site of Mpro were selected as the top-ranked compounds for experimental evaluation. The secondary screen optimized the fragments identified in the crystallographic screen by building a focused library containing numerous compounds. The most promising lead compounds were compared with previously identified Mpro inhibitors. Compared with the drug-directed approaches, this approach resulted in a higher success rate of drug discovery because most biological targets are representative of disease pathways/mechanisms [14]. Currently, additional targets, receptors, and related mechanisms are being identified. It is advantageous for drug repurposing to construct disease-specific networks, characterize genetic expression, consider key targets, and identify disease-causing protein molecules associated with cells and metabolic pathways of interest in disease models [15] (Table 1.).

However, changes to their original use have only occasionally been successful. It must be acknowledged that several drugs, primarily in phase III or phase IV clinical trials, prove to be ineffective or exhibit grave side effects. Drug repositioning strategies face some challenges, especially with quantification. One of the main challenges of starting the development of a drug in this type of indications is that the patient populations quickly evolve and change over time (Fig. 2). At the beginning of the pandemic, the majority of patients were dealing with severe COVID, and not all drug candidates were efficacious at the tested doses for these patients. Patients

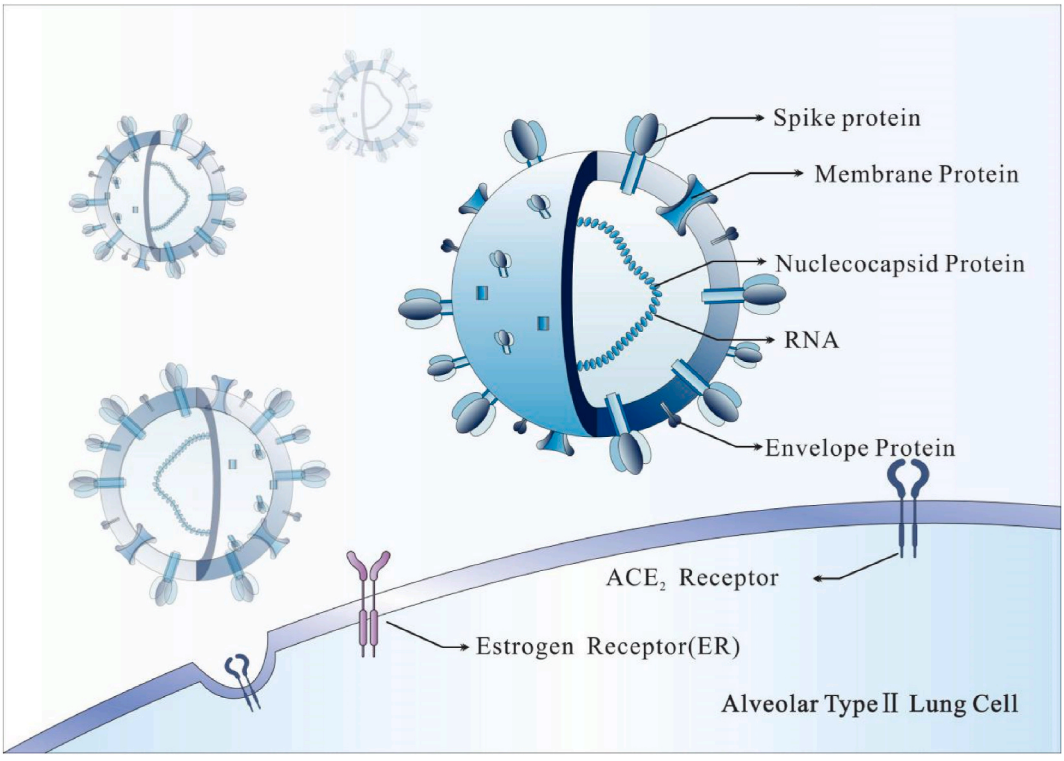


Fig. 1. Description of the structure and invasion pathway of the virus.

Table 1
Clinical trials of drug repositioning.

Drug name	Broad mechanism of action	Status	Phase	Purpose	NCT
Favipiravir	Antiviral drug	Recruiting	Phase IV	Treatment	NCT05502081
FNC	Anti-HIV infection drugs	Recruiting	Phase IV	Treatment	NCT05697055
FNC	Anti-HIV infection drugs	Completed	Phase III	Treatment	NCT05033145; NCT04668235
RV	Synthetic nucleoside drugs	Unknown Status	Phase III	Treatment	NCT04392427
Oseltamivir	Anti-influenza drug	Completed	Phase IV	Treatment	NCT02780622
Oseltamivir	Anti-influenza drug	Recruiting	Phase IV	Treatment	NCT04973462
Colchicine	Gout anti-inflammatory and analgesic drugs	Completed	Phase IV	Treatment	NCT05246072
Colchicine	Gout anti-inflammatory and analgesic drugs	Completed	Phase III	Treatment	NCT04472611; NCT04667780; NCT04724629; NCT04350320; NCT04328480
Colchicine	Gout anti-inflammatory and analgesic drugs	Recruiting	Phase III	Prevention	NCT04416334
Tocilizumab	IL-6 receptor antagonists	Completed	Phase IV	Treatment	NCT04730323
Tocilizumab	IL-6 receptor antagonists	Recruiting	Phase IV	Treatment	NCT04779047
Tocilizumab	IL-6 receptor antagonists	Completed	Phase III	Treatment	NCT04356937; NCT04600141; NCT04577534; NCT04330638
Interferon Lambda	Innate immune defense drugs	Completed	Phase II	Treatment	NCT04354259
Dexamethasone	Glucocorticoids	Active Not Recruiting	Phase IV	Treatment	NCT04530409
Dexamethasone	Glucocorticoids	Completed	Phase IV	Treatment	NCT05004753; NCT04707534
Dexamethasone	Glucocorticoids	Recruiting	Phase IV	Treatment	NCT05062681
Dexamethasone	Glucocorticoids	Completed	Phase III	Treatment	NCT04603729; NCT04909918; NCT04834375; NCT04640168
Tamoxifen	Nonsteroidal anti-estrogens	Not Yet Recruiting	Phase II	Treatment	NCT04389580
Raloxifene	SERM	Completed	Phase II/III	Treatment	NCT05172050
UDCA	Choleretic	Recruiting	Phase IV	Prevention	NCT05690646
AZM	Macrolide antibiotics	Completed	Phase IV	Treatment	NCT04370782
AZM	Macrolide antibiotics	Recruiting	Phase IV	Treatment	NCT04715295
AZM	Macrolide antibiotics	Completed	Phase III	Prevention	NCT04344379
AZM	Macrolide antibiotics	Completed	Phase III	Treatment	NCT04338698; NCT04673214; NCT04646109; NCT04530422; NCT04381962; NCT04358081
Doxycycline	Nonconventional antibiotics	Completed	Phase IV	Treatment	NCT04370782
Doxycycline	Nonconventional antibiotics	Recruiting	Phase IV	Prevention	NCT05072093
Doxycycline	Nonconventional antibiotics	Recruiting	Phase IV	Treatment	NCT04729140; NCT04715295
CEP	Anti-inflammatory and antioxidant	Completed	Phase II	Treatment	NCT05398705
Metformin	Biguanide antihyperglycemic agents	Active Not Recruiting	Phase III	Treatment	NCT04510194
Metformin	Biguanide antihyperglycemic agents	Not Yet Recruiting	Phase IV	Treatment	NCT02915198

Azvudine: FNC; Ribavirin: RV; SERMs: Selective estrogen receptor modulators; UDCA: Ursodeoxycholic acid; AZM: Azithromycin; CEP: Cepharanthine.

quickly evolved to a moderate population of the disease with a different disease progression and even response to intervention, especially for completely new and unknown viruses , making conclusions regarding the effectiveness of the candidate products very challenging.

3. Existing candidates

Over the past few years, clinical trials and drug repositioning studies have been conducted at different stages. Several studies are underway to select novel drugs to control the epidemic and to conduct *in vitro*, *in vivo*, and human clinical trials. Antivirals, immune boosters, anti-inflammatory agents, immunomodulators, antiparasitic agents, and endocrine system drugs are available, demonstrating a different role. The trials have led to the discovery of more potential pharmacological effects. A wide range of these drugs with multiple mechanisms of action have been selected as potential candidates for treating patients with SARS-CoV-2(Table 2.).

3.1. Antiviral therapy

Antivirals inhibit viral multiplication, provide time for the host immune system, ward off the viral attack, and repair damaged tissues, thereby moderating the disease [16]. Most mechanisms for inhibiting SARS-CoV-2 involve inhibiting viral replication via different approaches and reducing the damage caused by the inflammatory cytokine storm. Mixed results were obtained when several

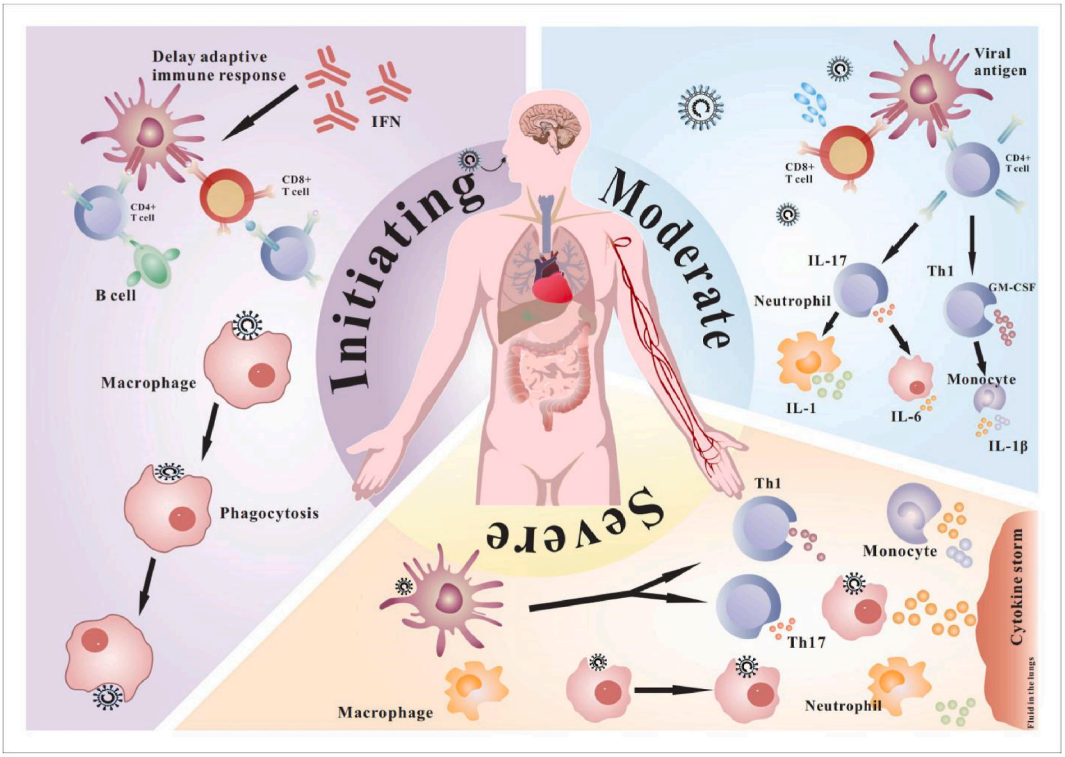


Fig. 2. Description of the different stages of the disease.

antiviral drugs were subjected to extensive *in vivo* and *in vitro* trials at the beginning of the outbreak.

3.1.1. Favipiravir

Favipiravir is an antiviral drug [17]that selectively and effectively inhibits RNA-dependent RNA polymerase (RdRp, nsp12) in RNA viruses. It is effective in animal models with lethal RNA viruses. The drug treats life-threatening human infections such as Ebola virus disease, Lassa fever, rabies, and severe fever with thrombocytopenia syndrome. In 2014, favipiravir was approved in Japan for treating influenza cases that are nonresponsive to conventional treatment [18]. Currently, researchers have conducted studies to treat novel viruses, including Ebola and SARS-CoV-2 [19–24]. The researchers affirmatively confirmed the efficacy of the combination or individual administration of the antiviral favipiravir.

The RdRp activity of SARS-CoV-2 was 10-fold higher than that of other viral RdRp [25,26]. In addition, the mechanism of action of favipiravir involving the direct inhibition of viral replication and transcription is unique among anti-influenza drugs. Because human cells do not contain the RdRp structural domain and possess a conserved RdRp catalytic structural domain, the broad-spectrum coverage of favipiravir renders it a promising candidate.

In mice infected with influenza virus, Favipiravir (200 mg/kg/day) protected mice from death by influenza virus infection. In mice artificially infected with the Ebola virus, Favipiravir effectively blocked virus production, achieving 95 % and 99.6 % antiviral efficacy after 2 and 6 days of treatment initiation, respectively. *In vitro* studies have demonstrated the antiviral activity of favipiravir (concentration: 0.25–3 mg mL−1) on the Vero-E6 cell line infected with SARS-CoV-2 using a real-time cell analyzer. *In vitro*, at an optimum concentration of 2 mg/mL, the lowest toxicity and sufficient antiviral activity were observed [27]. *In vivo*, studies revealed that high favipiravir doses significantly reduced pulmonary infectious virus titration and improved pulmonary histopathology in hamsters infected with SARS-CoV-2. Furthermore, high favipiravir doses were found to reduce the transmission of the virus in direct contact [28]. The bioavailability of favipiravir was approximately 97.6 %. The mean C_{max} of the recommended dosing regimen is 51.5 μg/mL [29]. The research findings demonstrated that favipiravir was safe and outperformed controls in reducing the duration of viral shedding in post-discharge recurrence-positive patients who were with SARS-CoV-2 RNA [30].

Among hospitalized patients, compared with standard treatment, favipiravir [31] exhibited higher viral clearance on day 5, higher fever remission rates on days 3–4, significant improvement in chest radiology, and lesser duration for clinical improvement. Regarding adverse events, the favipiravir group showed a higher incidence of hyperuricemia and elevated alanine aminotransferase but a lower incidence of nausea and vomiting. The severe adverse events of this drug have not been studied. If pregnancy is confirmed or suspected, favipiravir in women should be avoided [32]. Phase IV clinical trials of favipiravir for COVID-19 have been completed, and treatment has been approved for marketing by the Central Drugs Standard Control Organization.

Table 2
Description of drug candidates and structure.

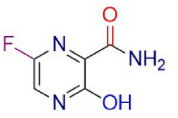
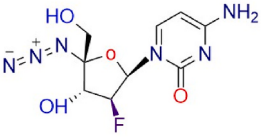
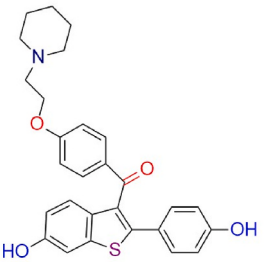
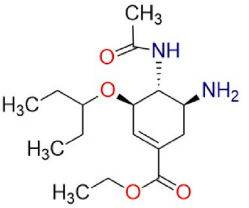
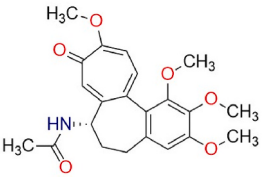
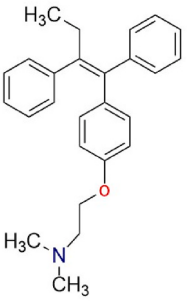
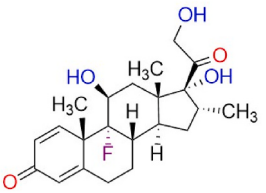
Generic Name	Structure
Favipiravir	
Azvudine	
Raloxifene	
Oseltamivir	
Colchicine	
Tamoxifen	
Dexamethasone	

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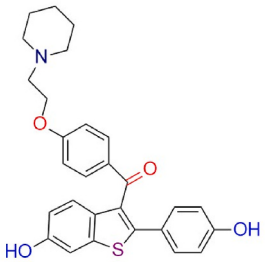
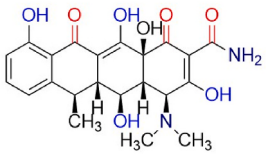
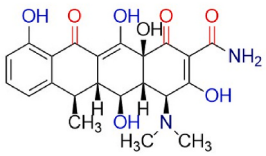
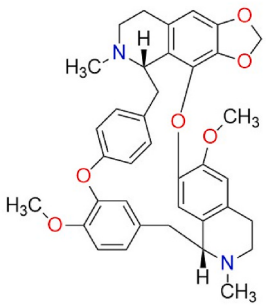
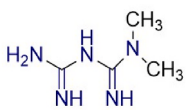
Table 2 (*continued*)

Generic Name	Structure
Raloxfene	
UDCA	
Dexamethasone	
Cepharanthine	
Metformin	

3.1.2. Azvudine

Azvudine (FNC) represents a novel nucleoside reverse transcriptase inhibitor with antiviral activity against HIV, hepatitis B virus, and hepatitis C virus [33]. Developed initially as an anti-HIV infection drug, a viral infectivity factor inhibitor, and an HIV-1 reverse transcriptase inhibitor, FNC received National Medical Products Administration approval from the State Drug Administration of China on July 20, 2021, for treating HIV infection as an oral tablet. In research on the COVID-19 virus, single-cell sequencing in rhesus monkeys and thymus homing characteristics in rats suggested that FNC promoted thymic function [34]. A randomized, open-label, controlled clinical trial of FNC tablets for mild and frequent COVID-19 showed that compared with standard antiviral therapy, FNC treatment resulted in a mean reduction in nucleic acid-negative conversion time of 4.5 days [35].

