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Review

# COVID-19 and therapeutic drugs repurposing in hand: The need for collaborative efforts

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## Summary

The novel pandemic severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible to cause coronavirus disease-2019 (COVID-19). It is a global pandemic disease and has reached a new dimension with a higher death ratio. On 2 June 2020, World Health Organization (WHO) data showed more than 6,194,500 confirmed and 376,300 deaths globally due to the COVID-19. There are currently no approved medications or vaccines which have been claimed to be effective in COVID-19 prevention or treatment. Drug repurposing of available drugs and research studies for the search of new therapeutic agents are underway in various countries to try different combinations to treat their patients. It is too early to be sure of them as safe treatments because some reports seem to suggest some alarming side effects. However, a lot of work needs to be done to achieve a successful treatment result and the full safety and efficacy of the trial drugs will take some time to be developed. In this narrative perspective review, we addressed evidence-based literature on various possible antiviral medications, plant-derived antivirals drugs, and other valuable treatment options for COVID-19 management.

Mots clés
Effets indésirables
Coronavirus disease 2019 (COVID-19)
Réutilisation des médicaments
Médicaments

## Résumé

### COVID-19 et réutilisation thérapeutique des anciennes molécules : la nécessité d'efforts collaboratifs

*Le nouveau syndrome respiratoire aigu sévère pandémique coronavirus 2 (SRAS-CoV-2) est responsable de la maladie à coronavirus-2019 (COVID-19). Il s'agit d'une pandémie de nouvelle dimension avec un taux de mortalité plus élevé. Le 2 juin 2020, les données de l'Organisation*

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*Mondiale de la Santé (OMS) ont révélé plus de 6 194 500 confirmés et 376 300 décès dans le monde en raison du COVID-19. Il n'y a actuellement aucun médicament ou vaccin approuvé efficace pour prévenir ou traiter le COVID-19. La réorientation des médicaments disponibles et des études pour la recherche de nouveaux agents thérapeutiques sont en cours dans divers pays pour essayer différentes combinaisons susceptible de traiter les patients. Il est trop tôt pour juger de la sécurité d'utilisation traitements car certains rapports semblent suggérer des effets secondaires alarmants. Cependant, cela ne doit pas limiter les efforts pour obtenir un traitement réussi sur et efficace tant que des médicaments d'essai ne seront pas développés. Dans cette revue, nous avons abordé la littérature factuelle sur divers médicaments antiviraux possibles, les médicaments antiviraux d'origine végétale et d'autres options de traitement précieuses pour la gestion du COVID-19.*

## Introduction

The Severe acute respiratory syndrome (SARS) epidemic, which started in 2002, ended up numbering about 8,000 infected people and 770 dead, contributing to global costs of up to $100 billion. In comparison, Middle East respiratory syndrome (MERS) was characterized by fewer infections but stronger nosocomial outbreaks and a slightly higher mortality rate (approximately 35%) and has not been eliminated to date [1] with more than 90,000 confirmed cases and more than 2,500 deaths [2]. The current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic has reached a new dimension with an estimated death of around 2–3 percent, which is 10 times higher than that of seasonal influenza [2,3]. The infection due to this virus is also known as coronavirus disease-2019 (COVID-19). COVID-19 was declared a public health emergency by the World Health Organization (WHO) [4]. According to the WHO report on 2 June 2020, the cases of COVID-19 had been recorded worldwide with more than 6194500 confirmed and 376300 deaths [5].

Currently there are no medicines or vaccines that have been claimed to be useful in the prevention or treatment of COVID-19 [6,7]. Due to the absence of effective treatment and public health emergency, the COVID-19 pandemic is alarming the entire globe. International health care authorities are doing their efforts to provide quarantine and quick diagnosis for COVID-19 patients along with research to find an effective treatment that can control and prevent the present dangerous consequences of the disease. Drug repositioning (repurposing) is an investigation of existing drugs for new therapeutic purposes. It is a line of scientific research that aims to develop safe and effective treatments for COVID-19 [8]. Several existing antiviral drugs, previously developed or used as treatments for SARS, MERS, HIV, and malaria are being investigated as COVID-19 treatments and some of which are being used in clinical trials [6,7]. In this perspective review, we have discussed the various potential drugs used as anti-COVID-19 therapy.

## Antimalarial drugs

### *Chloroquine*

Chloroquine, with its wide spectrum antiviral activity, gained the primary attention for repurposing this medicine in the treatment of COVID-19. Chloroquine was previously used for malaria and is obtained from quinine which is present in the barks of cinchona plants that are native to Peru [9]. Chloroquine behaves like a potent bioactive agent against RNA viruses in in-vitro studies [10]. In the case of coronaviruses, the potential therapeutic benefits of chloroquine have been particularly reported for SARS-CoV-1. Chloroquine is examined against COVID-19 due to its versatile antiviral activity against most of the coronaviruses and specially SARS-CoV-1 [11], and the absence of any available useful treatment. A new study revealed that chloroquine inhibited COVID-19 in in-vitro and this medicine should be assessed in COVID-19 patients [12].

Experts in China suggested that individuals found with mild, moderate and severe cases of COVID-19 pneumonia and without chloroquine contraindications should be treated with 500 mg chloroquine therapy twice daily for consecutive ten days [7,13]. The China National Center for Biotechnology Development recently reported that chloroquine is among the three available medicines with potential activity against the COVID-19. Initial information from the Chinese authorities revealed that almost 100 infected individuals treated with chloroquine experienced a faster decline in fever, improved lung computed tomography (CT) images and required a shorter recovery time compared to control groups, with no potential side effects. They also recommended the addition of chloroquine in the COVID-19 treatment guidelines [13,14].

As a result, chloroquine is likely the first-line treatment in China and other countries to treat fatal COVID-19. Although the prolonged usage of chloroquine in malarial treatment demonstrates the safety of acute chloroquine administration in humans. Moreover, we can't neglect the low risk of macular retinopathy which relies on the cumulative dose and the

presence of cardiomyopathy as a serious side effect induced by chloroquine [15]. Currently, chloroquine is the medicine of choice among available drugs that can knock the severity of COVID-19. Till now, at least 10 clinical studies are being carried out to investigate chloroquine as an anti COVID-19 treatment [7,8]. However, a survey of adverse effects in patients infected with COVID-19 is still needed for a better therapeutic decision.

### *Hydroxychloroquine*

Hydroxychloroquine (a chloroquine analog) has both antimalarial and anti-inflammatory activities. It is used for the treatment of malaria, arthritis (rheumatoid), porphyria cutanea tarda, systemic lupus erythematosus, dengue and has somewhat higher potency against the COVID-19 [16]. The safety profile of hydroxychloroquine is better than that of chloroquine during long-term usage and allows a higher daily dose and has fewer concerns about drug-drug interactions [16,17]. Based on limited anecdotal and in-vitro data, hydroxychloroquine is presently suggested for the therapy of COVID-19 patients in many nations. Hydroxychloroquine has well-known safety history with the major concern being cardiotoxic (prolonged QT syndrome) with prolonged use in individuals with renal or hepatic malfunction and immune suppression, however, reportedly well tolerated in COVID-19 patients [17]. Hydroxychloroquine has been given to hospital admitted COVID-19 patients in several countries because of its wider availability and high in-vitro activity against COVID-19.

Currently, hydroxychloroquine is being studied in clinical trials as COVID-19 therapy with mild, moderate and severe cases [17]. According to a recent trial, hydroxychloroquine is useful in removing viral nasopharyngeal carriage of COVID-19 in a few days (less than a week) [18]. Presently no reports from Randomized Clinical Trials (RCTs) are available to update clinical guidance on the usage, dose or duration of hydroxychloroquine for therapy or prophylaxis of COVID-19. The normal dose and duration of hydroxychloroquine for COVID-19 therapy is unknown however, some U.S clinicians described anecdotal variations in hydroxychloroquine dosing such as 400 mg BID on day one, then daily for 5 days; 400 mg BID on day one, then 200 mg BID for 4 days; 600 mg BID on day one, then 400 mg daily on days 2-5 [17]. On the other hand, the China International Exchange and Promotive Association for Medical and Health Care (CPAM) has issued novel guidelines for 2019 COVID-19 and recommended the use of Hydroxychloroquine (orally 400 mg once daily) when chloroquine is not available [7].

## Antimalarial and antibiotic combination

### *Hydroxychloroquine and azithromycin*

The synergistic effect of the combination of azithromycin and hydroxychloroquine was also demonstrated in a recent study [18]. Azithromycin is active in vitro against Ebola [19] and Zika [20] viruses and to control severe respiratory infections in patients with viral infection [21]. A study revealed that hydroxychloroquine alone or in combination with azithromycin reduced COVID-19 RNA detection in upper respiratory tract specimens compared to a non-control group [21]. Azithromycin and hydroxychloroquine are linked with prolong QT and caution is required when using these medicines in individuals with chronic renal failure, hepatic patients or those patients who are using medicines that can interact to produce arrhythmias [17]. More studies on this combination are required, as this combination can both act as an antiviral treatment against COVID-19 and control bacterial super-infections [18]. Concerns were raised with respect to the veracity of the data and analyses conducted by the multinational, observational, real-world study in patients with COVID-19 on the regimen containing hydroxychloroquine or chloroquine (with or without a macrolide). Although several multicentre randomised controlled trials are underway, there is an urgent need to provide accurate clinical guidance regarding this regimen [22].

## Antiviral drugs

### *Lopinavir-Ritonavir*

Lopinavir (a type 1 aspartate protease inhibitor of human immunodeficiency virus; HIV) was used in 2003 against SARS- CoV due to its in-vitro inhibitory activity [23]. A combination of ritonavir with lopinavir increases its plasma half-life by inhibiting cytochrome P450. Lopinavir has activity against the MERS-CoV, both in vitro [24] and in an animal model [25]. The case study indicates that the combination of lopinavir-ritonavir with ribavirin and interferon alfa caused virologic removal [26]. Chinese guidelines recommended the use of lopinavir-ritonavir tablets (400 mg/100 mg orally twice daily) in critically ill elderly COVID-19 patients [7]. However, there are no considerable data on the efficacy of this approach in human beings. Lopinavir-ritonavir has not shown a guarantee for the therapy of COVID-19 hospitalized patients with pneumonia in a recently organized randomized, controlled, open-label clinical trial in China [27].

### *Remdesivir*

Remdesivir is an intravenous investigational drug with strong antiviral activity. It has activity against COVID-19 and other related beta-coronaviruses. This drug is not effective in Ebola, but in a laboratory, study remdesivir can prevent human cells from being infected with COVID-19. Furthermore, findings have identified that remdesivir is highly effective in controlling COVID-19 infection in vitro [12]. According to the CDC, the investigational agent (remdesivir) is currently being used in COVID-19 patients in the U.S [17]. FDA grant emergency approval to usage of remdesivir for COVID-19 [28]. However, a remdesivir was not associated with statistically significant clinical benefits in adult hospitalized COVID-19 patients [29]. Further confirmatory large multinational studies are needed to evaluate it efficacy and safety in COVID-19 patients [29,30].

***Favipiravir***

Favipiravir (FPV) is an anti-viral agent that selectively and strongly inhibits RNA-dependent RNA polymerase (RdRp) viruses. Favipiravir has anti-viral activity against the influenza virus and well-demonstrated actions against all three influenza A, B, and C [31]. According to a recent experimental study in China, FPV has shown substantially improved therapeutic effects on COVID-19 in terms of infection progression and viral removal. Furthermore, this research also indicates that the duration of treatment of FPV can be extended if required due to less adverse reactions [32]. According to the Guardian news report and official at the Chinese Ministry of Science and Technology reported that favipiravir has recorded promising results in clinical trials in Shenzhen and Wuhan involving 340 patients [33]. Turkey has also begun FPV for COVID-19 patients and according to the Turkish Ministry of Health, FPV has resulted in improvement in intensive care patients, decreasing their time in care from 11-12 days to 4 days [34]. According to a randomized clinical trial of Favipiravir vs. Arbidol for COVID-19 patients, FPV can be considered a preferable therapy due to its higher seven-day clinical recovery rate and a more reduction in the incidence of fever and cough except with some antiviral-associated adverse effects [35]. Favipiravir is also considered to be teratogenic; thus, if a pregnancy is confirmed or suspected, favipiravir administration should be avoided in women [36]. However, any approval for the use of FPV will, of course, entail further clinical testing, followed by the approval of widespread use by the relevant regulatory body for medical care in each country.

***Oseltamivir***

Oseltamivir is an antiviral drug used to treat and prevent influenza in patients aged 1 year and older [37]. Oseltamivir has been recommended for people at high risk of infection before or after pandemic influenza exposure [38]. Oseltamivir is also used in clinical trials with various combinations of chloroquine and favipiravir [39]. Further clinical trials and broad randomized controlled trials are needed to confirm the effective role of Oseltamivir in COVID-19 patients.

***Ribavirin***

Ribavirin has strong antiviral activity and is used treatment of hepatitis C, respiratory syncytial virus (RSV) infection and certain viral hemorrhagic fever [40]. According to the Chinese 7th Edition Guidelines [41] and a review of human case reports in China [42] recommended the combination of ribavirin with Lopinavir/Ritonavir and pegylated interferon and reported that it is effective in viral clearance in COVID-19 patients.

***Sofosbuvir***

Sofosbuvir is also an approved FDA drug. It acts as a nucleotide polymerase inhibitor and used for the treatment of the hepatitis C virus (HCV) [43]. This drug has previously been used for the treatment of the Zika virus [44]. It has been used in combination with interferon or ribavirin [45]. Sofosbuvir-based regimens used for treating chronic HCV infection are considered safe with minimal adverse effects on the respiratory system. A recent research indicates sofosbuvir's efficacy as a potent drug against the newly developed COVID-19 [43]. However, in COVID-19, greater multicenter studies are needed for further evaluation.

## Antihelmintics/antiparasitic agent

Ivermectin is a broad-spectrum antiparasitic agent approved by the FDA that has anti-viral activity against a wide variety of viruses [46]. It has been demonstrated to limit infection by RNA viruses and also effective against the DNA pseudorabies virus (PRV). According to a recent report, ivermectin may be a useful antiviral to reduce COVID-19 [47]. Ivermectin has a safety profile established for human use and previous analysis shows that high-dose ivermectin has comparable safety to standard low-dose treatment. Although there is not enough evidence to conclude the safety profile in pregnancy [48]. A critical next step in further assessment for the potential benefit of COVID-19 patients will be the examination of a multiple additional dosing regimen that mimics the current approved human use of ivermectin. However, the known safety profile shows that ivermectin is worthy of further consideration as a possible COVID-19 therapy [47].

## Interferon Alfa-2B

Interferons (IFNs) are essential components of the innate immune response and the first line of protection against virus infection. These are proteins in nature and derive their name from the word interfere as they interfere with viruses and prevent them from multiplying [49]. IFNs used to treat hepatitis C virus (HCV) infection, numerous malignancies, multiple sclerosis, HIV and AIDS [50]. The antiviral drug Interferon Alfa-2B is produced in China and is confirmed to have been effective in the treatment of HIV, human papillomavirus, Hepatitis B and C. According to studies, this medicine is useful in the treatment of viruses with characteristics identical to the novel coronavirus. The United Kingdom biotech company "Synairgen'' has been approved for a fast-track trial of IFN-Alfa-2B in COVID-19 patients. It is hoped that the administration of IFN-Alfa-2B will enhance the body's ability to fight the virus. The WHO has described it as the only drug in phase 2 trials that can be inhaled, which means that patients can administer it themselves through a small nebulizer powered by a battery [51]. However, the effectiveness of interferon therapy in COVID-19 has not yet been scientifically proved.

## Tocilizumab

Tocilizumab (TCZ) is a monoclonal antibody (a recombinant humanized anti-interleukin-6 receptor) that is mainly used in the treatment of systemic juvenile idiopathic arthritis (SJIA), polyarticular juvenile idiopathic arthritis (pJIA) and rheumatoid arthritis [52]. Recently, the FDA has approved a study to evaluate the use of tocilizumab in COVID-19 patients [53]. Details on

the prior use, mechanism of action and adverse effects of some repurposed drugs that may treat COVID-19 are discussed in *table I*.

## Anticoagulant treatment

Anticoagulants are the main treatment used to prevent and treat thrombosis. Unfractionated heparin (UFH) and low molecular weight heparin (LMWH) are the favored anticoagulants in acute thrombosis, due to their rapid antithrombotic activity [54]. Severe COVID-19 coagulopathy is usually problematic and is associated with high mortality [55]. The risk of venous thromboembolism (VTE) in severe COVID-19 patients is also increased due to the evidence of viral infection, respiratory dysfunction and long-term bed rest. In severe COVID-19 patients, treatment with anticoagulants (such as heparin) can help in reducing the pulmonary coagulopathy and venous thromboembolism [55]. It is documented that LMWH improves coagulation dysfunction in COVID-19 patients and exerts anti-inflammatory effects by reducing Interleukin 6 (IL-6) and increase the percentage of lymphocytes. It would also seem that LMWH may be used as a possible therapeutic drug for COVID-19 [56]. However, further studies are required to confirm and validate its efficacy and safety profile [55].

## Non-steroidal anti-inflammatory drugs (NSAIDs)

### *Ibuprofen*

The ibuprofen, a painkiller is a common alternative for people with headaches and fevers, two of the novel coronavirus

TABLE I

**Some repurposed drugs that might treat COVID-19.**

**Anciennes molécules proposées pour traiter l'affection à COVID-19.**

| Drug Name | Treated | Inhibition | Main adverse effects |
|---|---|---|---|
| Chloroquine | Malaria, influenza A [10], SARS [11], Human Coronavirus OC43 [12]. | Transcription and translation which significantly restricts DNA and RNA synthesis in the parasite. [10,12] | