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International Immunopharmacology 90 (2021) 107228

Contents lists available at ScienceDirect

International Immunopharmacology

journal homepage: www.elsevier.com/locate/intimp

Review

Therapeutic drugs for SARS-CoV-2 treatment: Current state and perspective

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ARTICLE INFO

Keywords:
COVID-19
Therapeutics
Drug interaction
Antiviral drugs
Health and safety

ABSTRACT

The disease caused by viral pneumonia called severe acute respiratory syndrome coronavirus type-2 (SARS-CoV-2) declared by the World Health Organization is a global pandemic that the world has witnessed since the last Ebola epidemic, SARS and MERS viruses. Many chemical compounds with antiviral activity are currently undergoing clinical investigation in order to find treatments for SARS-CoV-2 infected patients. On-going drug-drug interaction examinations on new, existing, and repurposed antiviral drugs are yet to provide adequate safety, toxicological, and effective monitoring protocols. This review presents an overview of direct and indirect antiviral drugs, antibiotics, and immune-stimulants used in the management of SARS-CoV-2. It also seeks to outline the recent development of drugs with anti-coronavirus effects; their mono and combination therapy in managing the disease vis-à-vis their biological sources and chemistry. Co-administration of these drugs and their interactions were discussed to provide significant insight into how adequate monitoring of patients towards effective health management could be achieved.

1. Introduction

Since time immemorial, there has been a periodic recurrence of viral outbreaks at both epidemic and pandemic levels. In the recent past were severe acute respiratory syndrome coronavirus (SARS-CoV), middle east respiratory syndrome coronavirus (MERS-CoV), Ebola, and Lassa virus to mention the least. In December 2019, a history of virus outbreak repeated itself through the emergence of a novel coronavirus disease (2019-nCoV) called severe acute respiratory syndrome coronavirus (SARS-CoV-2) which was first discovered in Wuhan, Hubei Province of the People's Republic of China. The virus has been reportedly transmitted from animal to man and causing severe respiratory disorders [1,2]. The spread of this virus has caused global health challenges and huge economic losses by which reason the World Health Organization

Abbreviations: NLRP3, (Nucleotide Oligomerization Domain)-like receptor protein 3 (NLRP3) Inflammasome activation; MERS-CoV, Middle East Respiratory Syndrome Corona Virus; SARS-CoV, Severe Acute Respiratory Syndrome Corona Virus, RpRd, RNA-dependent RNA polymerase; CQ, Chloroquine; HCQ, hydroxychloroquine; US-FDA, Food and Drug Administration; ACE2, Angiotensin-converting enzyme 2; EC50, Half maximal Effective concentration; WHO, World Health Organization; Mpro, Main Protease Enzymes; 3ClPro, 3-Chymotrypsin-like Protease; HA, Hemagglutinin; Hb, Haemoglobin; CC_{50}, Half-maximal Cytotoxic Concentration; EC_{50}, Half-maximal Effective Concentration; RpRd, RNA-dependent RNA polymerase; QTc, the Corrected interval between the wave of Q and T.

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https://doi.org/10.1016/j.intimp.2020.107228
Received 2 July 2020; Received in revised form 19 November 2020; Accepted 19 November 2020
Available online 27 November 2020

declared it a pandemic and threat to human existence. The virulence of the disease was initially not understood at the emergence until the increasing rate of spread of the virus with 80 cases of death and more than 4,000 cases confirmed in 5 days [3]. Scientific investigations showed that the newly discovered coronavirus has some definitive similarities with bat-linked genomes that were discovered in late 2002 and 2012 (reported as Severe Acute Respiratory Syndrome (SARS-CoV) and Middle East Respiratory Syndrome (MERS-CoV) respectively), transmitted to human from civet cats and dromedary camels respectively [4]. To forestall the transmission, measures taken by the Chinese Government include immediate shutdown and restriction of movement placed on dwellers at the host centres of the disease even during the famous Chinese Annual Spring Festival in China.

The Chinese health authorities examined case fatality indices of pneumonia among the victims in Wuhan city and an in-depth protein sequencing, eukaryotic cell culturing and characterization of air-way secreted fluid called Bronchoalveolar Lavage (BAL) revealed a unique Beta-coronavirus with close to 79% and 50% respective structural similarities with SARS-CoV 2002 and MERS-CoV 2012 [5]. Based on the established practice of virus naming, the World Health Organization (WHO) and the International Committee on Virus Taxonomy renamed this novel strain of 2019-nCoV to SARS-CoV-2 to portray the phylogenetic origins of the virus [6–8]. This review seeks to outline the recent development of drugs with anti-coronavirus effects; their mono and combination therapy in managing the disease vis-à-vis their biological sources and chemistry. Co-administration of these drugs and their interactions were discussed to provide significant insight for adequate monitoring of patients towards effective health management.

2. Review methodology

This review focuses on reported curative antiviral drugs, broad-spectrum antibiotics and their chemistry, active components from botanical sources as well as possible clinical trials and safety information. Post- SARS-CoV-2 health-related issues that may arise due to drug toxicity and interaction were discussed with precautionary measures suggested. Scientific articles and reports were sourced across many high impact journals and filtered with relevant keywords on drug agents for COVID-19.

The World Health Organization situation reports on COVID-19, PubMed, NCBI, Research Gate COVID-19, and Google search filters as well as other scientific databases on SARS-CoV-2 related information were carefully accessed towards the identification of the current medicinal agents that are being used in the treatment and management of the virus. Publications and scientific related articles that are under preprints, peer review, editorial comments, letters, and personal opinions were employed accordingly as stated in the reference section. Also, chemical structures were drawn using Chem-Draw Ultra 8.0 (Cambridge Soft, 100 Cambridge Park Drive, Cambridge, MA 02140) [9]

3. Active medicinal components and SARS-CoV-2

Herein, we discussed some direct and indirect antivirals, immunostimulants, antibiotics, natural medicinal agents, and other repurposed viable agents both traditional and orthodox with a natural and synthetic basis that are currently being investigated for novel coronavirus treatment. Some of these compounds are currently being subjected to clinical trials and have demonstrated preliminary activity against the virus. Notably, they have been reported in the 6th edition of Guidelines for the Prevention, Diagnosis, and Treatment of Novel Coronavirus-induced Pneumonia issued by the National Health Commission (NHC) of the People's Republic of China for tentative treatment of coronavirus infections. These compounds include Ribavirin, Lopinavir-ritonavir, Chloroquine, Favipiravir, and Arbidol [10]. Other drugs that are still undergoing clinical trials with promising activity include Remdesivir, Atazanavir, Presatovir, Carmofur, Emetine dihydrochloride, Omacetaxince (Homoharringtonine), Azithromycin Ivermectin, Colchicine, TMPRSS2, and Interferon α, were also discussed. The clinical features of these drugs and their mechanisms of action/target, EC_{50}, and CC_{50} were reviewed and summarized in Table 1.

3.1. Ribavirin

This is an FDA approved compound usually referred to as synthetic guanosine analogue with antiviral potential (Fig. 1a). It is used as a blend with other antiviral drugs and in most cases with interferon-alpha (IFN-a) for the treatment of several viral infections such as chronic hepatitis C virus, viral hemorrhagic fever, and respiratory syncytial virus [11]. Ribavirin was first commercialized in the early 1980s for the treatment of respiratory syncytial virus in children which makes it a premier and standard antiviral agent over the newly developed drugs. Aside from being regarded as a broad-spectrum antiviral agent against DNA and RNA, which can obscure the production of viral messenger RNA binding RNA-dependent RNA polymerase (RpRd). It is also a prodrug that metabolizes into nucleoside analogues blocking viral RNA and viral mRNA capping [12]. Ribavirin was found to be effective against Crimean-Congo hemorrhagic fever, Hantavirus infection, Lassa fever, and Venezuelan hemorrhagic fever. Meanwhile, promising results had emanated previously about the blend of ribavirin with Interferon-alpha for the treatment of MERS-CoV [13]. Conflicting data have equally been reported for patients with MERS-CoV infection that were treated with a blend of ribavirin and two forms of interferon-a; IFN-a 2b and IFN-b1 [14]. It can affect haemoglobin (Hb) counts of the red blood cells which is an undesirable side effect in patients with respiratory disorders; a feature that reduces its potential as a potent antiviral agent against coronavirus infection. However, during the SARS-CoV outbreak in 2003, few countries including China and Canada successfully administered high doses of a blend of ribavirin with antibiotics and hormone against the virus [15]. A possible combination of ribavirin with lopinavir-ritonavir has proven to be potent against SARS-CoV-2 [16].

3.2. Favipiravir

This is a newly discovered RNA-dependent RNA polymerase (RdRp) inhibitor similar to ribavirin earlier discussed (Fig. 1b). Apart from its anti-influenza viral activity, clinical experiments have revealed that it is capable of blocking the replication of flavi-, alpha-, filo-, bunya-, arena-, noro-, and other RNA viruses [17]. Favipiravir when in cells is transformed into an active phospho-ribosylated (F-RTP), a form that is recognized by viral RNA polymerase as a substrate thus inhibiting its activity in patients [18]. This further suggests the possible antiviral efficiency of Favipiravir against SARS-CoV-2 to which end the Clinical Medical Research Centre of the National Infectious Diseases in collaboration with Third People's Hospital of Shenzhen conducted a clinical trial on 14th February 2020 and obtained promising results. The preliminary results showed that the antiviral efficacy of Favipiravir is more than that of Lopinavir-ritonavir blend [19].

