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Review article

Potential drug development and therapeutic approaches for clinical intervention in COVID-19

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ABSTRACT

While the vaccination is now available to many countries and will slowly dissipate to others, effective therapeutics for COVID-19 is still illusive. The SARS-CoV-2 pandemic has posed an unprecedented challenge to researchers, scientists, and clinicians and affected the wellbeing of millions of people worldwide. Since the beginning of the pandemic, a multitude of existing anti-viral, antibiotic, antimalarial, and anticancer drugs have been tested, and some have shown potency in the treatment and management of COVID-19, albeit others failed to leave any positive impact and a few also became controversial as they showed mixed clinical outcomes. In the present article, we have brought together some of the candidate therapeutic drugs being repurposed or used in the clinical trials and discussed their clinical efficacy and safety for COVID-19.

1. Introduction

The sudden outbreak and rapid spread of novel coronavirus (subsequently named SARS-CoV-2) severely impacted the healthcare system and the global economy. SARS-CoV-2, reported in central China's Hubei Province in December 2019, mainly causes respiratory and intestinal infection in humans and other animals [1–3]. The International Committee on Taxonomy of Viruses labelled it as SARS-CoV-2, and the world health organization (WHO) named the disease as Coronavirus disease-2019 or COVID-19 caused by SARS-CoV-2 [4–5]. Previously, six coronaviruses have been described, namely human coronavirus (HCoV)-229E, HCoV-OC43, HCoV-NL63, HCoV-Hong Kong University 1 (HCoV-HKU1), severe acute respiratory syndrome coronavirus (SARS-CoV), and Middle East respiratory syndrome coronavirus (MERS-CoV). The first two human coronaviruses (HCoV-229E and HCoV-OC43) were discovered in the 1960s, which caused mild respiratory infections [6–9]. The first four CoVs were capable of causing pneumonia and bronchiolitis in children and are also associated with enteric and neurological diseases [9–14]. In Guangdong Province, China, SARS-CoV was first discovered in November 2002 and then spread in North America, Europe, and other Asian countries [15–17]. With a 10–15% mortality rate, SARS-CoV affected 8422 cases in 32 countries and resulted in 961 deaths [18]. The MERS-CoV epidemic outbreak first surfaced in Saudi Arabia in 2012 [19–20], but a significant outbreak occurred in the Republic of Korea in 2015 [21]. This virus affected a total number of 1401 individuals and lead to 543 deaths registering 39% of fatalities worldwide, while in Saudi Arabia alone, mortality was 37.5% [22].

SARS-CoV-2 has its unique features and has become a threat to global health. As of now, SARS-CoV-2 has spread around the globe, with more than 118 million cases confirmed and has caused fatality to over 2.6 million people. The coronaviruses belong to a family of viruses that possess a single-stranded positive-sense RNA genome [23]. Like other RNA viruses, this family also gets easily disseminated among humans and animals via close contact, sneezing, coughing, talking, or sharing common spaces [17].

1.1. Classification

International Committee on Taxonomy of Viruses (ICTV) in its tenth report, classified coronaviruses in order- Nidovirales, suborder- Cornidovirineae, family- Coronaviridae, and subfamily- Orthocoronavirinae. As per genomic and serological analysis, subfamily- Orthocoronavirinae is classified into 4 genera, namely: *Alphacoronavirus*, *Betacoronavirus*, *Gammacoronavirus*, and *Deltacoronavirus*. SARS-CoV-2 belongs to *Betacoronavirus* under subgenus- *Sarbecovirus* and has 96% genetic similarity with bat CoV RaTG13 indicating at its zoonotic origin.

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1.2. Mechanism of cell entry and replication of SARS-CoV-2

Since the outbreak of COVID-19, tremendous research is being carried out to understand its structure, mechanisms of infection and replication. Coronavirus contains a single-stranded positive-sense RNA, encircled inside a nucleocapsid (N). Apart from N protein, other structural proteins that are encoded in coronavirus include spike (S), membrane (M), and envelope (E) proteins [24–25]. The spike protein is a homotrimeric glycoprotein with 1255 amino acid residues, and each monomer can be sub-divided into S1 and S2 domains.[26] The mechanism of SARS-CoV-2 cell entry and replication has been illustrated in Fig. 1. Initially, the S1 domain of spike protein and surface receptor ACE2 mediates coronavirus binding to the host cell [2]. The S1 protein is then cleaved by transmembrane serine protease 2 (TMPRSS2) or by cathepsin L, and fusion peptide of S2 domain facilitates the fusion of E protein with cellular membranes [27–28]. After the virus enters the cell, it is uncoated and genomic RNA of the virus is then released into the cytoplasm and translated into two polyproteins, namely, PP1A and PP1AB [29–30]. The viral genome is then converted into a negative-sense viral RNA genome, used as a template to synthesize positive-sense genomic and sub-genomic viral RNA. Genomic RNA and nucleocapsid (N) protein are replicated or transcribed in the host cytoplasm. However, other viral structural proteins, such as spike (S), envelope (E), and membrane (M), are transcribed and translated into the endoplasmic reticulum, which is then inserted into the Golgi body [31–33]. The viral genomic RNA and proteins such as N, S, E, and M are further assembled in the ER–Golgi intermediate compartment (ERGIC). Finally, the newly generated positive-sense RNA genomes are released through the plasma membrane [33].

It has been shown that entry of SARS-CoV-2 is not possible in cells without ACE2 expression. Other receptors e.g. dipeptidyl peptidase 4 (DPP4) or aminopeptidase N do not mediate SARS-CoV-2 entry, indicating that ACE2 is essential for SARS-CoV-2 entry into the host cell [2]. The studies have shown that the S protein of SARS-CoV-2 has a much higher binding affinity towards ACE2, which is 10–20 fold greater than that of SARS-CoV [34], making SARS-CoV-2 more contagious than other coronaviruses. ACE2 is highly expressed on type II alveolar epithelial cells making lungs susceptible to SARS-CoV-2 infection [35–36]. However, its expression on the surface of epithelial cells in the nasopharynx, nasal mucosa, and oral cavity is low. Also, ACE2 is highly expressed on myocardial cells, urothelial cells, and the kidney's proximal tubule cells [35–36]. Besides, ACE2 and TMPRSS2 are abundantly expressed in the small intestine, particularly in the ileum. [37–38]. ACE2 is also highly expressed in lower airways among smokers and people with chronic obstructive pulmonary disease (COPD), which increases the severity of covid-19 among these people [39]. It has also been reported that ACE2 level is upregulated by interferons (IFNs) that increase the binding of SARS-CoV-2 via ACE2 [40]. Recent findings showed that overexpression

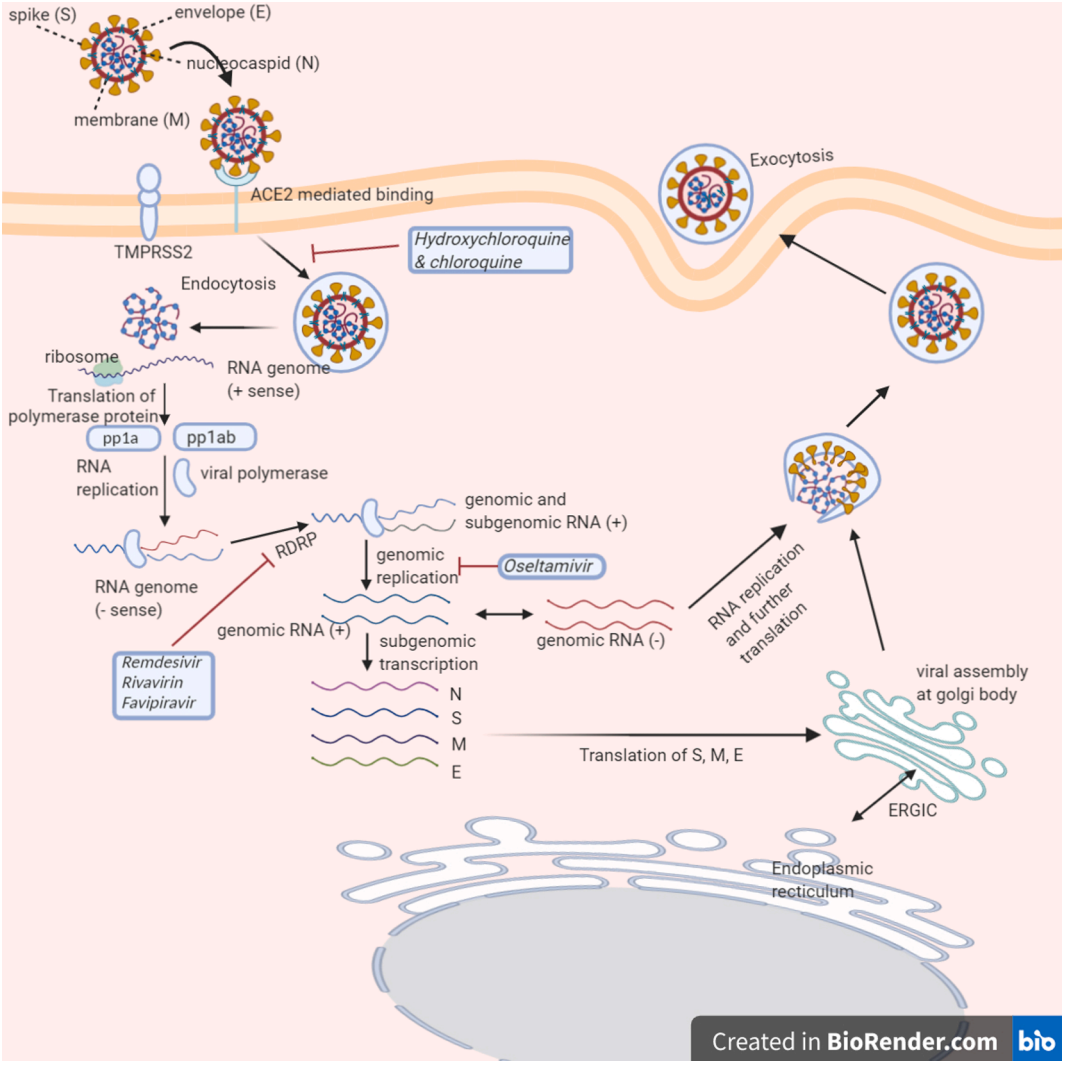

Fig. 1. Illustration of the mechanism of SARS-CoV-2 entry into the cell and its replication. **Therapeutic Approaches:** Under this section, various drug candidates being either used in trials or repurposed to treat COVID-19 are discussed.

of TMPRSS2 in Vero-E6 cells of African green monkeys considerably elevates SARS-CoV-2 infectivity [41]. Small-molecule serine protease inhibitors such as nafamostat and camostat prevent SARS-CoV-2 entry into host cells in a dose-dependent manner [42–43].

2. Anti-viral drugs

2.1. Remdesivir (GS5734)

It is an adenosine triphosphate derivative having an anti-viral property. Gilead Sciences initially developed it in 2009 to treat hepatitis C. However, it did not yield positive results against hepatitis C [44]. Therefore it was investigated to treat Ebola virus disease and Marburg virus infections in 2016 [45]. In 2017, Sheahan et al. showed its potential inhibitory activity in human respiratory epithelial cell cultures having EC50 values 0.07 μM against SARS-CoV and 0.069 μM against MERS-CoV [46].

Remdesivir is a prodrug of GS-441524, both of which undergo phosphorylation into an active nucleoside triphosphate in the host cell. The triphosphate form of Remdesivir or GS-441524 is analogous to adenosine triphosphate (ATP), thus it competes with ATP for interaction with viral RdRp enzymes. Remdesivir binding with viral RNA restricts RNA synthesis, resulting in decreased viral RNA production [47–48]. Several studies have shown the effects of remdesivir on coronaviruses both *in vitro* and *in vivo* using the mouse model and nonhuman primate models. Wang et al. demonstrated that remdesivir is effective in preventing virus infection. They measured cytotoxicity by CCK8 assay using VeroE6 cells and showed EC_{50} value of 0.77 μM; CC50 > 100 μM and selectivity index (SI) > 129.87. Further, it also showed potent inhibition towards SARS-CoV-2 virus infection in human liver cancer cells (Huh-7) [43]. Remdesivir also has superior antiviral activity than drugs lopinavir and ritonavir, and it effectively inhibited MERS-CoV replication *in vitro*, and showed EC_{50} 0.09 μM. In the non-human primate and mice models of MERS-CoV infection, both prophylactic and therapeutic remdesivir enhanced pulmonary function, minimized viral load in lung tissues, and reduced lung lesions' harshness [49–50]. A case study on the first COVID-19 patient in the USA by Holshue et al. indicated that intravenous administration of remdesivir helped significantly in the recovery of

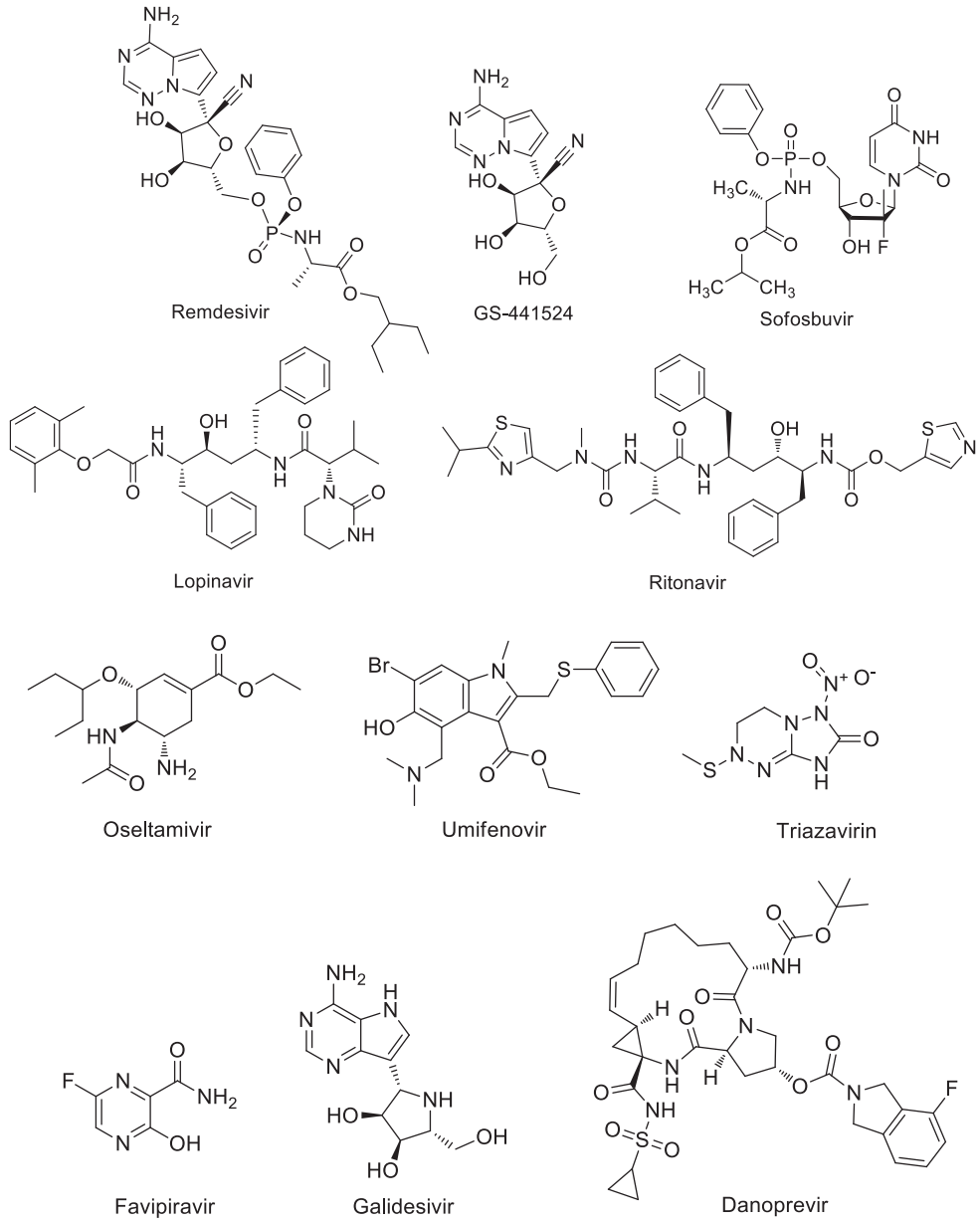

Fig. 2. Chemical structures of antiviral drugs with anti-SARS-CoV-2 activity.

the patients [51]. These findings support ongoing investigations of remdesivir as a potential therapeutic drug against COVID-19.

2.2. Lopinavir/ritonavir (Kaletra)

Lopinavir/ritonavir (Fig. 2), also known as Kaletra, are protease inhibitors approved by the FDA to treat HIV/AIDS infection. This drug is produced by combining a low dose of ritonavir with lopinavir [52–53]. Lopinavir alone has low bio-availability. However, ritonavir, a potent hepatic CYP-450 3A4 inhibitor, increased the inhibitory activity of protease inhibitors [54]. After the SARS outbreak in 2003, *in vitro* screening of various approved drugs against SARS-CoV indicated lopinavir as a potential SARS-CoV inhibitor. A cell-based assay of lopinavir against SARS-CoV in Vero E6 cells revealed IC_{50} value of 50 μM (Ki = 14 μM) [55]. The screening of compounds by Chen et al. against ten clinical isolates of SARS-CoV also identified lopinavir as potential antiviral agents [56].

Moreover, Chu et al. indicated that patients treated initially with lopinavir/ritonavir showed a lower risk of adverse clinical outcomes. The patients required less steroid usage and nosocomial infections. Further, the patients exhibited reduced viral load and elevation of peripheral lymphocyte count [57]. Based on these findings, the clinical studies for SARS-CoV-2 have also evolved. In a controlled, randomized, and open-label clinical trial involving adult COVID-19 patients, in addition to standard care patients were administered either 400 or 100 mg of lopinavir/ritonavir twice daily for 14 days or given standard care alone. The study did not yield expected outcomes [58]. On the contrary, the third confirmed positive case of COVID-19 in Korea was administered with lopinavir/ritonavir (200 mg/50 mg) orally on the 8th day of hospitalization. Interestingly, on the next day, the index patient's viral load started to decrease and showed little or undetectable SARS-CoV titers [59]. Hung et al. conducted a Phase II clinical study to treat COVID-19 patients with the triple combination of interferon beta-1b, lopinavir-ritonavir, and ribavirin. The results indicated that the triple combination of mentioned anti-viral drugs was safe and had a more significant advantage than lopinavir/ritonavir alone in reducing the symptoms in terms of viral shedding and hospital stay for patients [60].

2.3. Oseltamivir

Oseltamivir (Fig. 2) is FDA approved antiviral drug sold under the brand name Tamiflu. It is a competitive neuraminidase inhibitor used for the treatment of influenza A and B [61–62]. In a clinical study for the treatment of COVID-19 in Wuhan, China, most of the patients 124 (89.9%) treated with oseltamivir, showed no practical outcomes [63]. A Phase 4, randomized, prospective/retrospective, and controlled clinical study is currently underway to understand the comparative efficacy of Oseltamivir, Lopinavir/Ritonavir, and Abidol Hydrochloride [64]. In this study, different groups of patients will be treated with 75 mg of Oseltamivir twice per day for two weeks, 500 mg of Lopinavir/ritonavir twice per day for two weeks, and 0.2 g of Abidol hydrochloride three times per day for two weeks. A randomized control clinical study explores the efficacy of oseltamivir in combination with the drugs Hydroxychloroquine and Favipiravir to treat COVID-19 [65].

2.4. Umifenovir (Arbidol)

Umifenovir (Fig. 2) is an anti-viral drug normally used in influenza therapy [66]. Pécheur et al. have demonstrated a broad anti-viral spectrum of umifenovir against hepatitis C, Ebola virus, Human herpesvirus 8, and Tacaribe arenavirus [67]. Khamitov et al., in an *in vitro* study, demonstrated potential SARS-CoV inhibition potential of Umifenovir at a concentration of 95 μM [68]. In 2004, Masterlek™ patented Umifenovir for use as an antiviral drug against SARS-CoV [69]. A retrospective clinical trial demonstrated that combination therapy of umifenovir and lopinavir/ritonavir significantly increased the negative conversion rate of coronavirus compared with the monotherapy group with lopinavir/ritonavir alone [70]. Further, Chen et al. administered COVID-19 patients either with 1600 mg of favipiravir twice on the first day and with 600 mg in the subsequent days or 200 mg of umifenovir three times daily along with standard care for seven days [71]. The study disclosed that favipiravir is not as effective as umifenovir in the treatment of COVID-19 patients.

2.5. Favipiravir

Favipiravir (Fig. 2), a pyrazine carboxamide derivative, is an antiviral drug sold under the brand name Abigan or Avigan. It selectively inhibits RdRp enzymes of RNA viruses and used to treat influenza infection [72–73]. Favipiravir is a prodrug; it undergoes phosphoribosylation and phosphorylation in host cells to transform into active favipiravir-RTP, preventing viral RdRp [73]. Favipiravir also showed broad antiviral activities against other RNA viruses such as Arenaviridae, Bunyaviridae, Flaviviridae, Togaviridae, Picornaviridae, Caliciviridae, Filoviridae, and Rhabdoviridae [73]. It has shown its efficacy against the Ebola virus and potently inhibited Ebola virus infection *in vitro*, and provided 100% protection against aerosol E718 infection [74–75]. During the Ebola outbreak in 2014, a clinical study in Guinea showed decreased mortality rate in patients administered with favipiravir [76]. Favipiravir has also shown potent activity against the Nipah virus. Dawes et al. have demonstrated that favipiravir inhibited the transcription and replication of the Nipah and Hendra virus in an *in vitro* study. The study carried out in the Syrian hamster model showed that the animals treated with favipiravir orally twice daily or once daily subcutaneously for 14 days had complete protection from a lethal dose of Nipah virus [77]. Due to its broad-spectrum anti-viral activity and previous finding on its activity against Ebola and Nipah virus, many clinical studies have been initiated to investigate its efficacy in COVID-19. A clinical study demonstrated that favipiravir could elicit faster viral clearance. The CT scan showed better chest imaging outcomes than patients who received treatment with lopinavir/ritonavir [78]. Many other clinical trials are underway to evaluate its efficacy against COVID-19.

2.6. Triazavirin

Triazavirin (Fig. 2) is a synthetic purine nucleoside analog and a broad-spectrum antiviral drug. It is known to inhibit viral RNA synthesis [79]. It has shown a broad-spectrum antiviral activity against RNA viruses such as influenza A and B virus, Forest-Spring encephalitis, and tick-borne encephalitis [79–82]. Phase II & III clinical studies are underway to assess ribavirin's efficacy in retorting ongoing pandemic (NCT04581915).

2.7. Anti-HCV drugs

Many anti-HCV drugs have been found effective against novel coronavirus SARS-CoV-2. In SARS-CoV-2 virus infection various non-structural viral proteins such as NSP 1-14 help in RNA binding, replication, protein-phosphorylation, and counter interferon pathway [83]. In HCV replicative cycle, anti-HCV drugs target enzymes NS5A and NS5B of the virus. NS5A possesses pleiotropic actions that overlaps with many SARS-CoV-2 enzymes. NS5B is homologous to SARS-CoV-2 NSP12 RNA polymerases. Since SARS-CoV-2 and HCV are positive-sense RNA viruses, both share same replication mechanism involving RdRp that makes it a well-established target [84–85].

Sofosbuvir (SFV) inhibits HCV protein NS5B [86] and is also associated with anti-viral activity against the Zika, yellow fever, and chikungunya viruses [87–90]. Gao et al. reported that due to homology of their RNA polymerase, anti-HCV drugs sofosbuvir (SFV) could act against COVID-19 [91]. Elfiky et al. used molecular docking simulations to study interactions between SARS-CoV-2 RdRp and anti-viral drugs

(Ribavirin, Remdesivir, Sofosbuvir, Galidesivir, and Tenofovir), and reported that these drugs showed promising results against SARS-CoV-2 [92]. Authors found that Sofosbuvir could bind SARS-CoV-2 RdRp well and had binding energy −7.5 kcal/mol. Molecular docking analysis demonstrated that Sofosbuvir formed seven hydrogen bonding interactions with RDRp residues W508 (3), K512 (2), A653, W691, and 2 hydrophobic interactions with Y510 and D651 of SARS-CoV-2 RdRp. Buonaguro et al. have reported that Sofosbuvir had higher efficacy against the SARS-CoV-2 [93]. Therefore, the combination of sofosbuvir/daclatasvir has been evaluated in many small clinical trials as a therapeutic option for COVID-19 [94].

2.8. Galidesivir

Galidesivir (Fig. 2), an adenosine analog developed by BioCryst Pharmaceuticals, exhibited potent broad-spectrum activity against filovirus infections including Zika, Ebola, Yellow Fever, and Marburg virus disease by blocking viral RNA polymerase [95–96]. It also exhibited potent antiviral activity against other RNA virus families such as arenaviruses, bunyaviruses, paramyxoviruses, filoviruses, flaviviruses, phleboviruses, togaviruses, and coronaviruses. It is also being tested for COVID-19, and a double-blind, randomized and placebo-controlled clinical trial to evaluate its safety, pharmacokinetics and anti-viral effects against SARS-CoV-2 has been initiated (NCT03891420).

2.9. Danoprevir

Danoprevir (Fig. 2) is a potent protease inhibitor approved in 2018 in China to treat hepatitis C. It has an IC_{50} value of 0.29 nM against HCV protease [97]. The first clinical trial of danoprevir combined with ritonavir has shown a promising therapeutic option for COVID-19 treatment. The clinical trial data showed that combined therapy of danoprevir and ritonavir is safe, well-tolerated and no patient had displayed composite adverse outcomes during the study [98]. However, the study was limited by the small sample size, and the results need to be corroborated in large sample studies.

3. Anti-cancer drugs

3.1. Bevacizumab

Bevacizumab is a vascular endothelial growth factor inhibitor, which has been used for the clinical management of various types of cancers, including ovarian, renal, and colorectal cancer [99–100]. Its mechanism involves the inhibition of aberrant angiogenesis, which reduces the unusual vascular permeability and nutrients transport to cancer cells [101–102]. Evidence has shown that hypoxia and inflammation upregulate VEGF expression in COVID-19 patients, promoting edema, vascular permeability, and eventually ARDS. A recent study has revealed that COVID-19 patients have three times higher intussusceptive angiogenesis-induced vessel growth than influenza patients in the lungs [103]. Many clinical trial studies are under process to prove its efficacy in managing COVID-19 (NCT04344782, NCT04305106, and NCT04275414).

3.2. Ruxolitinib

Ruxolitinib (Fig. 3) inhibits Janus kinase (JAK) 1/2 currently being used to treat many myeloproliferative malignancies [104]. JAK transduces cytokine signals and promotes immune cell activation and genetic survival mechanisms [105]. It leads to hyperactivation of immune response, and its inhibition can disrupt cytokine production and retain normal inflammatory response. Many clinical trials are underway to investigate the efficacy of ruxolitinib in dampening the cytokine signaling and reduce the tissue damage from immune hyperactivity to infection (NCT04362137, NCT04377620). In particular, the RUXCOVID study (NCT04362137) is a randomized, multi-centred, and placebo-controlled phase 3 clinical trial to evaluate ruxolitinib's efficacy and safety in COVID-19 patients with cytokine storm. RUXCOVID-DEVENT (NCT04377620) is another randomized, multi-centred and placebo-controlled phase 3 clinical study using ruxolitinib in COVID-19 patients with ARDS who require mechanical ventilation. Moreover, in an ongoing phase 3 clinical study (NCT04424056), immune suppressors like anakinra (IL-1 inhibitor), tocilizumab (IL-6 inhibitor), are being investigated along with ruxolitinib, in COVID-19-associated disease. However, JAK inhibitors are associated with upper respiratory infections, thus should not be applied for the treatment of patients with other simultaneous infections, such as tuberculosis. Further, caution is

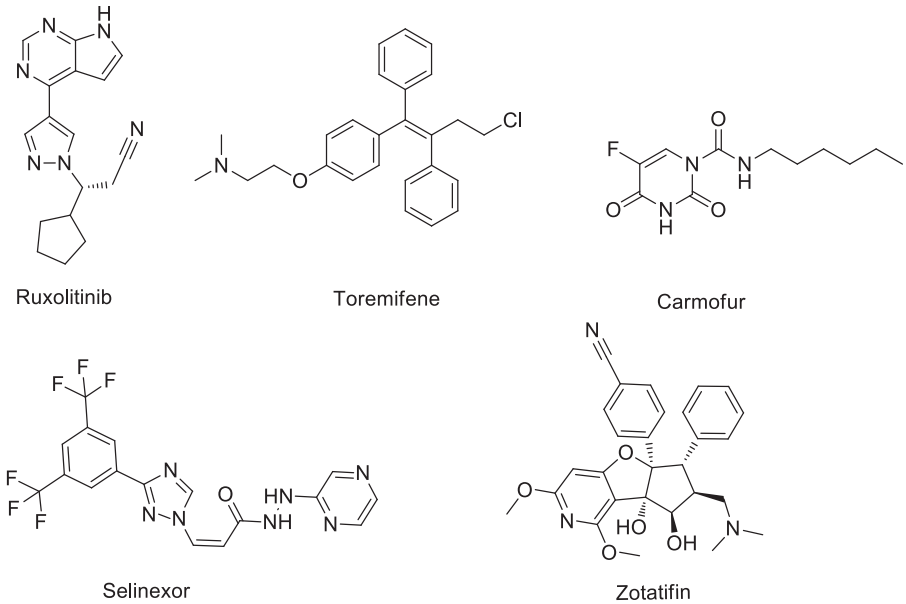

Fig. 3. Chemical structures of anti-cancer drugs with anti-SARS-CoV-2 activity.

required due to elevated risks of thrombotic incidents in COVID-19 [102].