Moreover, FNC treatment accelerated viral elimination (virus clearance time of approximately 5 days) and improved lung function. In patients with moderate COVID-19, it maintained vital signs and significantly reduced the time for symptom improvement. The oral administration of FNC tablets in rhesus monkeys with SARSCoV-2 infection and patients with COVID-19 reduced viral load, inflammation, and organ damage [34]. The drug showed no adverse events in patients with COVID-19 [36]. The drug was thus used to treat patients with COVID-19. A clinical trial (NCT05033145) using FNC demonstrated that the drug reduced viral load, inflammation, and organ damage. It is worth mentioning that Multiple clinical trials are ongoing (NCT05697055) based on small dosages (5 mg/day, for up to 14 days), rapid viral decline. Over 800 patients with mild, moderate, and severe disease have been enrolled in a phase III clinical trial (CXHL2000162), with viral load and clinical benefit as evaluation indicators, which are highly conducive to a comprehensive and integrated assessment of drug efficacy.

3.1.3. Ribavirin

Ribavirin (RV), a synthetic guanosine nucleoside, is intended for treating some forms of hepatitis C. RV represents a non-interferon–inducing viral inhibitor chemotherapeutic agent with broad-spectrum activity against several RNA and DNA viruses; it interferes with the synthesis of viral mRNA.The FDA gives dosing guidance for ribavirin tablets, capsules, or oral solution for one indication: that is, in combination with interferon alpha-2b for the treatment of chronic hepatitis C (CHC) [37,38],and only in patients 3 years of age and older (note: ribavirin alone is not effective for the treatment of CHC). In October 2016, the FDA approved Navinta's ribavirin inhaler for treating severe lower respiratory tract infections in hospitalized infants and children with respiratory syncytial virus (RSV) infection [39,40]. RV posed significant dose-limiting toxicities, such as hemolytic anemia, with reduced hemoglobin levels within the first 1–2 weeks of treatment [41]. Clinical studies demonstrate that RV has a significant therapeutic effect in the early stages of SARS-CoV-2 pathogenesis [42,43]. Numerous clinical studies conducted to date have shown no serious adverse effects. The dose used in the treatment of viral hepatitis C is the same as that used in the treatment of SARS-CoV-2 (500 mg/day), and the dose used in the treatment of viral respiratory tract infections is 450 mg/day.

3.1.4. Oseltamivir

Oseltamivir, a neuraminidase inhibitor, is used for preventing and treating influenza. It prevents and treats influenza A virus (including the H1N1 pandemic) and influenza B virus infections [44]. Oseltamivir exerts its antiviral activity by inhibiting the activity of viral neuraminidase found on the surface of the virus, thereby preventing host cell outgrowth, viral replication, and infectivity. Tan et al. [45] used computer evaluation and molecular docking analysis techniques to demonstrate that oseltamivir carboxylic acid was more conducive to effective binding to the active site of 3-chymotrypsin-like protease (3CLpro), thereby blocking viral replication. In a single-center retrospective cohort study, the administration of oseltamivir was associated with shorter hospital stays, earlier recovery and discharge, and lower mortality [46]. *In vitro* and retrospective studies found that oseltamivir was ineffective against SARS-CoV-2 *in vitro* and that its clinical use failed to improve the signs and symptoms of patients or delay the disease progression [45]. Notably, gastrointestinal symptoms can affect a small proportion of patients with COVID-19 [47]; a systematic assessment of oseltamivir (Influenza) showed a reduction in the proportion of diarrhea [48].

Therefore, it is speculated that there would be an additional benefit if oseltamivir is used for treating SARS-CoV-2 infection. The results are optimistic when the drug is combined with some antiviral agents.

3.2. Anti-inflammatory drugs and immunotherapy

SARS-CoV-2 triggered the proliferation of mast cells in the submucosa of the respiratory tract [49], thereby activating the NF-kB pathway and increasing the inflammatory responses. Consequently, there is a higher risk of inflammation-associated cytokine storms following viral infection [50]. In addition, T cell reduction and functional failures have been observed in patients with COVID-19 [51]. Therefore, particularly in critically ill patients infected with SARS-CoV-2, blocking the overactive inflammatory response, thereby activating innate and adaptive immune responses, could be an effective strategy for treating COVID-19. Researchers are currently targeting anti-inflammatory drug repositioning that cures or prevents multiorgan dysfunction and lung injury caused by infection-related inflammation[52–54]. Researchers are actively investigating immunotherapy, including but not limited to recovery plasma, mesenchymal stem cells, and monoclonal antibodies. Monoclonal antibodies are proteins synthesized in the laboratory to help the immune system fight viruses. Currently, monoclonal antibodies, such as Tocilizumab[55–57], and Bebtelovimab [58,59] are being widely and extensively tested in phase III/IV clinical trials.

3.2.1. Colchicine

Colchicine is derived from colchicum or autumn saffron, a plant in the lily family [60]. It is used as an alkaloid to relieve the painful symptoms of gout attacks and remedy the inflammatory symptoms of familial Mediterranean fever, an inherited auto-inflammatory disease [61,62]. Colchicine disrupts cell division by inhibiting the inflammatory response triggered by microtubulin. Specifically, Colchicine disrupts the inflammatory vesicle complex in the monocytes and neutrophils, activating interleukin-1 (IL-1) and IL-18 [63]. Cytokines are associated with the severity of COVID-19 by inhibiting the release of IL-1β [64].