3.3. Arbidol

Arbidol, known as "Umifenovir" (Fig. 1c) is an active antiviral agent that has greatly been used for the treatment of the influenza virus. For decades, it has been an effective agent, with no reported side effect, commonly administered in China and Russia to prevent severe pneumonia and cytokine dysregulation associated with viral infections [20]. It is a broad-spectrum antiviral agent with both *in-vitro* and *in-vivo* inhibitory potentials against various infectious diseases such as influenza, hepatitis B virus (HBV), hepatitis C virus (HCV), Hantaan virus, and other pathogenic human respiratory viruses. Aside from enhancing the immune response of host cells, Arbidol actively inhibits the binding of viral cell walls with the membrane of target cells, thus preventing its entry [21]. Arbidol has now been nominated as a first-aid therapy

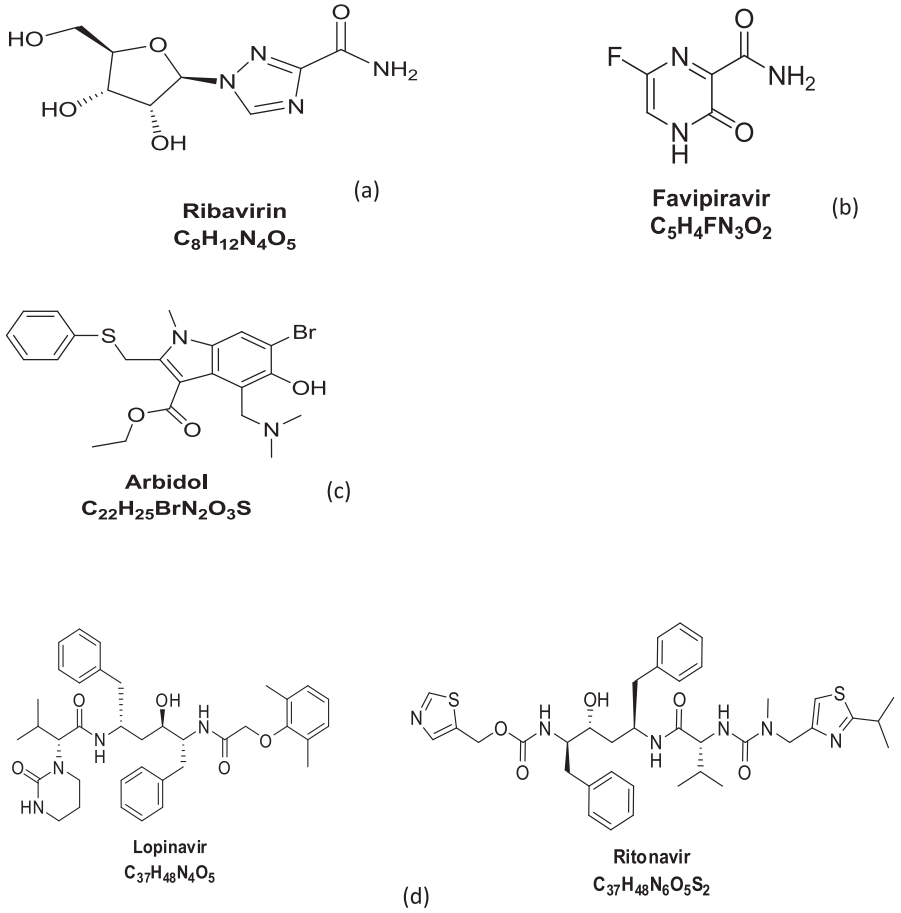


Fig. 1. (a-j): Chemical structures of some reported SARS-COV-2 Drug.

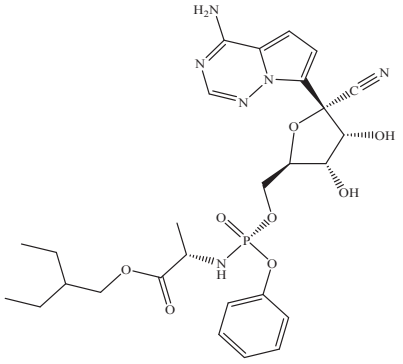
against novel coronavirus and studies are ongoing towards further optimization [22–24].

3.4. Lopinavir-ritonavir

This is a medication usually administered in combination with other antiviral drugs such as ribavirin for treating Human Immunodeficiency Virus HIV [25]. It (Fig. 1d) belongs to a class of protease inhibitors capable of targeting SARS-CoV non-structural protein 3Clpro [16]. Chu et al. [26] discovered that lopinavir-ritonavir combination therapy with ribavirin demonstrated anti-SARS-CoV activity *in-vitro* and also in clinical studies when used to treat patients under a non-randomized clinical trial. Less SARS patients died after receiving a dose of the combination compared with those in the control group who received doses of blends of ribavirin and Corticosteroids. When MERS-CoV emerged, intensive investigations into potential antiviral compounds identified lopinavir as active against the virus in vitro [27]. Its drug-drug therapy does not come without a minor side effect of diarrhoea. Nevertheless, it has been recommended as an effective anti-SARS-CoV-2 agent in China [16]. Further investigations are ongoing by some Chinese researchers and-clinicians into the therapeutic efficacy of Lopinavir-ritonavir.

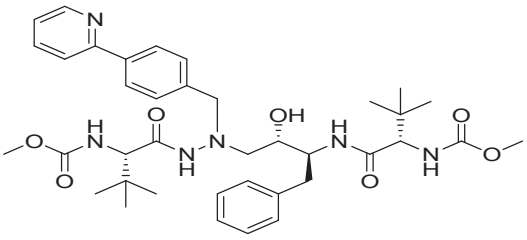
3.5. Remdesivir

Remdesivir is one of the most promising antiviral drugs tested for the treatment of coronavirus infection. It is a phosphoramidite prodrug of adenosine nucleotide [28] with a broad-spectrum *in-vitro* antiviral activity against a wide range of RNA viruses like Ebola virus, respiratory syncytial virus, Nipah virus, Hendra virus, Marburg virus, pathogenic viruses such as MERS-CoV and SARS-CoV and bat CoV strains [29,30]. Although it is a nucleotide analogue, Remdesivir has shown to inhibit viral RNA replication, prematurely terminate viral RNA transcription by targeting viral RNA-dependent RNA polymerase, and evade viral exo-ribonuclease proofreading [31]. To date, pharmacokinetic and clinical detail on Remdesivir is still obscure and critical investigations are ongoing. Markedly, concerns of antiviral resistance against its usage have been studied [31]. Very recently, the antiviral activity of Remdesivir was examined at an early stage after virus entry into Vero E6 cells detailing its mechanism of action as a nucleotide [32]. The EC_{90} results were observed to be 1.76 μM, suggesting its potency against the virus. In a mouse model study on SARS-CoV-2 pathogenesis, prophylactic and therapeutic activity [32] observed that early administration of the drug reduced lung viral load by an order of magnitude greater than 2 on day 4 or 5 post-infection, restrained the disease and improved respiratory function. More so, in a tissue culture model, a biologically important *in-vitro* model of pulmonary infection, Remdesivir displayed low half-maximal effective concentrations (EC_{50}s) of 0.069 and 0.074 μM for SARS-CoV and MERS-COV respectively which revealed its effectiveness against a wide range of highly divergent coronaviruses like the endemic CoVs hCoV-OC43 and hCoV-229E within the sub-micromolar EC_{50} [29,33]. In another animal model examination, a rhesus monkey model on the Ebola virus, 10 mg/kg dose administered daily for consecutive 12 days inhibits the Ebola virus replication and protects all infected animals against infection [34]. Based on the successful clinical experience of Remdesivir therapy on Ebola virus patient [35] as well as on the first SARS-CoV-2 confirmed case in Washington, United States of America



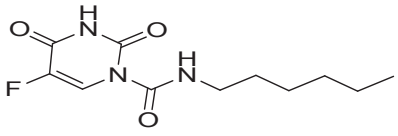
Remdesvir
$C_{27}H_{35}N_6O_8P$

(e)

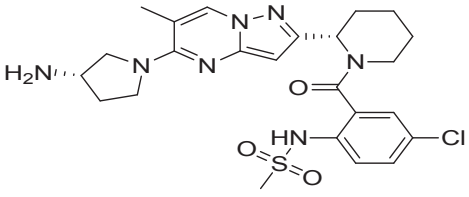


(f)

Azatavir
$C_{38}H_{52}N_6O_7$

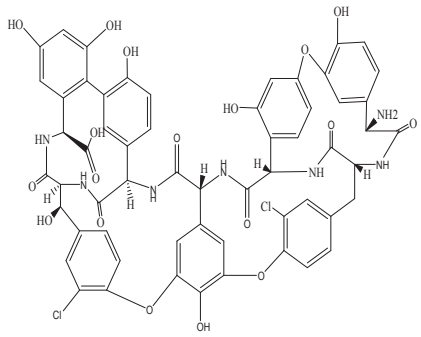


Carmofur (g)
$C_{11}H_{16}FN_3O_3$

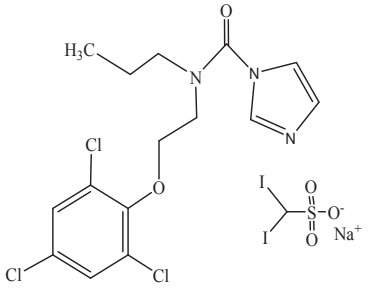


(h)

Presatovir
$C_{24}H_{30}ClN_7O_3S$



Teicoplanin (i)



Interferon (IFNs) (j)
$C_{16}H_{17}O_5Cl_3N_2I_2NaS$

Fig. 1. (*continued*).

(with a negative swab at day 1 after treatment) has suggested that Remdesivir is a promising antiviral therapy for COVID-19 treatment. The molecular mass of Remdesivir is 602.6 g/mol with a chemical formula of $C_{27}H_{35}O_8P$ (Fig. 1e).

3.6. Atazanavir

This is another anti-retroviral FDA approved medication commonly used for HIV treatment and prevention. Atazanavir is distinguished from other protease inhibitors in that it can only be administered one daily rather than requiring multiple doses per day and has lesser effects on the

patient's lipid profile [36,37]. As an azapeptide HIV-1 protease inhibitor, atazanavir binds to the protease active site and inhibits the enzyme activity. Owing to its antiviral activity [38] released a drug-target interaction deep learning model (denoted as MT-DTI model) result of atazanavir showing an inhibitory potency K_d of 94.94 nM against SARS-CoV-2 3C-like protease. This protease enzyme is also found in coronaviruses due to its cleavage potentials to the coronavirus polyprotein at different conserved sites. Atazanavir (Fig. 1f) has a molecular weight of 704 g/mol.

3.7. Carmofur

Carmofur is a promising candidate drug that has shown to inhibit SARS-CoV-2 main protease (Mpro) enzymes responsible for many coronaviruses with a half-maximal effective concentration (EC_{50}) of 24.30 μM and a half-maximal inhibitory concentration (IC_{50}) of 1.82 μM, showing its ability to inhibit viral replication in cells [39]. It is a derivative of fluorouracil, an antineoplastic agent that has demonstrated clinical benefit as a cancer therapy but reported to induce leukoencephalopathy. Carmofur (Fig. 1g) with the general formula of $C_{11}H_{16}FN_3O_3S$ and a mass number of 257 g/mol, is an orally administered anticancer drug, verified by FDA and potent for usage in the treatment of breast, colorectal and other types of solid cancer [40]. It is less toxic, inhibiting human acid ceramidase (AC), and has been utilized clinically for several years [41]. An *in-vitro* study has affirmed the potency of carmofur in terminating AC activities and the spread of cancer cells with a median effective concentration of 2965 nM [42]. Further studies revealed that the inhibition of fatty acid amide hydrolase (FAAH) and *N*-acylethanolamine acid amidase (NAAA) by carmofur as well as its therapeutic activity against several inflammation-related diseases makes it a potential therapeutic candidate in the treatment of SARS-CoV-2 infections [43]. This was further corroborated by a recent investigation, which confirmed the efficacy of carmofur in inhibiting SARS-CoV-2 main protease and broader effectiveness against the virus via an interaction between the crystal structure of the virus main protease and carmofur which could modify the catalytic (Cys145) properties of SARS-CoV-2 [40].

3.8. Presatovir

Presatovir is an off-label drug currently undergoing trials for its activity against coronavirus disease owing to its activity against the respiratory syncytial virus (RSV), a causative agent of lower respiratory tract infections. Presatovir is regarded as a candidate RSV fusion (F) protein inhibitor due to the pyrazolo[1,5-a] pyrimidine series of compounds containing a piperidine ring at 2-position of the pyrazolo[1,5-a] pyrimidine scaffold [44]. It has a general formula $C_{24}H_{30}ClN_7O_3S$ and a mass number of 532 g/mol (Fig. 1h).

3.9. Chloroquine and hydroxychloroquine

Chloroquine, a synthetic succedaneum of the quinine alkaloid isolated from Cinchona tree bark. It is a well-known antimalarial drug that was introduced into medicine in the 1940s (Fig. 2). It is a widely used antimalarial agent that was discovered to possess a broad-spectrum antiviral capacity [45]. Chloroquine, having a long history, is considered safe to inhibit parasitaemia levels in mosquitoes. Besides, it is widely used for the treatment of patients with malaria cases with mild and transitory side-effects. To date, many people currently use these two drugs; Chloroquine (CQ) and Hydroxychloroquine (HCQ). A derivative of CQ and HCQ which is usually administered orally to treat malaria can also be applied to treat symptoms of rheumatoid arthritis, systemic and discoid lupus erythematosus, pemphigus, lichen planus, sarcoidosis, scleroderma polymyositis, and porphyria cutanea tarda. Chloroquine was found also to be an effective antiviral agent that inhibits SARS-CoV infection and spread [14]. CQ and HCQ are both off-label drugs and have been proposed as a promising antiviral therapy for the treatment of COVID-19 patients especially in severe condition [46]. To assess the efficacy of CQ and HCQ in coronavirus infected patients, many compelling *in-vitro* and *in-vivo* studies, including clinical trials in different animal cells, viruses, and infected humans have been conducted [47–49]. Significantly, over eighty clinical trials of CQ and HCQ as well in their combination were reported worldwide. CQ alters the terminal glycosylation of the angiotensin-converting enzyme 2 (ACE2) receptor thereby suppressing SARS-CoV-2 S-protein binding and significantly reduces the viral replication by interfering with the fusion process of the virus [32]. In an *in-vitro* experiment conducted to investigate the elicit antiviral activity of CQ against SARS-CoV-2, a low micromolar dose of it inhibits the virus with half-maximal effective concentration (EC_{50}) of 1.13 μM and a half-cytotoxic concentration (CC_{50}) greater than 100 μM [32]. Several researchers across countries such as China, USA, Germany, UK, and many others have stepped up further investigations into the optimization of CQ as one of the most effective antiviral drugs to treat SARS-CoV-2. The results obtained from more than 100 patients demonstrated CQ as superior to inhibit exacerbation of pneumonia, improve lung imaging findings, promote virus-negative conversion, and shorten the disease course [50]. Another research investigation has demonstrated the potential CQ and HCQ as a

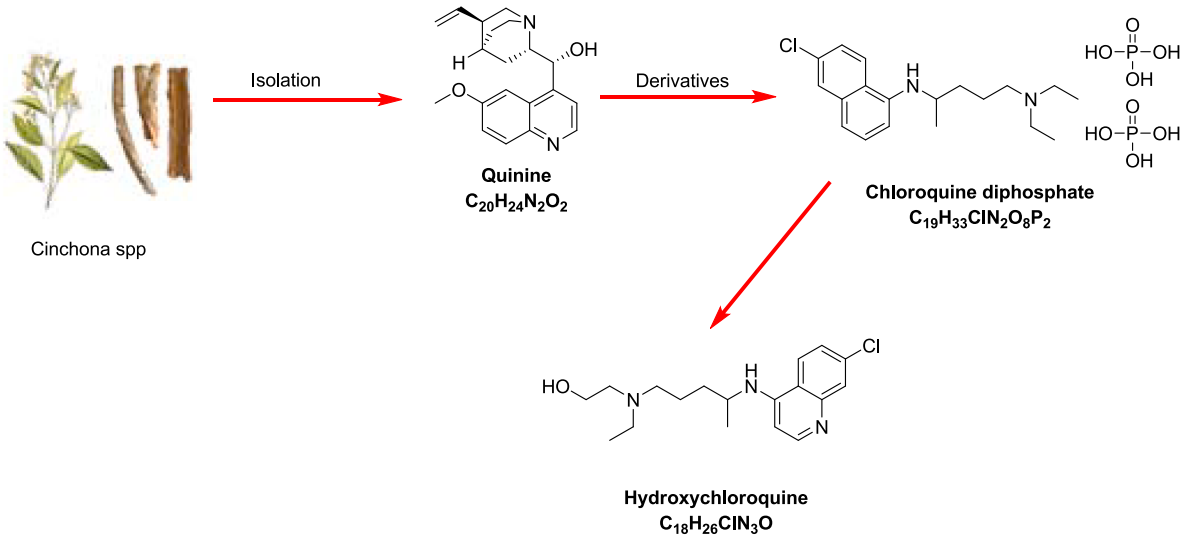


Fig. 2. *Cinchonia spp*, botanical source, and some isolated chemical compounds.

target regimen and effective antiviral therapy for COVID-19 treatment. CQ acts by increasing endosomal pH, preventing virus-cell fusion, altering protein degradation pathways through acidic hydrolases in the lysosomes, macromolecule synthesis in the endosomes, and post-translational modifications in the Golgi apparatus [51].

In a physiologically-based model *in-vitro* study of CQ and HCQ on SARS-CoV-2 Vero cells of some infected patients, an oral loading dose of 400 mg twice daily at day 1 followed by an oral maintenance dose of 200 mg twice daily for 4 days was recommended [52]. The results of the authors further displayed half-maximal effective concentration (EC_{50s}) of 0.72% and 5.47% μM for HCQ and CQ respectively. Additionally, it has been reported that the effect of HCQ on COVID-19 patients could be significantly improved with azithromycin [53]. At variance, a report document detailed that a long-term and combined usage of CQ or HCQ with any other drugs (such as azithromycin) induce QTc interval prolongation besides other severe side-effects like arrhythmogenic and cardiac problems, QRS widening, and negative entropy. CQ and HCQ are notable for inhibiting the P-glycoprotein transport system (in gut luminal and blood-brain barrier endothelial cells), which in turn increase cyclosporine and digoxin levels and ultimately to a more severe complicated result. Since the mode of actions of CQ and HCQ are identical, their activity on the virus may probably be the same. In a multinational registry analysis conducted on SARS-CoV-2 patients from 671 hospitals in six continents, who were placed on CQ, HCQ, the combination of antibiotics or without combination as a macrolide, there was a strong indication that CQ and HCQ when used alone or with antibiotics as drug regimens were associated with an increased frequency of ventricular arrhythmias and mortality rates in hospital among SARS-CoV-2 patients [54]. Although, these should not negate the ongoing HCQ clinical trials in managing the COVID-19. Adequate safety evaluation is therefore required before the recommendation of CQ and HCQ as candidate therapies for COVID-19 management.