3.3. Toremifene

Toremifene (Fig. 3) is a selective inhibitor of estrogen receptor applied in metastatic breast cancer therapy [106]. Toremifene is known to prevent viral and endosomal membrane fusion by disrupting the envelope glycoproteins [107]. Previously, in Ebola, SARS-CoV, and MERS-CoV it was shown to prevent virus growth [108]. Further, *in vivo* studies revealed the anti-viral activity of toremifene against Ebola by inhibiting entry and internalization [109]. It is also known to inhibit spike protein of SARS-CoV-2 and may interact with NSP14 protein, and thus it might potentially block viral entry and replication [110]. A recent *in silico* study has suggested that toremifene with an anthraquinone derivative emodin combat SARS-CoV-2 effectively [111]. Emodin inhibits the ORF3a protein of SARS-CoV and blocks interaction between SARS-CoV spike protein and ACE2 receptor [111–112].

3.4. Carmofur

Carmofur or 1-hexylcarbamoyl-5-fluorouracil (HCFU) (Fig. 3) is a pyrimidine analogue and derivative of fluorouracil. It is an approved antineoplastic agent administered orally [113] and used to treat colorectal cancer [114]. It has also exhibited clinical benefits against gastric, breast, and bladder cancers [115–117]. Carmofur is a potent inhibitor of acid ceramidase (AC), promoting cancer cell survival, growth, and death [118]. Recently, carmofur has been shown to block viral replication ($EC_{50} = 24.30$ μM) by inhibiting the main protease (Mpro) of SARS-CoV-2. The carmofur co-crystal structure with Mpro revealed that carmofur's reactive carbonyl group binds covalently to catalytic residue cys145 of protease. At the same time, the fatty acid tail occupies the hydrophobic S2 subsite [119].

3.5. Leronlimab (Pro 140)

It is a humanized monoclonal antibody that targets CCR5 receptors on the immune system's T lymphocytes [120]. It is being investigated for its efficacy in the treatment of triple-negative breast cancer (TNBC) (NCT03838367) and HIV infection (NCT03902522). Pro 140 has been reported to block HIV's entry into the cell by binding with the CCR5 receptor [121]. A recent report has shown that Pro 140 disrupts hyperimmune activation by disrupting CCL5/RANTES-CCR5 axis, and decreases viral load in SARS-CoV-2 infected patients [122]. Moreover, it is also currently being investigated for its clinical efficacy and safety in prolonged and severe respiratory illness during COVID-19 (NCT04678830, NCT04347239).

3.6. Selinexor

Selinexor (Fig. 3) is a selective inhibitor of nuclear export and an orally bioavailable anti-cancer drug [123]. It blocks the transport of proteins required in cancer cell growth from the nucleus to cytoplasm by binding with Exportin-1 (XPO1). This process stops cell cycle progression and results in apoptosis [124]. Selinexor can interfere with the transport of proteins that interact with SARS-CoV-2 proteins. It has been revealed that viral replication is reduced due to nuclear-cytoplasmic transporter inhibition leading to seizing of virus constituents in host nucleus [125]. Owing to these indications, Selinexor is currently being investigated in two phases II, controlled and randomized clinical trials in patients with COVID-19 to evaluate its efficacy (NCT04355676 and NCT04349098).

3.7. eFT226 (Zotatifin)

eFT226 (Zotatifin) (Fig. 3) is a potent and selective eukaryotic Initiation Factor 4A (eIF4A) inhibitor. It disrupts the assembly of the eIF4F initiation complex by promoting the binding of eIF4A to mRNA sequences. eIF4A is activated by B-cell receptor signaling and selectively upregulates oncogenes, thereby promoting cell proliferation, survival, and metastasis. Therefore, inhibition of eIF4A by eFT226 exhibited promising anti-tumor activity in preclinical evaluation [126–127]. Moreover, a recent study has disclosed the anti-viral activity of eFT226 against SARS-CoV-2 [128] and recognized more than 300 interactions between human proteins and SARS-CoV-2 and suggest eFT226 as potent drug against viral infection. Further, the study has also identified 66 druggable targets and 69 compounds that could interact with those targets. These findings encourage the entry of eFT226 into clinical trials to assess its safety, and pharmacokinetics and use in mild or moderate patients (NCT04632381).

3.8. Kinase inhibitors

The intracellular viral trafficking depends on endocytic and exocytic cellular pathways through signal transduction, indicating that kinase inhibitors could be likely anti-viral agents by effectively blocking endocytic or exocytic pathways [129]. Many reports have shown kinase inhibitors having potent anti-viral activities in many virus-induced diseases, including coronavirus infections [130–135]. A few of these candidates will be discussed here.

3.8.1. Imatinib

Imatinib is a 2-phenyl amino pyrimidine derivative (Fig. 4) used as an anti-cancer drug specifically for acute lymphocytic leukemia, chronic myelogenous leukemia, chronic eosinophilic leukemia, gastrointestinal stromal tumors, hypereosinophilic syndrome, myelodysplastic syndrome, and systemic mastocytosis. It explicitly inhibits bcr-abl tyrosine kinases and other tyrosine kinases such as c-kit, PDGF-R, ABL2, and DDR1. Imatinib was reported to inhibit SARS-CoV and MERS-CoV infection in cell culture assays [133,136–137]. The mechanistic study has proposed that ABL2 kinase activity is required for SARS-CoV infection. It indicates that inhibition of ABL2 with imatinib will block the fusion of coronavirus with the cell membrane [136–137]. Since the genome of SARS-CoV-2 is highly similar to that of SARS-CoV, both the viruses use ACE2 protein as receptors to bind with host cell [42,138]. It was hypothesized that imatinib might have anti-SARS-CoV-2 activity. Therefore, in several clinical trials, imatinib is being evaluated to study its efficacy in treating COVID-19 patients (NCT04357613, NCT04394416, NCT04346147, NCT04356495, EudraCT2020-001236-10). However, a recent *in vitro* study has shown that imatinib did not have anti-viral efficacy against SARS-CoV-2 replication [139].

3.8.2. Duvelisib

Duvelisib (Fig. 4) is a Phosphoinositide 3-kinase (PI3K) inhibitor used in the treatment of small lymphocytic lymphoma (SLL), chronic lymphocytic leukemia (CLL), and follicular lymphoma [140]. PI3K enzymes play a crucial role in regulating the cell cycle, apoptosis, DNA repair, angiogenesis, senescence, and cellular metabolism [141]. The PI3K inhibitors prevent these functions, which leads to apoptosis. It is to be noted that SARS-CoV-2 infection is associated with acute lung injury and systemic inflammatory response syndrome. Therefore, therapeutic interventions targeting pro-inflammatory agents such as chemokines and cytokines may reduce adverse inflammatory responses [142]. The preclinical results showed that duvelisib lowered pro-inflammatory cytokines in patients with lymphoma [143]. Therefore, duvelisib is currently being investigated as a treatment to reduce lung inflammation in Covid-19 patients in a phase 2 study at the Emory University Hospital (NCT04487886). The applicability of duvelisib in COVID-19 patients is due to its immune system activity but not due to its anti-cancer properties. In another phase 2 trial, the efficacy of duvelisib is being investigated as monotherapy in COVID-19 patients (NCT04372602).

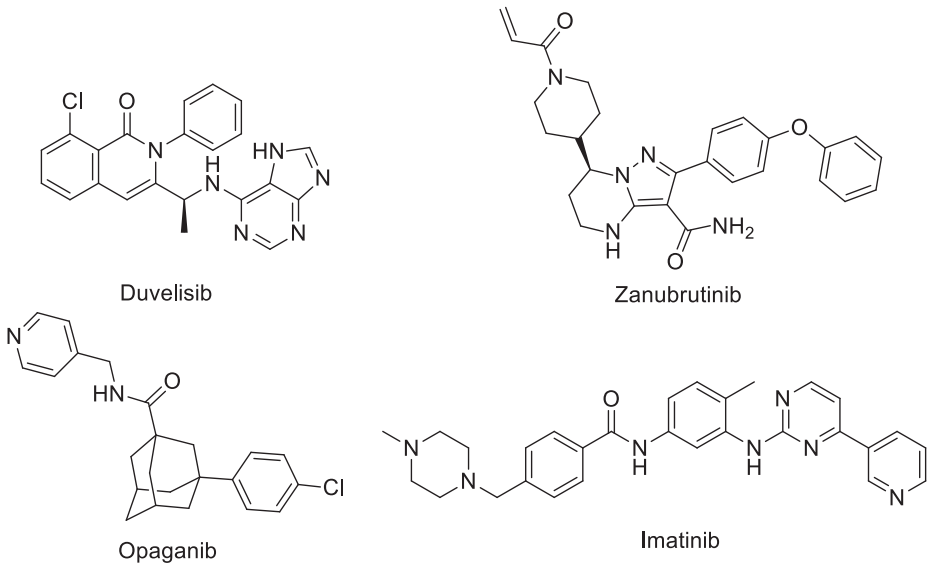

Fig. 4. Chemical structures of anti-cancer drugs (kinase inhibitors) with anti-SARS-CoV-2 activity.

3.8.3. Zanubrutinib

Bruton tyrosine kinase inhibition protects from lethal influenza-induced, immune-induced, and sepsis-induced acute lung injuries [144–146]. Zanubrutinib (Fig. 4), an orally bioavailable Bruton tyrosine kinase inhibitor used to treat mantle cell lymphoma [147], is being investigated for COVID-19 therapy. This study strives to assess zanubrutinib's efficacy as supportive care to increase the survival rate by preventing respiratory failure on day 28 in hospitalized patients with covid-19 and pulmonary distress (NCT04382586). Acalabrutinib is another second-generation inhibitor of BTK (Bruton tyrosine kinase) and is utilized in the therapy of mantle cell lymphoma [148]. Its safety, tolerability, and pharmacokinetics when co-administered with a Proton Pump inhibitor through a nasogastric tube has been investigated (NCT04497948). Ibrutinib is another BTK inhibitor utilized for therapy of B-cell malignancies and chronic graft-versus-host disease. The clinical trial observations suggest that Ibrutinib protects against hypoxia in COVID-19 and improves pulmonary functions [149]. A phase 2 clinical study has investigated its best dose, efficacy, and side effects (NCT04439006). Ibrutinib is expected to reduce the inflammatory response in the lungs without affecting overall immune function.

3.8.4. Opaganib

Opaganib (ABC294640) (Fig. 4) is a selective sphingosine kinase-2 (sk2) inhibitor [150] and is being investigated in clinical trials as anti-cancer drugs for advanced cholangiocarcinoma (NCT03377179) and metastatic castration-resistant prostate cancer (NCT04207255). Opaganib also inhibits viral replication, reduces the hyper-immune inflammatory response, and minimizes ARDS-related thrombosis, which results in complications and causes fatality in COVID-19 [151]. It has been shown that sk2 is a host factor for chikungunya virus that co-localizes with virus replication machinery [152]. It also helps Kaposi's sarcoma-associated herpes virus survival [153]. The preclinical *in vivo* studies have indicated that opaganib reduced fatality rates from influenza virus infection [154]. Further, it downregulates the levels of TNF-alpha and IL-6 in bronchoalveolar lavage fluids and reduced ameliorated Pseudomonas aeruginosa-induced lung injury [155]. The preclinical *in vivo* data have indicated that opaganib has potent antiviral activity against SARS-CoV-2 by inhibiting viral replication in human lung tissue [151]. Therefore, it is being investigated in phase 2, clinical study to assess its side effects and efficiency in COVID-19 (NCT04414618).

4. Serine protease inhibitor

The cell entry of SARS-CoV-2 depends on the expression of host angiotensin-converting enzyme 2 (ACE2) and transmembrane protease/serine subfamily member 2 (TMPRSS2). Thus, clinically proven serine protease inhibitor could be an important medication for COVID-19 infection because these inhibitors could block the S-protein of SARS-CoV-2 required for host cell entry. Hoffmann et al. recently showed that SARS-CoV-2, S protein-driven cell entry uses TMPRSS2 for priming [42]. It has also been reported that camostat mesilate (Fig. 5), a commercial serine protease inhibitor, inhibits TMPRSS2 and prevents SARS-CoV-2 infection [42]. In the first clinical trial of camostat mesilate for SARS-CoV-2 at the University of Aarhus, Denmark, Bittmann et al. demonstrated that it blocked the virus entry in Pneumocytes type 2 cells [156]. In a BALB/c mice model, camostat mesilate with a plasma half-life of 100 min reduced the SARS-CoV-2 infection when taken 600 mg (200 mg, three times) daily [157]. Another advantage of camostat mesilate is its low cost.

Another serine protease inhibitor, Nafamostat mesilate (Fig. 5), also prevents the SARS-CoV-2 infection, as it inhibits membrane fusion of MERS-CoV S protein by inhibiting TMPRSS2 protease activity [158–159]. Wang et al. measured the activity of Nafamostat mesilate against SARS-CoV-2 entry in Vero E6 cells and showed 50% maximal effective concentration (EC_{50}) of 22.50 μM against SARS-CoV-2 infection ($CC_{50} > 100$ μM, SI > 4.44) [43].

5. Antiparasitics and antibiotics

5.1. Ivermectin

Ever since ivermectin (Fig. 6) appeared in the late 1970 s, it has become a truly revolutionary drug. It has been regarded as a 'Wonder drug' for improving the human health, nutrition, and wellbeing of billions of people [160]. It is a broad-spectrum antiparasitic and anthelmintic agent used to treat internal nematode infections, including Strongyloidiasis, Onchocerciasis, filariasis, cutaneous larva migrans, Gnathostomiasis, Ascariasis, and Trichuriasis [160]. It is also used for the oral treatment of ectoparasitic infections, such as scabies (mite infestation) and Pediculosis (lice infestation) [160]. Ivermectin is a macrocyclic lactone, which was derived from avermectin B1. It is structurally similar to macrolide antibiotics, although it lacks antibacterial activity [161]. In recent years, the ivermectin has been demonstrated to possess antiviral activity against several viruses including

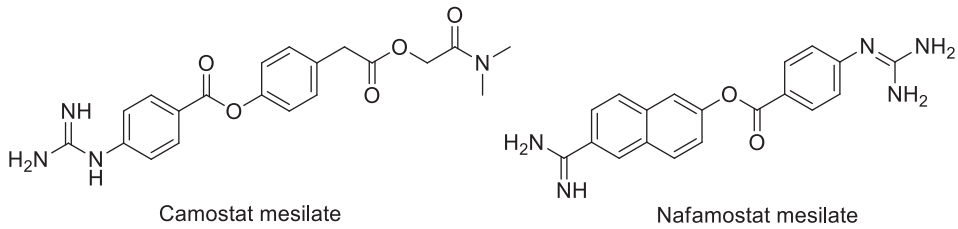

Fig. 5. Chemical structures of serine protease inhibitors with anti-SARS-CoV-2 activity.

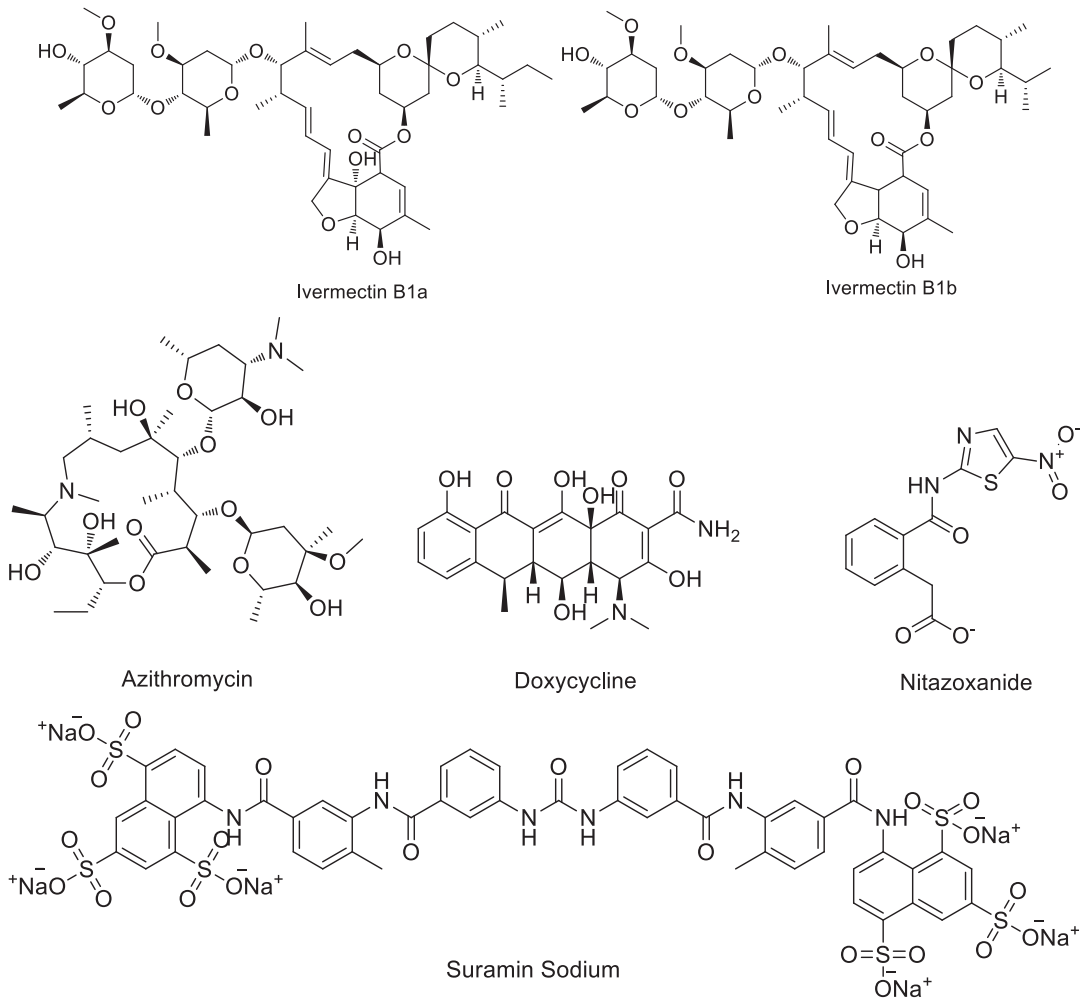

Fig. 6. Chemical structures of antiparasitic and antibiotic drugs with anti-SARS-CoV-2 activity.

HIV-1, SV40, dengue, West Nile, Venezuelan equine encephalitis, influenza, and pseudorabies viruses [162–167]. A study has also demonstrated that ivermectin showed potent inhibition (~5000-fold at 48 h) of replicating SARS-CoV-2 clinical isolate in Vero/hSLAM cells [168]. Moreover, an *in silico* study has demonstrated an admirable binding affinity of ivermectin towards SARS-CoV-2 protease [169]. Many clinical trials have been completed, and some are still underway to determine its safety and efficacy against SARS-CoV-2 (NCT04434144, NCT04747678, NCT04529525, NCT04438850, NCT04390022, NCT04425863, NCT04425850, NCT04407507, NCT04523831, NCT04381884, NCT04360356).

5.2. Doxycycline

Doxycycline (Fig. 6) is a broad-spectrum tetracycline drug used as antibiotics and anti-parasitics. It is often administered orally to treat chronic prostatitis, Lyme disease, sinusitis, acne, rosacea, pelvic inflammatory disease, rickettsial, gonorrhea, chlamydia, and non-gonococcal urethritis [170–174]. It has high lipophilic property due to which it can easily permeate cells, making it quickly absorbed and highly distributed [175–176]. Doxycycline inhibited translation in bacteria by binding to 30S ribosome [176]. Since it's active against erythrocytic stages of *Plasmodium falciparum*, it is used to prevent and treat malaria along with other malarial drugs [177]. While treating onchocerciasis, doxycycline targets symbiotic endobacteria Wolbachia, causing adult female worms' long-term sterility and reducing filarial nematodes [178]. Doxycycline has also been shown to inhibit dengue virus replication in Vero cells by interacting with the virus's E protein [179]. It has exhibited activity against infection of Chikungunya virus [180]. The mortality due to COVID-19 is associated with virally driven

hyper inflammation and cytokine storm. Therefore, doxycycline has been suggested for the case of COVID-19 as it can significantly lower the pro-inflammatory cytokines, including IL-6 [181–182]. It is currently in several clinical trials to manage COVID-19 in combination with other therapies (NCT04729140, NCT04715295, NCT04433078, NCT04371952).

5.3. Azithromycin

Azithromycin (Fig. 6) is a broad-spectrum macrolide antibiotic drug administered orally or intravenously to treat several bacterial infections. It is used for respiratory tract infections, otitis media, venereal chlamydia, nongonococcal urethritis, typhoid, streptococcal infection, etc. [183]. Azithromycin binds with 50S ribosome subunit and inhibits protein translation in bacteria [184]. Azithromycin exhibited anti-viral activity *in vitro* and *in vivo* studies against Ebola, respiratory syncytial virus, Zika, influenza H1N1 virus, rhinovirus, and enterovirus [185–190]. It has also been reported that azithromycin with hydroxychloroquine gave synergistic anti-viral activity against SARS-CoV-2 *in vitro* and a clinical study [191–192]. It is being evaluated in clinics as combinatorial therapy with other drugs to manage COVID-19 (NCT04334382, NCT04329832, NCT04699097, NCT04354597, NCT04359316, NCT04374903, NCT04332107).

5.4. Carrimycin

Carrimycin, an antibiotic drug with a trade name 'Bite,' was developed in China specifically to treat upper respiratory infections [193]. It also has anti-viral, anti-inflammatory, and anti-fibrosis effects. In early 2020, it was reported that carrimycin could inhibit the replication of SARS-CoV-2 without causing significant side effects [194]. It has been approved for the phase 4 clinical trial. A randomized, multi-centre, and open-controlled study is currently being conducted to study its efficiency and toxicity in COVID-19 patients under Beijing YouAn Hospital's sponsorship (NCT04286503) [193–194].

5.5. Suramin sodium

Suramin Sodium (Fig. 6) is an anti-parasitic drug administered intravenously to treat African trypanosomiasis and onchocerciasis [195]. Suramin Sodium had also been reported to effectively inhibit reverse transcriptase in many retroviruses. It is also a potent therapy for various solid tumors such as prostate carcinoma and adrenocortical carcinoma and a potent inhibitor of epidermal growth factor (EGF), basic fibroblast growth factor, insulin-like growth factor, platelet-derived growth factor, vascular endothelial growth factor, tumor growth factor-beta (TGF-β) [195]. A single-arm study of 20 patients with covid-19 has been recruited to evaluate its efficiency and side effects in COVID-19 therapy.

5.6. Nitazoxanide

Nitazoxanide (Fig. 6), an antiparasitic drug nowadays suggested for treating COVID-19, controls the hyperimmune response. Its has been clinically tested for its bronchodilation and anti-SARS-CoV-2 effects [196]. Nitazoxanide also inhibits bovine coronavirus (L9), human enteric coronavirus (4408), murine coronavirus, and mouse hepatitis virus (A59). Cao et al. reported that both Nitazoxanide and its metabolite tizoxanide inhibits MERS-CoV growth in LLC-MK2 cell lines with the IC_{50} values of 0.92 and 0.83 μg/ml, respectively [197].

Wang et al. evaluated anti-viral effects of Nitazoxanide in SARS-CoV-2 infection in VeroE6 cells [43]. The CCK8 assay determined the cytotoxicity of Nitazoxanide, and half cytotoxic concentration was found (CC_{50}) > 35.53 μM with a selectivity index (SI) > 16.76. Nitazoxanide inhibited SARS-CoV-2 contagion in VeroE6 at a sub-micromolar dose having EC_{50} of 2.12 μM.

Kelleni et al. suggested that the combination of nitazoxanide/azithromycin could be a safer and effective regimen for the early stage of COVID-19 patients [198]. Pepperrell and his colleagues reported the clinical studies of nitazoxanide to evaluate the drug's safety. They also examined the minimum cost of drug production in the treatment of COVID-19 which came to be an estimated $4.08 for 14-day course [199]. A number of clinical studies are underway for using Nitazoxanide as standalone or combinatorial drug for COVID-19 therapy [196].

6. Anti-malarial drugs

Chloroquine phosphate as well as its derivative hydroxychloroquine are utilized as potential anti-viral drugs due to their relevant anti-viral mechanism [200–201]. Chloroquine phosphate inhibits ACE2 phosphorylation, whereas hydroxychloroquine promotes endosomal pH and is implicated in the virus entry [202–203]. Early reports showed that Chloroquine phosphate inhibits SARS-CoV infection with a high *in vitro* activity [202,204–205]. Moreover, Chloroquine is a low cost drug with little side effects, which could be a potential candidate for novel SARS-CoV-2. Latest studies showed that these drugs showed promising results against novel SARS-CoV-2 replications [206].

6.1. Chloroquine

Wang et al. evaluated the anti-viral efficiency of some well-known broad-spectrum anti-viral drugs against a clinical isolate of SARS-CoV-2 *in vitro*, where Chloroquine (Fig. 7) potently blocked virus infection at low-micromolar concentration with an EC_{50} value of 1.13 μM and showed high selectivity index (SI > 88.50) [43]. Authors also showed of its effectiveness against nCoV-2019 infection in Vero E6 cells at an EC_{50} value of 6.90 μM.

Liu et al. evaluated an anti- SARS-CoV-2 effect of Chloroquine in an *in vitro* study and observed that it inhibited the transport of virus from early endosomes to endolysosomes [207]. Its cytotoxicity was measured in VeroE6 cells by CCK8 assay, and its 50% CC_{50} values of was 273.20 μM. The EC_{50} was 2.71 μM, with a selectivity index of 100.81. Yao et al. also reported EC_{50} of Chloroquine at 23.90 and 5.47 μM at 24 and 48 h, respectively [208].

6.2. Hydroxychloroquine

Clinical trial of hydroxychloroquine (Fig. 7) in COVID-19 patients was conducted by Gautret et al. (2020). The initial results show a significant reduction in the viral carriage, and was more efficient in eliminating the virus [191]. It was observed that within three to six days, hydroxychloroquine could clear viral nasopharyngeal carriage of SARS-CoV-2 in COVID-19 patients with a serum concentration of 0.46 μg/ml. Hydroxychloroquine and azithromycin together showed a synergetic effect.

Liu et al. examined the anti-viral activity of hydroxychloroquine against SARS-CoV-2 infection *in vitro* [207]. The cytotoxicity of hydroxychloroquine was carried out in African green monkey kidney VeroE6 cells, which revealed CC50 values of hydroxychloroquine at 249.50 μM and EC_{50} of hydroxychloroquine was found 4.51 μM. It has also been reported that hydroxychloroquine showed some anti-inflammatory activity and was less toxic than Chloroquine [207].

Yao et al. studied hydroxychloroquine's pharmacological activity in SARS-CoV-2 infected VeroE6 cells using pharmacokinetic model [208]. Based on this models, 400 mg of hydroxychloroquine sulfate BD (twice a day) for one day and 200 mg given BD for four days is advised for COVID-19. Its EC_{50} value was 6.14 and 0.72 μM at 24 and 48 h, respectively.

6.3. Piperaquine/dihydroartemisinine

Sold under the brand name Eurartesim, it contains a fixed dose of

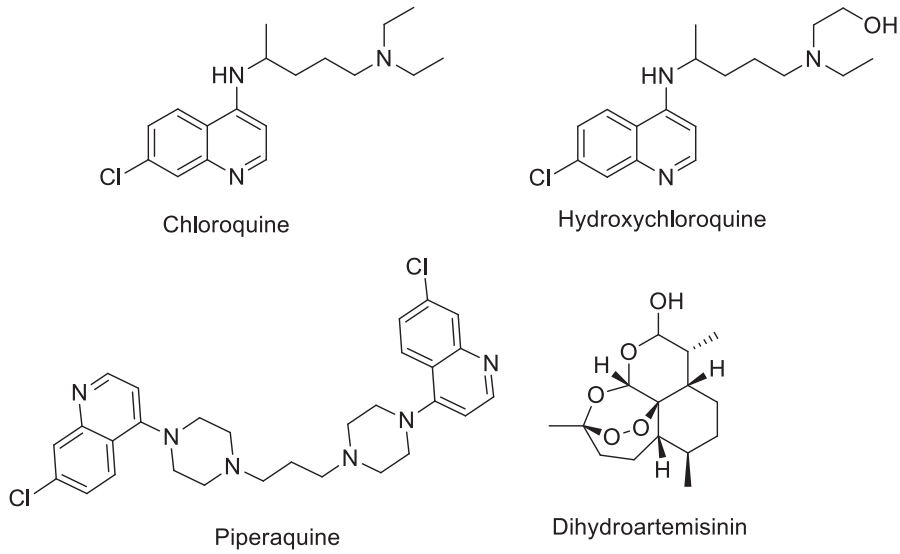

Fig. 7. Chemical structures of anti-malarial drugs with anti-SARS-CoV-2 activity.

piperaquine and dihydroartemisinin (Fig. 7) and used in malaria caused by *Plasmodium falciparum* and *Plasmodium vivax* [209–210]. A phase 4 clinical trial has been initiated to study the efficacy of this combination in treating COVID-19 (ChiCTR2000030082).

7. Anti-inflammatory

7.1. NSAIDs

NSAIDs are commonly used to reduce fever and muscle pain in COVID-19 positive patients, but NSAIDs for COVID-19 patients have been controversial [211,211]. ACE2, an entry point for SARS-CoV-2, plays a major in COVID-19 [212]. Studies showed that NSAIDs like ibuprofen (Fig. 8) increase the expression of ACE2 [213]. Some other studies have also shown a positive correlation between level of expression of ACE2 and risk of SARS-CoV-2 infection [214]. Wu et al. showed that NSAIDs also inhibited host immune response against coronavirus. On the other hand, Castro et al. showed that combined use of ibuprofen and naproxen (Fig. 8) decreased hospitalization among COVID-19 patients with who did not require mechanical ventilation [215].

Hong et al. (2020) conducted a trial of celecoxib (Fig. 8) in COVID-19 patients at 200 mg twice (full) or once (half) per day. Remission rate of COVID-19 for full and half doses of celecoxib were 100% and 82%, respectively against 57% in control [216]. Pulmonary opacification and pneumonia were alleviated by Celecoxib faster than control as measured by chest CT scan. These findings indicate that celecoxib helped in recovery of mild and severe COVID-19 and prevented advancement from severe to a critical condition. Cardiovascular patients suffering from COVID-19 can be treated with celecoxib as per the indication of safety and drug efficiency findings [216].

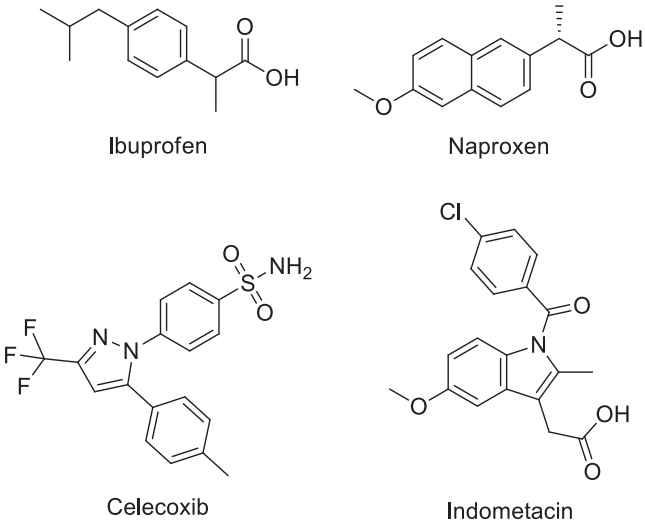

Fig. 8. Chemical structures of NSAIDs with anti-SARS-CoV-2 activity.

Another NSAID, indomethacin (Fig. 8) also possesses potential antiviral activity against canine coronavirus and human SARS-CoV [217]. Indomethacin blocked viral RNA synthesis and did not affect entry into host cells or coronavirus binding. Oral administration of indomethacin in infected dogs inhibited shedding of canine CoV by 2–3 fold. It is suggested that indomethacin exhibits antiviral action in canine CoV-infected dogs and SARS-CoV-2-infected Vero E6 cells [218]. Recently, sustained-release formulation of indomethacin at a dose of 75 mg BD in COVID-19 patients showed enhanced response within 3 days. These findings suggest that indomethacin could be a potent COVID-19 treatment option [219]. Further, celecoxib screening was done using virtual screening procedure with 50 μM and it suppressed the activity of chymotrypsin-like protease of SARS-CoV-2 by 12% [220].

Being a cytopathic virus, SARS-CoV-2 may induce pyroptosis of infected cells following inflammasome activation subsequent gasdermin D (GSDMD) activation. It results in the leakage of pro-inflammatory cytokines due to pores formation in host cell membrane leading to severe tissue damage and hyper-inflammation. Therefore, GSDMD protein could also be explored as a molecular target for the treatment of COVID-19 to dampened inflammation by blocking the leakage of pro-inflammatory cytokines and chemokines. [221].

8. Non-specific anti-viral, anti-Inflammatory and immunosuppressive drugs

8.1. Corticosteroids

A class of steroid hormones called corticosteroids (Fig. 9), including glucocorticoids and mineralocorticoids, are released from the adrenal cortex. The synthetic analogs of these hormones have been known as anti-inflammatory and immunosuppressive drugs, which can treat various conditions such as allergy, asthma, multiple sclerosis, septic shock, rheumatoid arthritis, and lung tissue disorders. Unfortunately, their uses are limited by the adverse side effects such as skin atrophy, osteoporosis, diabetes, glaucoma, abdominal obesity, cataracts, growth

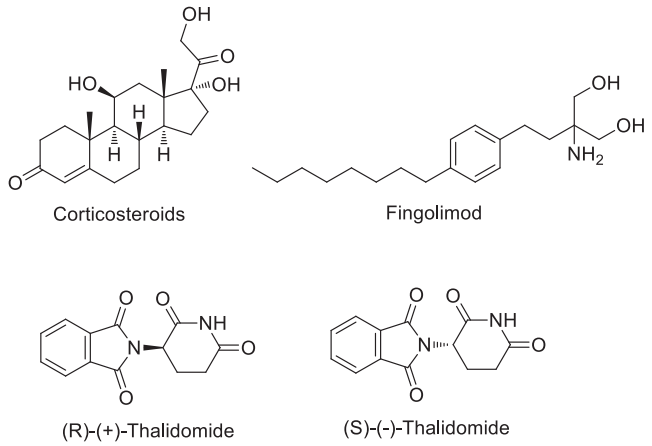

Fig. 9. Chemical structures of immunomodulatory drugs with anti-SARS-CoV-2 activity.

retardation, avascular necrosis and infection, and hypertension [222]. It has been proved that a COVID-19 infection results in a hyper-inflammatory response which caused high mortality [223]. Therefore, corticosteroids can be used as a potent drug for diminishing lung inflammations. The EC_{90} value of 6.3 μM Ciclesonide corticosteroid has been reported to block SARS-CoV-2 replication *in vitro* in a study on VeroE6 cells. The previous study showed that treatment of SARS and MERS patients with corticosteroids showed no improved survival but rather indicated delayed viral clearance from respiratory tract and blood associated with hyperglycemia, avascular necrosis, and psychosis [224–225]. However, in a retrospective study of 201 ARDS patients in Wuhan Jinyintan Hospital in China revealed that COVID-19 therapy with methylprednisolone reduced their possibility of death. However, this study was limited by a small sample size [226]. In a controlled, open-label study where 2104 patients were given dexamethasone, and 4321 patients were treated with the usual care, it resulted in lower 28-day mortality among patients receiving either oxygen alone or mechanical ventilation however not in those without oxygen or ventilation [227]. However, use of corticosteroids as COVID-19 therapeutics to minimize cytokine-related pulmonary damage is controversial due to adverse outcomes [228].

8.2. Fingolimod

Fingolimod (Fig. 9) is an immunomodulatory drug that modulates sphingosine-1-phosphate–a receptor and inhibits lymphocytes. It is used for the treatment of relapsing-remitting multiple sclerosis. The down-regulation of S1PRs reduces the egress of autoreactive lymphocytes from lymphoid tissues [229–230]. A phase II clinical study to assess fingolimod's efficiency was initiated, but later it was withdrawn (NCT04280588).

8.3. Thalidomide

An immunomodulatory drug, thalidomide (Fig. 8), is used for treating multiple inflammatory diseases, such as erythema nodosum leprosum, rheumatoid arthritis, multiple myeloma, Crohn's disease, lupus erythematosus, and prostate cancer [231]. It is also known for stimulating T cells, inhibiting cell proliferation, anti-inflammation, pulmonary fibrosis, and diminishing lung injury [232]. Previously, it has been reported that thalidomide considerably increased the survival rate, reduce the infiltration levels of inflammatory cells and chemokines (IP-10, RANTES), and cytokine (TNF-α, IL-6), and inhibited activated p-NF-κB p65 in H1N1 influenza-infected mice [231]. Therefore, thalidomide may be beneficial in the treatment of COVID-19. The combination of thalidomide with a low dose of glucocorticoid could calm the patients by reducing oxygen intake and relieving the digestive system in COVID-19 patients [232]. It was also reported that the combination of thalidomide with celecoxib could reduce the cytokine storm induced by SARS-CoV-2 [233]. A Prospective, randomized, multi-center, double-blind, Placebo-controlled clinical study of thalidomide or combination of thalidomide with hormones is currently going on to assess the efficiency and side effects in COVID-19 (NCT04273529, NCT04273581).

8.4. Intravenous immunoglobulin

Antibodies or Immunoglobulins (Ig) are produced by plasma cells in the inoculated individuals. They recognize and bind to respective antigens, such as viruses or bacteria, and destroy them. Intravenous immunoglobulins (IVIG) are derived from donors who have recovered from active infection to treat patients with immunodeficiencies, neuro-immunological disorders, autoimmune conditions, and infection-associated sequelae [234]. In the case of severe COVID-19, IVIG's anti-inflammatory functions may reduce inflammatory response and reduce autoreactive antibodies. Moreover, IgG dimers in IVIG inhibit the activation of FcγR on innate immune effector cells [234].

On the contrary, it has been reported that in the case of COVID-19, the function of intravenous immunoglobulin is not to boost the immune system but to suppress a hyper-immune response. It takes place via its immunomodulatory effect [235]. However, the current randomized, double blind, placebo controlled phase III clinical studies focus on understanding its efficiency and safety in COVID-19 patients (NCT04261426, NCT04350580, NCT04411667, NCT04400058).

8.5. Interferons

Interferons (IFNs) are a class of cytokines that can inhibit bacterial and viral infections and neoplasia which can be divided into two classes as type I (IFN-α and IFN-β) and type II (IFN-γ) [236]. It has been used to treat many viral infections such as Hepatitis B and C virus control multiple sclerosis [237–239]. A placebo controlled, double blinded clinical study conducted in the UK revealed that hospitalized non-ventilated COVID-19 patients treated with interferon beta-1a for 14 days (once daily) probably recovered due to ambulation without restrictions, had less chance of developing severe disease, and had reduced breathlessness, in comparison with a placebo-controlled group [240]. A randomized, open-label, Phase 2 clinical trial evaluated the efficacy and safety in treating COVID-19 patients by combining Interferon Beta-1b, Ribavirin, and Lopinavir/Ritonavir showed reduced viral load and reduced the mortality rate in the combination therapy group than in the control group. The patients treated with combined therapy had more remarkable clinical improvement, and shorter hospital stay [240]. In a retrospective cohort based study in China, moderate COVID-19 patients were treated with nebulized interferon alfa-2b or with the combination of nebulized interferon alfa-2b and umifenovir or umifenovir alone. The result showed reduced systemic inflammation and shorter time for viral clearance from upper airways on treatment with interferon alfa-2b than with umifenovir alone [240]. In another phase 2 study with nebulized interferon beta-1a in COVID-19 adult patients showed considerably higher odds of clinical improvement than those who received placebo [241].

8.6. Interleukin-2 (IL-2)

Interleukins are a group of cytokines that signal specific cells to regulate the immune systems. They facilitate communication among the immune system cells, regulate transcription factors, and control cell differentiation, proliferation, inflammation, and antibody secretion [242–243]. The pro-inflammatory cytokine IL-2 is secreted by Th-1 cells, which credibly participates in T Cells activation to produce TNF-α and IFN-γ. IL-2 is known for promoting the cytolytic activity of natural killer cells (NK). Thus, the therapeutic applications to stimulate the

immune system are supposedly beneficial in COVID 19 patients [244–245]. A phase 1 clinical study has shown the higher production of $CD4^+$ T, $CD8^+$ T, and NK cells in COVID-19 infected patients when treated with a low dose of IL-2 intramuscularly (ChiCTR2000030167).

9. Herbal medicines

Although lesser clinical evidence is available to support traditional medicines' efficacy in the treatment of COVID-19, its use seemed to be one of the viable methods during this time of crisis. During the SARS epidemic in 2003, China used traditional Chinese medicines and standard medicines to treat around 40–60% of SARS-infected patients [246]. The Chinese traditional medicines helped control the fever, cleared chest infection faster, reduced the need for consumption of steroids, and gave relief from other symptoms [247]. Further, it has also been used in the treatment of H1N1 influenza during its outbreak. The high similarity in pathogenesis, genomics, and epidemiologic between SARS-CoV-2 and SARS-CoV has encouraged traditional medicines to treat COVID-19 [247–248]. Based on the overall symptoms and treatment results of COVID-19, traditional Chinese medicines have been advised to prescribe traditional medicines such as decoctions of qingfei paidu, sheganmahuang, gancaoganjiang, and qingfei touxie fuzheng recipe [249].

The guidelines China and the South Korean have recommended the Qingfei Paidu decoction to treat COVID-19 patients [250]. The Qingfei Paidu decoction consists of different herbal medicine such as *Ephedrae Herba*, *Gypsum Fibrosum*, *Glycyrrhizae Radix* et *Rhizoma Praeprata cum Melle, Cinnamomi Ramulus, Armeniacae Semen Amarum, Alismatis Rhizoma, Polyporus, Rhizoma Praepratum cum Zingibere et Alumine, Atractylodis Macrocephalae Rhizoma, Scutellariae Radix, Poria, Bupleuri Radix, Pinelliae Zingiberis Rhizoma Recens, Asteris Radix et Rhizoma, Aurantii Fructus Immaturus, Farfarae Flos, Belamcandae Rhizoma, Asari Radix et Rhizoma, Dioscoreae Rhizoma, Pogostemonis Herba, and Citri Reticulatae Pericarpium* [249]. According to the recent report, this herbal formula targets the lungs and spleen in COVID-19 patients, thereby elevates immunity and lowers inflammation [250]. The traditional Chinese medicine formula called Lianhuaqingwen has been reported recently to inhibit coronavirus replication *in vitro* and remarkably lowered cytokines production such as CXCL-10/IP-10, IL-6, TNF-α, and CCL-2/MCP-1 at mRNA level [251]. However, the exact molecular mechanisms of traditional medicines are unknown and more evidence will be required to conclude its efficacy.

Although there is no conclusive evidence for the treatment of COVID-19 using Ayurvedic medicine, some of the proven herbal immunomodulatory medications can be employed to thwart its symptoms [252]. The Council of Scientific and Industrial Research (CSIR) and the AYUSH ministry have collaboratively initiated clinical trials to validate Ayurvedic herbs' formulation to treat COVID-19. They are Ashwagandha, Guduchi + Pippali Yashtimadhu, and a polyherbal formulation (AYUSH-64).[253–254] The compositions of AYUSH-64 are stem bark of *Alstonia scholaris*, roots of *Picrorhiza kurroa*, *Swertia chirata*, and the seed of *Caesalpinia crista* [255]. They have also initiated a clinical study comparing the effectiveness of Hydroxychloroquine with Ashwagandha (*Withania somnifera*) in health care workers [253,256].

The studies have shown that the ingredients of AYUSH-64 exhibited immunomodulatory and anti-inflammatory activities. The *in vivo* studies showed that total alkaloids from *Alstonia scholaris* suppress the production of IL-8 and TNF-α in bronchoalveolar lavage fluid and lungs [257–258]. *Swertia chirata* is a potent inhibitor of NF-kB and prevents its DNA binding thereby suppressing IL-8 expression in cystic fibrosis. Further, xanthones from *Swertia chirata* have the potential to inhibit COX-2 and suppress the production of pro-inflammatory TNF-α and cytokines IL-6 [259]. *In vitro* study using *Swertia chirata* extracts has also shown anti-viral activity against type-1 Herpes simplex virus (HSV) [260]. Moreover, *Swertia chirata* plant extract inhibited the expression of viral protein (Vpr) in Hela cells harboring the TREx plasmid encoding full-length Vpr [261]. Seed extract of *Caesalpinia crista* increase antibody production in rats demonstrating favorable immunostimulant properties. It also displayed analgesic, anti-inflammatory, and antipyretic activities [262–264].

10. Perspective and conclusion

The SARS-CoV-2 pandemic continues to spread worldwide, and more than 118 million people have been infected, and the lives of over 2.6 million people have been lost as many countries facing 2nd and 3rd waves of COVID-19. This pandemic calls for the urgent and rapid development of effective therapeutics and vaccines within a limited time. Although extensive research has been carried out since the pandemic began, no effective therapeutic drugs have been discovered or developed as yet. A COVID-19 vaccine may be the best defense against SARS-CoV-2, but there is no guarantee that vaccines will protect a hundred percent of the people. Moreover, the virus has a high mutation rate; therefore, it is uncertain that the vaccine prepared against one strain will protect against other mutated strains of SARS-CoV-2. For instance, a new strain of SARS-CoV-2 detected in the UK has a high transmission rate due to genetic mutation in the spike protein. Therefore, in addition to the vaccines, the focus of research on developing effective drugs for the therapy of COVID-19 should be emphasized. Moreover, the viral disease outbreak will not end with the COVID-19 pandemic. Thus any anti-viral therapeutic development will add potent armors to the fight against viral disease outbreaks in the future.

Although the development of small-molecule inhibitors against SARS-CoV-2 is an alternative solution, its application has many limitations for targeted therapies. The adverse side effects are often associated with small molecule inhibitors as their competitive inhibition behavior frequently leads to off target actions. Moreover, mutation of target proteins can also be influenced by prolonged exposure of small molecule, leading to drug resistance [265]. Further, prolonged inhibition may promote protein accumulation and compensatory protein overexpression. As a result, depletion of target molecule partially and repression of downstream pathways will not be sufficient. Therefore, a new technique called induced protein degradation, such as proteolysis-targeting chimeras (PROTACs) can be exploited to enhance the drug compounds' antiviral activity against SARS-CoV-2. PROTACs will perform specific inhibition and degrade the viral targets and might increase the potency by many folds. A recent study showed that PROTACs developed against HCV protease reduced susceptibility to resistance mutations [266]. The development of PROTAC can be done by selecting a feasible target protein of SARS-CoV-2, such as E protein, responsible for viral replication. The E protein lacks glycosylation, and thereby, the protein epitopes are not shielded by large sugar moieties, making binding of small molecules easier. Targeting E protein has emerged as a potent anti-viral strategy to develop inhibitors for coronaviruses such as SARS. Disruption of E protein can lead to virulence and affect viral assembly, morphology, and secretion.

Herbal medicines and natural products have good credentials for being prophylactic in many diseases, including respiratory infections. Therefore, in this global crisis, exploring different herbal medicines to derive effective prophylactics from treating COVID-19 is a promising approach. Effective herbal products for COVID-19 treatment should be based on scientific rationale and well-planned research. Their efficacy can be enhanced by producing synthetic derivatives of the bioactive compound present in them.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Declaration of Competing Interest

The authors declare no conflict of interest.

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