In an experimental model of acute respiratory distress syndrome (ARDS), colchicine reduced inflammatory lung injury and respiratory failure by interfering with leukocyte activation and recruitment [65]. SARS-CoV-2 activates the inflammatory process by activating protein 3 of the pyrin structural domain (NLRP3); specifically, NLRP3 activation occurs early in SARS-CoV-2 infection and triggers a cytokine storm. Colchicine can target NLRP3 inflammatory vesicles to reduce excessive inflammation.

Simultaneously, a phase III, randomized, double-blind, adaptive, placebo-controlled, multicenter trial was conducted in Brazil, Canada, Greece, South Africa, Spain, and the USA. In patients with PCR-confirmed COVID-19, colchicine resulted in lower mortality or hospitalization rates than placebo. The control group received medication according to the COVID-19 routine (protocol), and patients in the intervention group received a loading dose of colchicine 1.5 mg on top of the usual treatment, followed by 0.5 mg 60 min later if no gastrointestinal adverse effects were observed. a single dose of 1.0 mg colchicine was given in the context of coadministration of azithromycin. Maintenance doses were all 0.5 mg colchicine twice daily (once daily for patients weighing $<$60 kg). The 10-day cumulative event-free survival rates were 83 % and 97 % in the control and colchicine groups, respectively ($P = 0.03$). Available clinical trials have proven that High Doses of Colchicine significantly improve or clear SARS-CoV-2 [66,67], only improving the time to clinical deterioration relative to mild to moderate patients.

3.2.2. Tocilizumab

Tocilizumab is an IL-6 receptor antagonist used for treating rheumatoid arthritis [68], cytokine release syndrome (CRS), systemic juvenile idiopathic arthritis [69], and giant cell arteritis [70] and is administered by an intravenous and/or subcutaneous injection. IL-6 is a cytokine produced by T cells, B cells, lymphocytes, monocytes, and fibroblasts. IL-6 evokes antibody production, induces cytotoxic T-cell differentiation, and inhibits regulatory T-cell differentiation [71]. Tocilizumab binds to soluble and membrane-bound IL-6 receptors and prevents IL–6–mediated inflammation. Tocilizumab has been investigated as a possible treatment for severe COVID-19 in 2019. Despite the lack of direct antiviral effects, tocilizumab reduced immune-induced organ damage caused by severe SARS-CoV2 infection [72].

The pooled risk ratio estimates indicated that tocilizumab treatment predicted better overall survival in patients with COVID-19, particularly in severe cases [73]. A systematic evaluation and meta-analysis documented an even stronger association of tocilizumab treatment with good prognosis in patients with COVID-19 requiring mechanical ventilation, despite a higher incidence of secondary infections [74]. A phase IV clinical trial (NCT04730323) using tocilizumab in patients with COVID19-associated CRS claimed that this drug is an effective treatment option for critically ill patients with COVID-19, substantially reducing their oxygen requirements and thereby reducing ICU stay duration, the median length of stay, and mortality [56]. Clinical trials have also shown that Tocilizumab treats patients with mild-to-moderate COVID-19 who are at a high risk of developing severe COVID-19 [55,74,75]. The drug significantly reduces the probability of COVID-19 patients developing serious illness [56,72].

3.2.3. Dexamethasone

Dexamethasone is a glucocorticoid with potent anti-inflammatory properties used for treating various inflammatory diseases, including bronchial asthma and endocrine and rheumatic diseases; it is commonly intramuscularly and intravenously administered. Apart from binding to specific nuclear steroid receptors, dexamethasone interferes with NF-kB activation and apoptotic pathways. This drug upregulates CTLA-8 mRNA and protein in CD4 and CD4 T cells and blocks CD28-mediated cell cycle entry and differentiation [76]. Lower corticosteroid doses possess anti-inflammatory effects and promote anti-inflammatory genes, such as IL-10, whereas higher doses exert immunosuppressive effects [77]. A randomized clinical trial indicated that dexamethasone caused a significant increase in the number of days of survival and prevented the need for mechanical ventilation in patients with moderate or severe COVID-19.

A phase IV clinical study (NCT04530409) demonstrated that the timing of corticosteroid administration is vital for recovery and reducing mortality in COVID-19. Patients with the most severe form of COVID-19 experience a hyperinflammatory state (cytokine storm) that shares features with a rare blood disorder called hemophagocytic lymph histiocytosis. Immunosuppression can help these patients. By contrast, immunosuppression in the early stages of viral infection may increase viral replication and exacerbate the disease. A multicenter randomized controlled trial in Spain [78] demonstrated that the early administration of dexamethasone reduced the duration of mechanical ventilation and overall mortality in patients with established moderate-to-severe ARDS.

The timing of dexamethasone use is critical for treating SARS-CoV-2 infection; moreover, its combination with other drugs has the potential for therapeutic advances. A prospective controlled nonrandomized study [79] indicated that treatment with raltegravir/dexamethasone significantly reduced mortality and length of hospital stay and accelerated SARS-CoV-2 clearance compared with dexamethasone alone. Regarding treatment, the safety assessments of systemic corticosteroids compared with low-dose (6 mg–8 mg) dexamethasone suggested a reduction in all-cause mortality after 30 days with high-dose (12 mg or higher) dexamethasone [80]; The role of glucocorticoids in improving survival in patients with severe SARS-CoV-2 is primarily established, with excellent anti-inflammatory effects. Glucocorticoids are currently not recommended in mildly ill patients; prolonged use of broad-spectrum antibiotics should be avoided.

3.2.4. Poly (ADP-ribose) polymerase 1 inhibitor

Future research directions should focus on selecting different types of hormones, a more refined population of beneficiaries and the exploration of dosing. The activation of poly (ADP-ribose) polymerase 1 (PARP1), a post-translational modifying enzyme, has proven to be associated with several inflammatory and viral diseases [81]. PARP1 inhibits viral growth by suppressing viral replication and blocking the binding of nucleocapsid proteins to viral RNA [82]. PARP1 inhibitors are used in clinical practice for treating certain cancers, such as breast, ovarian, and pancreatic cancers. The mechanism of its inhibition of SARS-CoV-2 may involve an essential RNA-binding protein—HuR—that interacts with PARP1 and is hetero-protonated by PARP1 [83]. HuR influences the expression levels of target genes in cells by modulating the stability and translation efficiency of target mRNAs, which comprise cytokines/chemokines and proinflammatory factors. Chemokines play an important role in adaptive immune response [84,85]. The interaction between PARP-1 and the nuclear factor-κB (NF-κB) pathway promotes the production of proinflammatory cytokines, such as TNF-α, IL-6, INF-γ, E-selectin, and ICAM-1 and the expression of nitric oxide synthase[86–88]. The PARP inhibitor PJ34 significantly inhibited lipopolysaccharide (LPS)-induced lung inflammation in mice [83]. Several *in vitro* studies revealed that negative PARP inhibitors can significantly block SARS-CoV-2 virus replication, suggesting a potential therapeutic approach to PARP inhibitors against COVID-19 or its variants [81,89]. Notably, the theoretical aspects of PARP as a therapeutic option are currently well established. Clinical trials are expected to be conducted to prove its feasibility.

3.3. Selective estrogen receptor modulator

COVID-19 pandemic data indicated sex differences in morbidity and mortality, with men showing a higher likelihood of experiencing complications from SARS-CoV-2 infection and, in particular, middle-aged and older men having a much higher risk of mortality

and severe illness compared with women [90]. Women, particularly premenopausal women, were protected [91]. Immune reactivity surrounding ovulation correlates with high estradiol concentrations. Postmenopausal hormone replacement therapy (HRT) and combined contraceptive use produced side effects similar to an effective immune response and protection against viral infection [92]. Therefore, selective estrogen modulators (SERMs) are the primary determinant of sex differences; the immunomodulatory role of estrogen in SARS-CoV-2 infection is of greater interest as it may explain the male morbidity, mortality, and susceptibility to the severity of this disease. It is widely known is that estrogen exerts significant anti-inflammatory and immunomodulatory effects in COVID-19 [92,93]. Recent studies have shown that SARS-CoV-2 S proteins bind to and regulate estrogen receptors. Estrogen reduces SARS-CoV-2 infectivity by modulating proinflammatory signaling pathways [94–96]. Owing to the off-target effects of HRT, new nonhormonal agents, such as raloxifene and tamoxifen, have been developed via the evaluation of selective pharmacological effects on tissue-specific therapeutic targets to reduce adverse events.

3.3.1. Tamoxifen

Tamoxifen is a nonsteroidal antiestrogen used for treating estrogen receptor-positive breast cancer and preventing the incidence of breast cancer in high-risk groups [96,97]. The antiviral rationale may be related to viral entry and replication inhibition and cytopathic effects (CPEs). Tamoxifen interferes with SARS-CoV-2 entry by promoting endolysosomal alkalinization, altering endolysosomal kinetics, and directly inhibiting androgen receptor signaling via three approaches [98]. Zu et al. evaluated the antiviral activity of two drugs [99] and found that tamoxifen demonstrated potent antiviral activity. Tamoxifen inhibited SARS-CoV-2 infection in Caco-2 cells in a dose-dependent manner and this drug strongly antagonized SARS-CoV-2 infection *in vitro*. Correlative studies supported the immunomodulatory role of estrogen, which plays an acute role in viral infection and wound repair and reduces the devastating effects of the virus on the lungs and the severity of symptoms. The combination of isotretinoin and tamoxifen being evaluated in another trial (NCT04389580) is expected by researchers to treat or remit adult patients with severe SARS-COV-2. Although *in vitro* efficacy evidence is clear [99,100], limited clinical evidence supports its antiviral efficacy.

In addition, raloxifene counteracted the spike-mediated activation of ADAM17 in human lung cells. In a multicenter, double-blind, parallel-group phase II/III trial, raloxifene was investigated for treating adult patients with early mild-to-moderate COVID-19; the findings demonstrated a reduced time to viral elimination and a safety profile consistent with other reports. Imamura et al. showed synergistic antiviral effects of raloxifene and pioglitazone via induced pluripotent stem cell screening.

3.3.2. Raloxifene

Raloxifene, being a selective estrogen receptor modulator (SERM), binds to estrogen receptors [101]. Iaconis et al. [102]claimed that raloxifene as a potential pharmacological agent against SARS-CoV-2. Iaconis et al. tested the drug using the most common SARS-CoV-2 variant and found its ability to contrast viral CPEs superior. As predicted by computational studies, tamoxifen treatment did not directly affect spike/ACE2 interactions or viral internalization in infected cell lines. The validation of the hypothesis that raloxifene and tamoxifen are both effective will set the foundation for further research into estrogen receptor modulation as a therapeutic tool for treating other infectious diseases.

3.4. Miscellaneous

3.4.1. Ursodeoxycholic acid

UDCA is frequently prescribed for treating steroidal gallbladder stones, biliary depression, and bile-depleted liver diseases [103,104]. An overdose occurs as a result of diarrhea. Typically, overdose is a rare event owing to poor absorption of UDCA at higher doses and excessive elimination in feces. Computational analysis revealed that UDCA is membrane-bound and reduces the internalization of SARS-Cov2 in host cells [105]. Studies [106,107] have revealed that UDCA inhibits ACE2 expression in human nasal epithelium and contributes to the inhibition of abnormal airway epithelial cell migration. Therefore, UDCA has been shown to "target" SARS-CoV-2's passage into human cells at a receptor on the cell surface called ACE2. Because the drug targets the host cell rather than the virus, it can prevent infection by the new coronavirus and may have the ability to prevent infection by future mutants of the new coronavirus. Moreover, UDCA increases alveolar fluid clearance in ARDS [108]. Hence, preventing SARS-CoV-2 infection may be achieved by inhibiting cytokine storm syndrome. UDCA therapy may be beneficial in reducing COVID-19 infection risk, alleviating symptoms, and shortening the recovery time in patients with chronic liver disease [109]. However, there is too little data from clinical studies on UDCA, and UDCA treatment does not appear to have significant effects on the outcome of COVID-19. Specially designed prospective studies are needed to evaluate efficacy in preventing infection and severe disease [110].

3.4.2. Doxycycline

Doxycycline is a nontraditional broad-spectrum antibiotic synthesized from hygromycin with a proven safety profile. Indicated for treating a wide range of infections with gram-positive and gram-negative bacteria, aerobic and anaerobic bacteria, and other types of bacteria [111], doxycycline plays a considerable role for treating pneumonia and has several advantages, including cardiac safety, easy lung tissue accessibility, and potential antiviral and immunomodulatory effects exerted via various mechanisms [112]. Mahmud et al. demonstrated that patients with mild-to-moderate COVID-19 infection treated with ivermectin and doxycycline recovered earlier and were less likely to be exacerbated [113]. Stambouli [114]conducted a phase IV clinical trial (NCT04370782) with doxycycline and zinc prophylaxis in patients with reduced risk of SARS-CoV-2. Clinical trials have shown that doxycycline alone can significantly improve symptoms in patients at a high risk of severe disease [115].

Doxycycline 100 mg twice daily for seven days proved to be safe and non-inferior in terms of efficacy when compared to

hydroxychloroquine-azithromycin for preventing clinical worsening of mild symptomatic or asymptomatic COVID-19 and achieving virological suppression [116]. Regarding clinical data performance, doxycycline is a potential and promising clinical drug candidate, particularly for patients at a high risk of severe pulmonary disease, but not for conventional therapy [117]. However, *in vitro* experiments with Doxycycline have inadequate data to support this. Caution should be exercised that any imbalance caused by inappropriate or indiscriminate use of repurposed drugs leads to a catastrophic increase in antimicrobial resistance.

3.4.3. Cepharanthine

Cepharanthine (CEP), with its naturally occurring alkaloid origin from Stephania cepharantha Hayata, has demonstrated unique anti-inflammatory, antioxidant, immunomodulatory, antiparasitic, and antiviral properties [118]. The analysis of CEP by transcriptomics effectively reversed most dysregulated genes and pathways in infected cells [119], including the endoplasmic reticulum stress/unfolded protein response and heat shock factor-mediated heat shock response. These are genomic expressions of viral disruptions and genes associated with cellular stress responses. CEP inhibits NF-κB activation, lipid peroxidation, nitric oxide production, cytokine production, and cyclooxygenase expression [120]. The anti–COVID–19 activity of CEP has been demonstrated in *in vitro* assays [121]. Currently, many *in vitro* experiments have demonstrated the antiviral efficacy of CEP against SARS-CoV-2 [122–126]. A new study analyses the broad-spectrum anti–COVID–19 activity of a series of metabolites in the natural biosynthetic pathway of CEP [127]. All these findings are critical for viral replication and inflammatory responses. Currently, Cepharanthine is a promising drug; however, several *in vivo* or clinical trials are required to validate its safety and reliability for robustness and adaptability of clinical treatment.

3.4.4. Metformin

Metformin, a biguanide antihyperglycemic drug, is the first-line therapy used for treating type II diabetes mellitus (T2DM) [128, 129]. Moreover, it is used for treating insulin resistance in polycystic ovary syndrome [130]. The precise mechanism of action of metformin has extensively been studied in recent years[131–133]. Because metformin exerts multiple actions in addition to hypoglycemic effects, including anti-inflammatory effects, it can be speculated that it may positively influence the prognosis of T2DM patients with COVID-19 [134]. In a zebrafish model, metformin alleviated cytokine storms, reduced viral entry into cells, and prevented microvascular damage and secondary fibrosis [135]. An intriguing point is regarding its unique microcirculatory protective effect because the deterioration of COVID-19 disease largely occurs owing to severe defects in microvascular structure and function

Table 3
Mechanisms, targets, and clinical side effects of the candidates.

Drug name	Target	Mechanism	In vitro data supports (or does not support) efficacy	clinical side effect
Favipiravir	RdRp	Blocking virus transcription and replication	Support	A higher incidence of hyperuricemia and elevated alanine aminotransferase
Azvudine	RdRp	Blocking virus transcription and replication; Promotes thymic function	Support	No side effects
Ribavirin	RNA polymerase	Blocking virus transcription and replication;	Support	No side effects
Oseltamivir	3CLpro	Binding the active site of 3CLpro	Not Support	No side effects
Colchicine	NLRP3	Reducing cytokine storms; Interferes with leukocyte activation	Support	Abdominal pain, nausea, vomiting, diarrhea, and hypovolemia, multiorgan failure
Tocilizumab	IL-6	Reducing cytokine storms; Inhibits the production of fibronectin, albumin, and transferrin	Support	No side effects
PARP1	HuR	Interacts with PARP1 and is hetero-protonated by PARP1	Support	N/A
Dexamethasone	Inflammatory cytokines	Reducing cytokine storms;	Support	Glaucoma, cataracts, fluid retention, high blood pressure, psychological effects , weight gain or increased risk of infections and osteoporosis
Tamoxifen	lysosome	Altered endolysosomal kinetics; Promotion of endolysosomal alkalinization; Direct inhibition of AR signaling	Support	N/A
Raloxifene	ADAM17	Counteracting Spike-mediated activation of ADAM17 in human lung cells	Support	No side effects
Ursodeoxycholic acid	FXR	Blocking FXR proteins directly reduces the amount of ACE2	Support	N/A
Doxycycline	3CLpro	Regulation of 3CLpro; down-regulation of inflammatory factors	Not Support	Antibiotic-resistant
Cepharanthine	NSP13	Reversal of most dysregulated genes and pathways in infected cells; Inhibition of expression of relevant inflammatory factors	Support	N/A
Metformin	IL-6	Enhanced ACE2 expression; down-regulation of inflammatory factors	Support	Acidosis and lactic acidosis

[136]. Metformin inhibits NLRP3 inflammatory vesicle activation and IL-1β production in cultured and alveolar macrophages as well as inhibits nondependent IL-6 secretion by inflammatory vesicles, resulting in the attenuation of LPS- and SARS-CoV-2–induced acute respiratory distress syndrome (ARDS) [137]. In addition, the safety of metformin as a first-line antihyperglycemic agent is unquestionable. Clinical and preclinical data suggest that metformin provides cardiopulmonary protection against COVID-19 by enhancing ACE2 expression [138,139]. In clinical trials, a further apparent benefit of metformin use observed before diagnosis [140,141]may be owing to the inhibition of neutrophil extracellular trap formation by this drug during infection and periods of disease exposure with SARS-CoV-2, rather than its anti-inflammatory activity. A related meta-analysis showed that mortality and severity in patients with T2DM were attenuated by the effects of metformin treatment [142]. Particular attention is required for the indicated population; however, reports of increased acidosis and lactic acidosis in patients with more severe COVID-19 caution that metformin should be discontinued in patients with hypoxemia or acute renal disease. A multicenter, quad-blind, parallel randomized phase III clinical trial proves that a 42 % reduction in the risk of developing long SARS-CoV-2 infection was observed when metformin was orally administered for 14 days and followed up to 300 days post-infection and a 63 % reduction in the risk of developing long SARS-CoV-2 infection was observed when metformin was used within 4 days of symptom onset [143]. Another clinical [144]demonstrated that metformin treatment reduced hospitalization, emergency room risk, and mortality due to new coronavirus infections by about 40 %. Therefore, metformin can alleviate SARS-CoV-2 infection in patients with T2DM and is promising for long SARS-CoV-2 infection. However, prospective studies on the clinical and metabolic role of metformin in COVID-19 are required [139].

4. Discussion

Drug repositioning represents an attractive approach to address an unsatisfied clinical need in infectious diseases. Looking for relationships between new coronaviruses and chronic diseases, metabolic diseases, and cancerous tumors. Interestingly, adult patients with underlying diseases are more or less symptomatically distinct, and the severity of SARS-CoV-2 is low in patients who are taking drugs for chronic diseases. In addition, we considered whether the medications typically taken by patients with chronic or metabolic diseases might affect this. In addition, we have to consider repurposing drug dosing regimens, as different indications with different disease stages require different doses. The fact that some drugs only work in the early stages or in mild-to-moderate patients, and that comorbidities, age of the population to be treated, etc., change rapidly,and even response to interventions, makes conclusions about the efficacy of a product candidate very challenging.

Despite the superior results in *in vitro* and *in vivo* trials, several drugs tested in extensive clinical trials (Table 3.), such as favipiravir, do not support routine clinical use owing to side effects. Oseltamivir, tamoxifen, and dexamethasone are more suitable for clinical use in combination for treating patients with severe SARS-CoV-2 infection. Tamoxifen and dexamethasone are more suitable for clinical combination therapy in patients with mild or severe Sars-CoV-2 infection. Notably, FNC and raloxifene can act against mutated Sars-CoV-2 infection. In contrast to other repurposed antirheumatic drugs used in patients with COVID-19, colchicine possesses multiple antiviral and anti-inflammatory capacities and exerts multiple effects on the inflammatory cascade response. Despite its lower potency compared with glucocorticoids (particularly dexamethasone), colchicine is available for oral administration. Additional time and research will be needed to verify these exciting new findings and possible new effects.

We must find effective ways to prevent infection, severe disease, and long-term sequelae, thereby solving this challenging issue that plagues the world. Simultaneously, we ought to be aware that several drugs exert many potential multiple effects but this does not mean they will definitively affect the patients with mutated SARS-CoV-2 infection or endangered patients. Further, we reiterate that most drugs are prescribed and should not be taken by individuals with no indications or for preventing Sars-CoV-2 and that blind use increases the risk of adverse events.

From a historical point of view, the strategy of drug repositioning has solved numerous diseases that were challenging[144–148]. In the face of the current pandemic crisis, this strategy is undoubtedly one of the most substantial contributors to the fight against viruses in the past and the future.

Disclosure statement

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CRediT authorship contribution statement

Yutong Liang: Writing – review & editing, Writing – original draft, Conceptualization. **Xiaoxiao Quan:** Resources. **Ruolan Gu:** Formal analysis. **Zhiyun Meng:** Writing – review & editing. **Hui Gan:** Methodology. **Zhuona Wu:** Funding acquisition. **Yunbo Sun:** Methodology. **Huajie Pan:** Resources. **Peng Han:** Funding acquisition. **Shuchen Liu:** Writing – review & editing. **Guifang Dou:** Writing – review & editing.

Declaration of competing interest

I also certify that I have disclosed any financial or non-financial relationships that may be interpreted as constituting a conflict of interest about this manuscript. I understand that this information will be subject to peer review, and I am willing to provide further information or clarification if required.

I confirm that I have no known conflicts of interest that would influence the results or interpretation of the data presented in this manuscript, and I understand that failure to disclose a conflict of interest is unethical and may result in sanctioning imposed on me.

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