3.10. Emetine dihydrochloride

Emetine dihydrochloride, principally from ipecac root, has been used extensively as an anti-protozoan approved drug for amoebiasis treatment (Fig. 3). It blocks ribosomal protein synthesis by inhibiting the movement of ribosomes along mRNA and inhibits DNA replication in early S-phase [55]. Owing to its antiviral activity against both RNA and DNA viruses, Khandelwal et al. [56] reported that emetine demonstrated a significant antiviral activity capable of fighting against four serotypes of dengue virus and inhibiting viral infection. Very recently, in an *in-vitro* model study, emetine was observed to inhibit MERS-CoV and HCoV-OC43 with EC_{50} of 0.16 and 0.34 μM respectively within a submicromolar range [57]. In another *in-vitro* study carried out to investigate the antiviral activity of several chemical compounds against SARS-CoV-2 in Vero E6 cells, emetine demonstrated the lowest half-maximal effective concentrations (EC_{50}) of 0.46 μM, showing its ability to inhibit coronavirus replication. The authors further detailed that a synergistic administration of emetine (0.195 μM) and Remesdivir (at 6.25 μM) may result in 64.9% viral inhibition, supporting that combination therapy may help to reduce (EC_{50}) of the compound below the therapeutic plasma concentrations and provide clinical benefit [58]. SARS-CoV-2 in Vero E6 cell with the compound demonstrated a half-maximal effective concentration (EC_{50}) of 2.55 μM showing its potency against the virus [58].

3.11. Teicoplanin and other glycoprotein drugs (Dalbavancin, oritavancin, and telavancin)

Teicoplanin was previously known as Teichomycin A_2 because it was co-purified together with moenomycin-like teichomycin A_1 that was isolated from a soil sample in India in 1978 [59–61]. It acts as a glycopeptide that binds with the D-ala-D-ala terminus of the lipid (II) in the peptidoglycan to cause bacterial cell deaths and is being used in many nations to combat infections and multiple drug antibiotics resistance pathogens such as *Staphylococcus aureus* [60]. The complexity of Teicoplanin is that it is a mixture of different derivatives of closely related compounds and possibly be differentiated based on their length, the aliphatic chains, and its possible mechanism. The chemistry, biosynthesis alongside the gene-phylogenetic studies has been discussed [61–64]. Teicoplanin is an antibiotic (Fig. 1i) that is capable of inhibiting methicillin-resistant pathogens and is currently being used in the management and treatment of SARS-CoV-2 patients in the world. The mechanism revealed that teicoplanin inhibits the host cell's cathepsin L and cathepsin B and is attached to the viral glycoprotein thereby unfolding the receptor-binding domain subsequently released in the

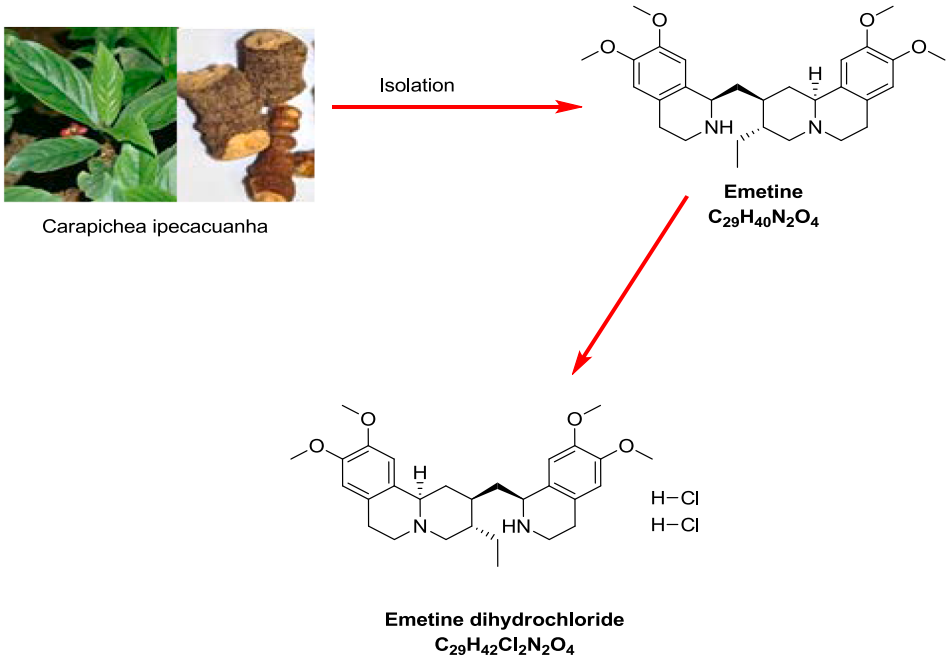


Fig. 3. *Carapichea ipecacuanha*, botanical source, and some isolated chemical compounds.

cytoplasm of the host cells. These glycopeptides have previously shown inhibiting action on some human viruses in the coronavirus family including Ebola, MERS-CoV, influenza, hepatitis C virus, HIV, and also on SARS-CoV-2 virus [65,66]. Similar studies also indicated the potent role of teicoplanin and its derivatives (vancomycin, dalbavancin, oritavancin, and telavancin) as novel inhibitors of cathepsin L-dependent viruses even in Coronaviridae family [67–69]. It was reported that teicoplanin inhibited SARS-CoV-2 in a dose-dependent manner when tested on HIV-luc/2019-nCoV-S pseudovirus and the inhibitory concentration of 1.66 uM which is potent to suppress the entry of the SARSCoV-2 virus in different types of cells alongside with some -gram-positive bacterial infection [70]. Teicoplanin has a safe history and advantage as an antibacterial regimen. It is usually administered intramuscularly or by intravenous injection. Based on previous clinical studies carried out on 1300 patients [71], teicoplanin showed about 90 percent effective rates and compatibility for adult, children and the elderly when administered as a mono- or combined antibacterial therapy. Although, lower rates were achieved among patients with fever, diabetes, malignant diseases and other immune-compromised disorders with possible nephron and ototoxicity. Teicoplanin can be used in the prevention and treatment of serious infections caused by gram-positive bacteria [72]. It has been reported that a combination of teicoplanin and ciprofloxacin is more effective in relieving respiratory tract infections [59]. However, adequate monitoring and clinical observations must be ensured when prescribing teicoplanin with patients who have a history of vancomycin hypersensitivity.

3.12. Azithromycin

Among several potential drugs tested against SARS-CoV-2, Azithromycin is a broad-spectrum antibiotics macrolide that is currently in use for the management of infected patients in many countries based on an open-label non-randomized clinical trial [53,73]. It is a well-known brand and a 15-membered ring macrolide (azalide) antibiotic (Fig. 4). This drug 9-deoxy-9a-aza-9a-methyl-9a-homoerythomycin ($C_{38}H_{72}N_2O_{12}$) is different from Erythromycin with the presence of a methyl-substituted nitrogen atom in the macrolide ring with P_{KA} values of 8.1 and 8.8 respectively [74]. Azithromycin is a unique broad-spectrum antibiotic owing to its rapid and effective tissue and serum penetration in addition to its potency against gram-positive and gram-negative bacteria. Azithromycin has found application in the treatment of fungal infections, respiratory tract infections, viral infections, inflammations and many other immunomodulatory disorders [75–77]. Many ongoing clinical trials are also seeing the potentials of azithromycin combined with chloroquine in managing SARS- CoV-2 while some reports have expressed concerns over prolonged QTc and safety of administration among other underlying side effects as diabetes, heart-related diseases, mental illnesses among others. [78–84] The administration of azithromycin on different patients showed no significant evidence that it cures COVID-19 but could only suppress bacterial infections in the host. As earlier pointed out that in combination with chloroquine, azithromycin causes a significant improvement in patients with malaria without any indication of risk due to QTc prolongation above that of chloroquine. [85–87] The addition of zinc sulphate alongside hydroxychloroquine and azithromycin played an important role in the increased number of SARS-CoV-2 patients being discharged therefore zinc sulphate can also be used as prophylaxis [88].

In Morocco, it was reported that concomitant administration of hydroxychloroquine and azithromycin increased the number of cured SARS-CoV-2 patients and decreased mortality rates [89]. Azithromycin was also reported to be compatible with breastfeeding coronavirus nursing mothers and during pregnancy but with caution and adequate monitoring [90]. Notably, treatment with azithromycin combined with hydroxychloroquine showed a more prolonged QTc than treatment with only azithromycin [91]. An insight into the pharmacokinetics of hydroxychloroquine and azithromycin combination therapy explains the effect of this combination as a function of their accumulation on the lysosomal cells in the local concentration via ion-trapping mediation. The need for further clinical studies to possibly unravel the safety and risk benefits is therefore essential [92]. Furthermore, Bayesian application with statistical analysis on the effects of combining hydroxychloroquine and azithromycin also yielded viral load reduction [93]. Azithromycin and bee derived products (such as honey) were suggested especially among high-risk SARS-CoV-2 frontline health workers as

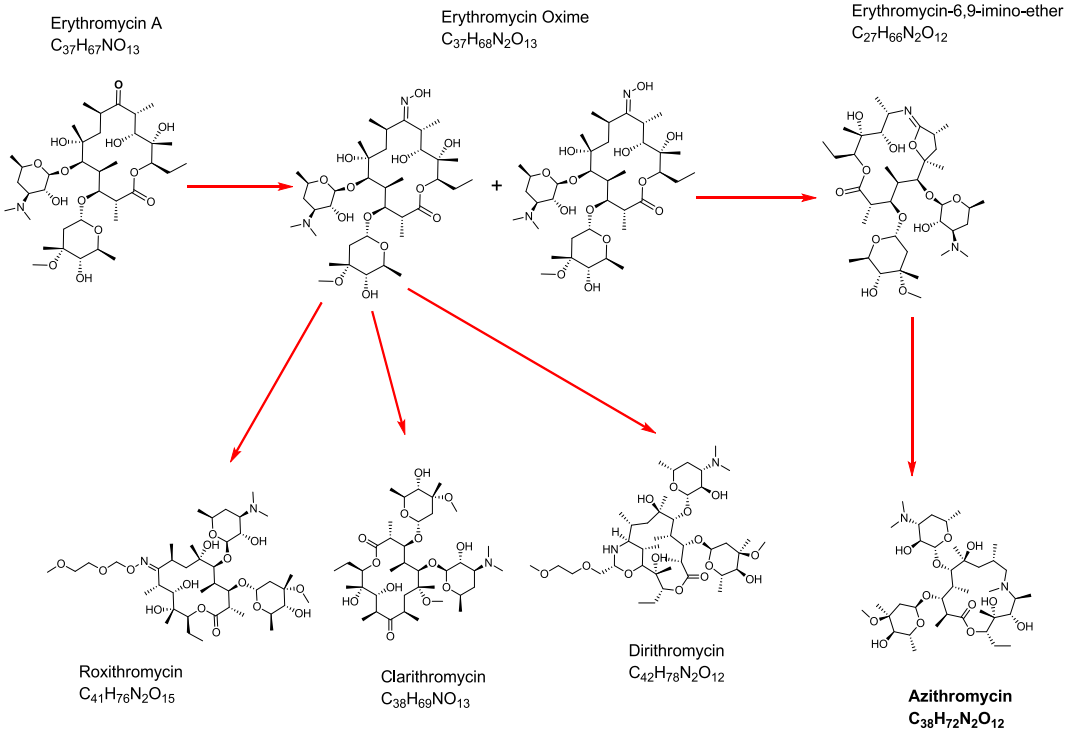


Fig. 4. Chemical structure of Azithromycin from Erythromycin A.

prophylactic treatment; further investigations into some of the compounds in the bee products are suggested [94].

3.13. Ivermectin

Ivermectin is an anti-parasitic broad-spectrum drug that was reported to inhibit the interaction between HIV-1 replicates [95]. Chemically, the compound reveals two subsets: the 1st subset possesses an olefinic bond at C-22 while the 2nd subset bond is hydrated with a hydroxyl (–OH) group at position 23 known as 22, 23-dihydro derivative of avermectin B_1 which is a macrolide lactone produced by actinomycetes *Streptomyces avermitilis* [96] (Fig. 5). Utilizations of ivermectin are numerous and potent to combat other viruses that have been fully documented [97–100]. This broad-spectrum activity on viruses is due to the importin alpha/beta-1 during infection [101,102]. Quest for drugs to combat this novel coronavirus revealed a possible role for ivermectin and importin alpha/beta-1 during infection as a signal-dependent nucleocytoplasmic shuttling of the SARs-CoV nucleocapsid protein mediated nuclear import [103–106]. In Australia, the antiviral activity of ivermectin on SARS-CoV-2 infected cells in an *in-vitro* study revealed a 93 percent reduction in the viral RNA present in the supernatant and 99.80 percent reduction in cell-associated with viral RNA. It was observed that ivermectin treatment led to a rapid reduction in viral RNA load by about 5000-fold in 48 hrs [104]. The pharmacokinetic perspective of this drug was analysed based on the pharmacokinetic data from clinically relevant and excessive dosing studies available; It was indicated that the SARS-CoV-2 inhibitory concentrations are not likely to be attainable in humans and that a single dosage is practically inappropriate because of the infected cells which were exposed at different concentrations negate the pharmacokinetics findings of some previously used doses pooled in the treatment regimen of ivermectin [107] and therefore suggests a need for further clinical trials to determine the best level of inhibitory concentration. It was reported that the combination of ivermectin and hydroxychloroquine could work synergistically with adequate clinical monitoring when administered [108]. In a screening of 1,408 patients gathered from 3 continents and carefully matched with age, gender/ethnicity, comorbidities, and illness severity score group consideration; it was concluded that administration of ivermectin on COVID-19 patients decreased death rates and reduced the length of hospital admission with the hope that an ivermectin drug used for filarial worm treatment (a neglected tropical disease) would be potent enough to combat the current SARS-CoV-2 alongside with clinical trials on the standard practices [109]. However, some researchers suspected possible toxicity with the use of ivermectin but recommended careful consideration of risk-benefit ratios and clinical trials to fully understand the pharmacokinetics and safety of administration [110,111]. It was demonstrated that both ivermectin and chloroquine are capable to inhibit replication of the SARS-CoV-2 *in-vitro* with a suggestion that a combination of these drugs could be effective especially in malaria-endemic regions where chloroquine is still an effective drug to combat *Plasmodium vivax* blood-stage therapeutic [112].

3.14. Colchicine, (-) -N-5,6,7,9-tetrahydro 1, 2, 3, 10- tetra methoxy-9-oxybenzone-7-yl (s)- acetamide

This is an iso-quinoline alkaloid originated from *Colchicum autumnale* belonging to the family of Liliaceae [113] (Fig. 6). Traditionally, it has been used in gout management, Mediterranean fever, liver cirrhosis, chronic myelocytic leukaemia, hepatic disorders, cardiovascular diseases, and also in potential anticancer drugs [114,115]. The biosynthesis of colchicine involves mainly phenylalanine and tyrosine. It is a very toxic antitumor drug and has been reported in patients with kidney and liver failure, however, derivatives such as dem-colchicine, trimethyl-colchicine acid methyl-ester, 2-dimethyl thiocolchicine, 3-dimethyl

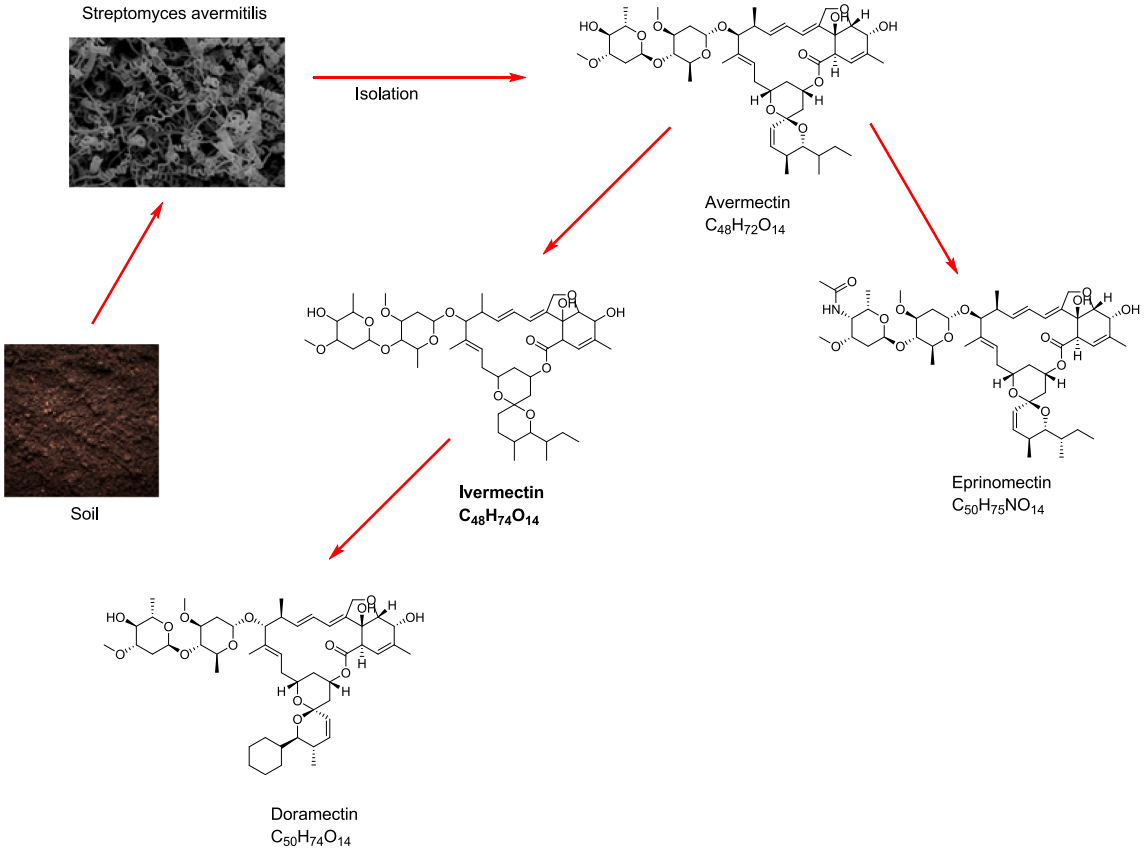


Fig. 5. *Streptomyces avermitilis*, bacterial source, Ivermectin, and some isolated chemical compounds.

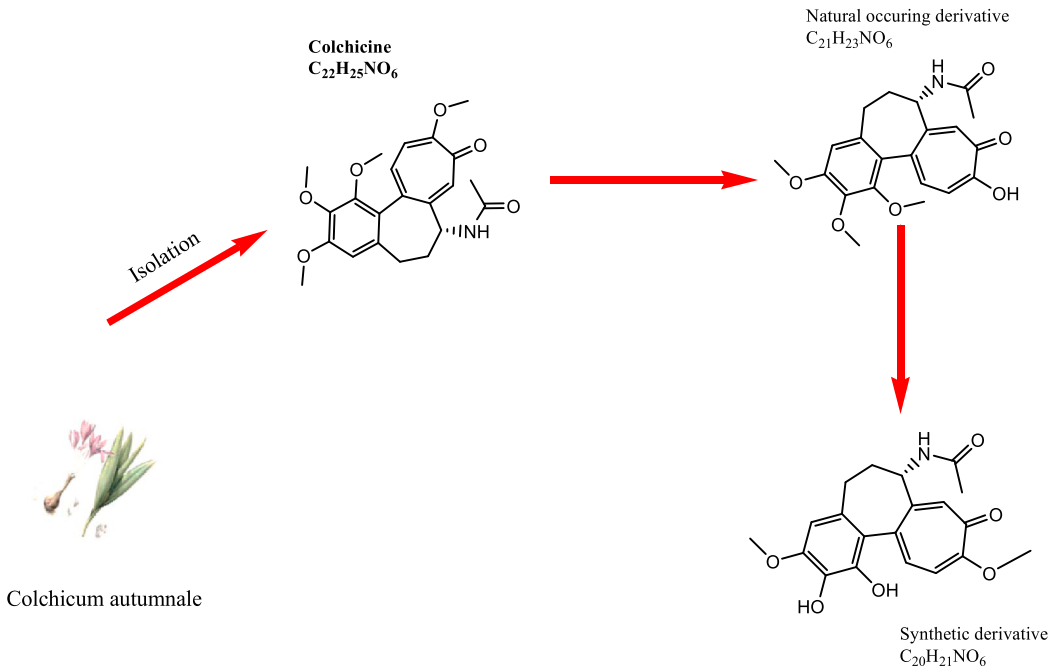


Fig. 6. *Colchicum spp*, botanical source, and some isolated chemical compounds.

thio-colchicine and the biosynthetic colchicine's which are less toxic are used as anti-leukaemia agents [116,117]. Colchicine has anti-inflammatory effects on the IL-1 and IL–6 axes which further prolong neutrophils and macrophages actions as well as the multiple cellular actions in the assembly of the nucleotide-binding domain and leucine-rich repeat protein inflammasome [118]. It is a non-selective inhibitor of Nucleotide Oligomerization Domain)-like receptor protein 3 (NLRP3) inflammasome that plays a huge role in anti-inflammatory diseases and binds to unpolymerized tubulin heterodimers, forming a stable complex that can effectively inhibit microtubule dynamics upon binding to microtubules ends [118,119]. In addition to this, colchicine plays an important role in managing patients with SARS-CoV-2 especially patients with myocardial infarction related cases even at acute and chronic phase periods [120]. Colchicine was recommended possibly on its clinical trial to see if it could assist in the clinical management of SARS-CoV-2 patients and reduce the inflammation caused by the virus [121]. According to [122], severe acute respiratory infections can cause pulmonary and systemic inflammation among SARS-CoV-2 patients and could lead to cardiac injury, heart failure, and respiratory complications. Significant evidence was reported that colchicine could ameliorate the effect of inflammation and hyper inflammation activity on SARS-CoV-2 patients and that it could be used as a supporting therapy with possible clinical trials suggested [123]. In another study, there was a significant finding on the physicochemical properties, chemical properties, and the mechanism of action and the conclusion that it may not be beneficial to patients since it has effects of increasing cytosolic pH and by implication might increase the rate of acute respiratory distress syndrome and multiple organ failure among SARS-CoV-2 patients [124]. In Israel, experimental studies were conducted using real-world data, a conclusion was reached that colchicine could be utilized based on the NLRP3 inflammasome which can be activated and triggered by different SARS-CoV-2 proteins and therefore could lead to severe adult respiratory distress syndrome. [125]. Colchicine clinical trials should be done carefully among patients with the underlying heart and other myocardial disorders towards saving more lives.

3.15. Omacetaxine (Homoharringtonine)

Homoharringtonine is a traditional antiviral compound that is effective for reducing viral load at about 0.05 or 0.2 mg/kg doses, inhibiting vesicular stomatitis virus at 50 nM, new castle virus at 100 nM, and porcine epidemic diarrhoea virus at 150 nM [126]. It is a *Cephalotaxus fortunei* derived plant alkaloid (Fig. 7) with antitumor activity capable of inhibiting the first cycle of the elongation phase of eukaryotic translation [127,128]. The semi-synthetic form of homorringtonine is called Omacetaxine [73,129] which is responsible for the treatment of chronic myeloid leukaemia refractory to tyrosine kinase inhibitors [130]. The anti-SARS-CoV-2 effect of homoharringtonine was recently examined while it has been reported to inhibit the virus with EC_{50} value 2.10 μM [58]. A maximal plasma concentration of 36 ng/mL (0.066 μM) obtained on day 11 from a pharmacokinetic study conducted by Nemunaitis et al., [131] with 1.25 mg/m^2 omaxacetine administered subcutaneously every 12 h (twice daily) on patients with solid tumours and hematologic malignancies revealed a much lower EC_{50} than the concentration against SARS-CoV-2 virus *in-vitro*.

3.16. Transmembrane Protease Serine2 (TMPRSS2) inhibitor

Camostat Mesylate, Flumadin, Nafamostat, Trasylol which are Transmembrane Protease Serine-2 (TMPRSS2), and other synthetic inhibitors used in managing prostate cancer have been expressed in the epithelial cells of specific tissues including those in the autodigestive tract [128]. Previous reports revealed that the Coronaviridae family including influenza virus have also utilized TMPRSS2 for viral entry via the hemagglutinin protein (HA) attached to angiotensin-converting enzyme (ACE2) being expressed on respiratory epithelial cells [132–136]. Hoffmann et al. [137] conducted an *in-vitro* study using Camostat mesylate, a protease inhibitor and observed a partial inhibition at the entry stage of the SARS-CoV-2 virus in the epithelial lung cells. This suggests that protease inhibitors could combat the novel 2019 coronavirus. Furthermore, the authors argued that Nafamostat mesylate offered more antiviral protection than camostat mesylate (Foipan) which is in use in Japan to treat SARS-CoV-2 infected patients. They also proposed that Nafamostat mesylate should be subjected to clinical investigations to evaluate its curative activity and strength to inhibit SARS-CoV-2 and further recommended that camostat mesylate, Nafamostat, and bromhexine hydrochloride (BHH) be considered for inhibition of TMPRSS2 in the control of COVID-19 [138]. Interestingly, in a

Table 1
Summary of some clinical features involving drugs reviewed in the present work against SARS-COV-2.

Drugs	Mechanisms of Action/ Targets	Some clinical features					EC_{50} (μM)	CC_{50} (μM)	References
		[a]Clinical Trial ID	Interventions	Control	Study Design (Phase/ Location /Enrolment No.)	Summarized Outcomes			
Combined Therapies									
Lopinavir-Ritonavir	Lopinavir and ritonavir areprotease inhibitors, which block viral replication, Ritonavir is a CYP3A inhibitor which functions primarily to reduce the metabolism of lopinavir, thereby boosting lopinavir levels.	NCT04343768	Hydroxychloroquine + Lopinavir/Ritonavir + Interferon Beta-1A (in first group) and + Interferon Beta-1B (in second group)	Hydroxychloroquine + Lopinavir/Ritonavir	Randomized (Completed/ Iran /60)	No results on clinical outcomes with the full protocol as provided by WHO and National clinical trial on outcome measures but the phases completed.	26.63		[26,58,149]
Ribavirin	Ribavirin, a guanosine analogue inhibits viral RNA polymerase and mRNA capping.	NCT04276688	Lopinavir/ritonavir 400 mg/100 mg twice daily for 14 days + Ribavirin 400 mg twice daily for 14 days + Interferon Beta-1B 0.25 mg subcutaneous injection alternate day for 3 days	Lopinavir/ritonavir 400 mg/100 mg twice daily for 14 days	Randomized (Completed/ HongKong/127)	Three combinations were safe and superior to Lopinavir–Ritonavir alone and shortening virus shedding, alleviating symptoms, and facilitating discharge of patients with mild to moderate COVID-19	109.50	>400	[150,32,151]
Arbidol	Arbidol inhibits by interfering with multiple steps of the virus replication cycle. The stages of SARS-CoV-2 replication targeted by arbidol is during the virus entry process, the post-entry stages, or the entire process of infection (Full-time). Arbidol efficiently blocked both viral entry and post-entry stages.	NCT04476719	Atafenovir 200 mg KAPSUL (Capsules containing 207.009 mg Umifenovir hydrochloride monohydrate equivalent to 200 mg Umifenovir hydrochloride.	Arbidol 100 mg KAPSUL (Capsules containing 103.504 mg Umifenovir hydrochloride monohydrate equivalent to 100 mg Umifenovir hydrochloride	Open-label, Randomized, Single oral dose, two-period, cross over. (Phase 1/Turkey /18)	To assess the bioequivalence of atafenovir 200 mg Kapsul In comparison with Arbidol 100 mg Kapsul in healthy male subjects under fasting conditions alongside with ethical protocols and strong confidence intervals evaluation.	4.11	31.79	[32]
Direct antiviral (Monotherapy)									
Favipiravir	RNA-dependent RNA polymerase (RdRp) inhibitor. Blocking the replication of other RNA viruses. Activated into its phosphoribosylated form (favipiravir-RTP) in cells, which then inhibits viral RNA polymerase activity	NCT04336904	Day 1: 1800 mg, BID; Day 2 – 14: 600 mg, TID	Placebo Dosage: Day 1: 1800 mg, BID; Day 2 and thereafter: 600 mg, TID, for a maximum of 14 days.	Multi-centre, randomized, double-blind, placebo-controlled (1:1) Phase 3 (Italy/100)	This is a multi-centre, randomized, double-blind, placebo-controlled (1:1) clinical study to explore the efficacy and safety of Favipiravir in the treatment of adult subjects with COVID-19-moderate type.	61.88	>400	[18,150]
Remdesivir	Remdesivir is a nucleotide analogue with the triphosphate	NCT04292899	Standard of care with and without mechanical ventilation +	Standard of care	Randomized completed (USA/4891)	The magnitude of benefit cannot be determined because	0.77	>100	[151,152]

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Table 1 (*continued*)

Drugs	Mechanisms of Action/ Targets	Some clinical features					EC_{50} (μM)	CC_{50} (μM)	References
		[a]Clinical Trial ID	Interventions	Control	Study Design (Phase/ Location /Enrolment No.)	Summarized Outcomes			
	form i.e., RDV-TP being used as a substrate for many viral RNA-dependent RNA polymerase (RdRp) complexes. RDV-TP has been reported to inhibit the viral RNA synthesis via a specific mechanism of delayed chain termination for coronaviruses including SARS-CoV-2 RdRp. It has been observed that RDV-TP specifically resembles Adenosine triphosphate (ATP) molecule and competes with the nucleotide during the viral RNA synthesis.		Remdesivir Administered as an *IV* for 5 and 10 days separately (RDV 200 mg Day 1 and 100 mg from Day 2–5 or 2–10 according to the grouping)			there was no placebo control, however, the most common adverse events noticed were nausea worsening respiratory failure, elevated alanine aminotransferase level, and constipation.			
Atazanavir	Atazanavir is of high interest because of its bioavailability within the respiratory tract. ATV could dock in the active site of SARS-CoV-2 Mpro, with greater strength even than Lopinavir. ATV inhibits SARS-CoV-2 replication, alone or in combination with ritonavir (RTV) in Vero cells, human pulmonary epithelial cell line, and primary monocytes, impairing virus-induced enhancement of IL-6 and TNF-α levels.	NCT04452565	NA-831 (60 mg orally twice a day for one day, followed by 30 mg once a day for four consecutive days (Five days in total)) and Atazanavir (400 mg orally twice a day for one day, followed by 200 mg daily for four consecutive days (five days total))	NA-831 60 mg orally twice a day for one day, followed by 30 mg once a day for four consecutive days (Five days in total)	Randomized Controlled Phase 2/3 (USA/525)	Currently recruiting in the Phase 2/3 trial to evaluate four treatment strategies for non-critically ill hospitalized participants(not requiring ICU admission and/or mechanical ventilation)with SARS CoV-2 infection, in which participants will receive NA-831 or Atazanavir with or without Dexamethasone.			[153]
Indirect antiviral									
Hydroxychloroquine (HCQ)	Hydroxychloroquine exhibits antiviral potency by inhibiting virus entry into host cells. The pathway can be related to post-translation alteration of newly synthesized proteins via glycosylation inhibition	NCT04328285	HCQ 200 mg: 2 tablets on the evening of Day 1 and 2 tablets on the morning at Day 2 and 1 tablet once daily afterwards	Placebo of HCQ, 2 tablets on the evening on Day 1, and 2 tablets on the morning at Day 2 and 1 tablet once daily afterwards.	Randomized, double-blinded, placebo-controlled. Phase 3 (France/ 600)	In a placebo-controlled trial, lopinavir is being compared to hydroxychloroquine, which is used to treat malaria, rheumatoid arthritis, and lupus erythematosus, as a preventative treatment for COVID-19 in exposed	0.72		[52,154]

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Table 1 (*continued*)

Drugs	Mechanisms of Action/ Targets	Some clinical features					EC_{50} (μM)	CC_{50} (μM)	References
		[a]Clinical Trial ID	Interventions	Control	Study Design (Phase/ Location /Enrolment No.)	Summarized Outcomes			
						health-care workers with the primary outcome being the occurrence of the infection (NCT04328285)			
Omacetaxine (Homoharringtonine)	No clear mechanism of action recorded against SARS-CoV-2 but its actions in other viruses implicates ribosomal bond to prevent protein translation	N/A	N/A	N/A	N/A	Clinical investigation is required to ascertain its mechanism of action and the ideal dose against SARS-Co-2	2.10	59.75	[58,73,127]
Emetine dihydrochloride	Prevention of DNA and RNA replication in Vero E6 cells.		A broad-spectrum antiviral drug with in vitro activity against MERS-CoV at an EC_{50} of 0.34 μM	Used in combination with Remdesivir and the nucleoside analogue GS-5734 to exhibit synergistic inhibitory effect against SARS-CoV-2 replication		Use for the treatment of generality of viral infection.	0.50 (Reduction in viral RNA) 0.46 (Reduction in infectious viruses)	56.46	[58,155]
Presatovir	Inhibition of fusion intercellular mediated by the F protein	NCT02135614			Randomize, double-blind, placebo-controlled studies Phase 2b clinical trial	Used against the respiratory syncytial virus (RSV) resistance development and treatment			[156]
Chloroquine (CQ)	Chloroquine as Hydroxychloroquine earlier described exhibits its antiviral potency equally by inhibiting virus entry into host cells. The pathway can be related to post-translation alteration of newly synthesized proteins via glycosylation inhibition Chloroquine is also proposed to inhibit the glycosylation of ACE2 receptor chains, thus limiting ligand recognition of these receptors, rendering the viral spike protein unable to mediate cell entry.	NCT04342650	CQ 450 mg twice daily (3 tablets of 150 mg, every 12 h) on day 1, followed by CQ 450 mg once daily (3 tablets of 150 mg) from D2 to D5. Oral administration.	150 mg placebo tablets (oral)	Randomized completed (Brazil/152)	The preliminary findings from the Clinical trial suggest that a higher dosage of CQ in COVID-19 should be carefully administered because of safety concerns regarding QTc prolongation and its potential safety hazards	1.13	>100	[151,154,157,158]
Antibiotics (combined therapies)									
Azithromycin		NCT04329832		N/A			2.12		[53,86,158]

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Table 1 (*continued*)

Drugs	Mechanisms of Action/ Targets	Some clinical features					EC_{50} (μM)	CC_{50} (μM)	References
		[a]Clinical Trial ID	Interventions	Control	Study Design (Phase/ Location /Enrolment No.)	Summarized Outcomes			
	Azithromycin in combination therapy with hydroxychloroquine Inhibits endosomal acidification via early endosomal pathway		Azithromycin 500 mg on day 1 plus 250 mg daily on days 2–5 (maybe administered intravenously per clinician preference). If the patient has already received azithromycin before randomization (no more than 2 days), the prior doses will count toward the 5-day total.		Randomized Phase 2 (USA/85)	A formalized protocol for trials with Bayesian statistical evidence approached currently ongoing. Statistical approach contributes to the network of meta-analyses of therapeutics of COVID-19			
Ivermectin	The hypothesized mechanism of action is through inhibiting IMPα/β1-mediated nuclear import of viral proteins by dissociation of the heterodimer which is the same for other RNA viruses.	NCT04343092	Ivermectin 12 mg /weekly) + Hydroxychloroquine 400 mg/daily + azithromycin 500 mg daily (Ivermectin 0.2 mg /kg (single dose at once = 2 tablets of 6 mg/weekly)	N/A	Pilot Randomized completed (Iraq/100)	This study showed that adding IVM to HCQ and AZT had a better cure rate and shorter time to stay in the hospital compared with controls but it was relatively safe without observable safety signals. results are needed to be validated in a larger prospective follow up study			[104]
Colchicine	Microtubule polymerization inhibitor by binding with the beta-tubulin subunit to prevent it from assembling (Tubulin-colchicine complex). Also, it inhibits Monosodium urate (MSU), as well as the inhibitory effect on neutrophil functions.	NCT04392141	Oral administration of Colchicine + Herbal Phenolic Monoterpene Fractions	N/A	Randomized Phase 2 (Iran/200)	No significant results yet but it's an ongoing oral administration with some herbal phenolic monoterpene fractions will be added to standard treatment in patients with COVID-19.			[159]
Immuno-stimulants									
Transmembrane Protease Serine2 (TMPRSS2) inhibitor	The inhibitors block viral activity by preventing TMPRSS2′s action on S protein processing (inhibit SARs-CoV-2 entry into the host cell).	NCT04509999	Bicalutamide 150 mg oral tablet daily at 1:1 randomization for up to 4 weeks	Standard of care and placebo	Randomized Phase 3 (USA/100)	The study is an ongoing clinical trial that proposes to test bicalutamide at 150 mg oral daily dosing in a double-blind placebo-controlled randomized trial in male patients with early symptomatic COVID-19 disease			[160]
Interferon (IFNs)	Type I and III IFNs are broad-spectrum antivirals both direct	NCT04389645	IP-10 in CDS protocol. Dynamic IP-10 measurements in	N/A	ObservationalCompleted (Israel/52)	The longitudinal and real-time IP-10 measurements could			[161–163]

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Table 1 (*continued*)

Drugs	Mechanisms of Action/ Targets	Some clinical features					EC_{50} (μM)	CC_{50} (μM)	References
		[a]Clinical Trial ID	Interventions	Control	Study Design (Phase/ Location /Enrolment No.)	Summarized Outcomes			
	inhibitory effects on viral replication in the upper airway, reducing viral spread to the lungs and transmission, and supporting an immune response to clear virus infection.		hospitalized COVID-19 positive patients			help with personalizing immunomodulatory treatment regimens for COVID-19 patients and may support better patient outcomes.			
Teicoplanin and other glycoprotein drugs (Dalbavancin, oritavancin, and telavancin)	Teicoplanin exhibits antiviral activity in the early stage of the viral life cycle of viruses such as Ebola virus, MERS-CoV, and SARS-CoV via inhibition of the low-pH cleavage of the viral spike protein by host cell's cathepsin L and cathepsin B in the late endosomes thereby preventing the release of viral RNA and replication.	NCT04492501	Assessing efficacy and safety of standard treatment including steroids, Remedisvir, Tocilizumab, mesenchymal stem cell therapy therapeutic plasma exchange in addition to standard treatment as well in combination with convalescent Plasma with other investigational treatments inlined with standard treatment Operational Definitions	Interventional retrospective case-control, single centre-based cohort study	An open-label Phase II Non-randomized (Pakistan/600)	Investigators will use different investigational treatment as mono or in combination to see mortality and morbidity benefit based on the limited evidence available so far. These investigational modalities include Therapeutic plasma exchange (TPE), Convalescent Plasma (CP), Remdesivir, Tocilizumab, and Mesenchymal stem cell (MSC) therapy in addition to standard supportive treatment.	8.78 concentration reached for a daily dose of 400 mg which is higher than 1.66 μM to inhibit 50% of viruses (IC50) in vitro		[159,163]

BID = twice in a day; TID = thrice in a day; IV = intravenous injection.
EC_{50} = half-maximal Effective concentration; CC_{50} = half-maximal cytotoxic concentration; N/A = Not applicable.
[a] Database of U.S. National Library of Medicine (clinicaltrials.gov).[161–163]

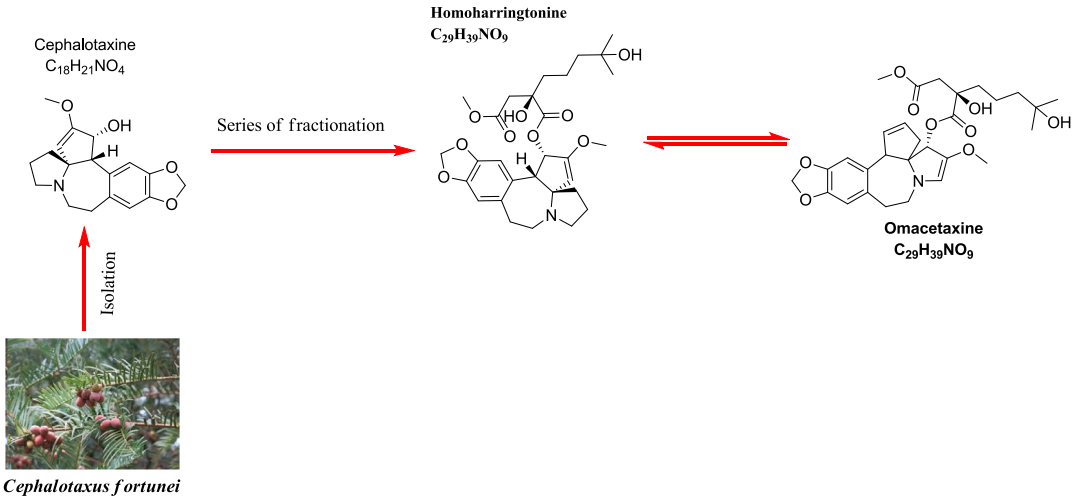

Fig. 7. *Cephalotaxus fortune*, botanical source, and some isolated chemical compounds.

large cohort study especially on African-American SARS-CoV-2 male patients diagnosed with *Diabetes mellitus* and Asthma using their sputum cells, the result showed that there was a higher expression of ACE2 and TMPRSS2 in diabetics patients with lower expression of ACE2 and TMPRSS2 in asthmatic patients. This suggests further investigation into the effective regimen among people with diabetes and asthma COVID-19 patients with effective monitoring including its role in the lung, renal, heart, and neurones of patients with SARS-CoV-2 [139–141]. Bestle et al. [142] found out that TMPRSS2, as well as FURIN protease enzymes which are abundant in the respiratory tract, could activate their surface glycoprotein and this suggests that they are potential drugs in the treatment of SARS-CoV-2.

3.17. Interferon (IFNs)

Interferon- a and b are naturally broad-spectrum antiviral active agents (Fig. 1j). The administration of IFNs can be used as prophylaxis as well as early therapy based on the principle of "supplement to compensate". Type-1 IFNs suppress chronic hepatitis B and C viral infections. The antiviral effect of interferon b (IFN- b) is still unknown however, it has an immune-modulating activity of improving the conditions of marmosets infected with MERS-CoV [143,144]. To assess the efficacy of interferon on SARS-CoV-2, several reports have demonstrated the antiviral effect with lambda Interferon (IFN-γ), a Type III interferon sharing low homology with Type-1 IFNs and IL-10, which has shown more potency against a variety of viruses including SARS-CoV and MERS-CoV [145]. IFN-γ therapy was recently proposed to possess an antiviral immune-modulating activity for reducing viral load and hyper-inflammation; it also prevents mass tissue damage in the lung. Besides, a pegylated IFNb-γ which is readily in existence as the only therapeutic agent has also been shown to possess an effective safety profile in human [146].

4. Projection and human health risk

It was noticed that there are different dosage regimens, drug combination trials, and skill-based experience treatment by clinicians on different patients with an underlying medical health history. This suggests complications in many developing and low-income countries with little or no quality standard health coverage in managing the post-SARS-CoV-2 health crisis. There is a need for more research and investigations into the lead drugs that could cure and manage the confirmed cases with the expectation of producing an effective and accessible vaccine to curtail the virus spread. Also, adequate monitoring of dosage regimen and drug combination, as well as ethical consideration, should be ensured while dealing with COVID-19 potential experimental drugs. Although, it is a pandemic situation, human rights to life including choice of drugs, allergy, pains and other difficult challenges and quality laboratory investigations before clinical trials should be considered. Safe health record-keeping, monitoring, toxicity check, dosage formulation, dug-drug interaction, mechanism of action, and side effect are paramount especially as post-COVID health-related management is concerned. However, it was advised that couples should avoid pregnancy during the pandemic and *in-vitro* fertilization should be carefully examined to prevent the potential threat to developing embryos [147] in spite no evidence of SARS-CoV-2 virus in semen of males recovering from the novel coronavirus after 30 days of diagnosis [148]. This also suggests quality and adequate examination of new-born babies during this pandemic to ensure they are not carriers of the COVID-19 virus. Furthermore, unprotected sexual related activities should be cautioned while it is hoped there would be scientific investigations into the protective measures during sexual intercourse.

Governments and health organizations should continually ensure access to a clean environment, clean water, quality life, housing, and basic amenities to meet the Global Health Security Agenda (GHSA), which could help alleviate some potential human health risks, especially among developing countries.

5. Conclusion and recommendations

This review has highlighted reported curative antiviral drugs and broad-spectrum antibiotics (both traditional and orthodox) used in the treatment of SARS-CoV-2; their chemistry, botanical sources, and active components as well as possible clinical trials and safety information. However, there is still a need for continued investigation of herbal medicines and isolation of compounds that could completely inhibit the virus. A full understanding of their mechanisms of action which would help in drug development needs to be known. Further in-depth studies on vaccines and molecular investigations into potential RNA targets should be a crucial priority. Best practices for virus prevention which include observing personal hygiene, following health guidelines by a way of physical distancing, and social responsibility among people are important in alleviating the coronavirus spread.

6. Funding*

This review article did not receive any grant from funding agencies.

7. Authors' contribution*

All authors contributed equally and approved the final version of the manuscript.

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.

Acknowledgements

We acknowledge the painstaking efforts of the anonymous reviewers toward the enhanced improvement of this work.

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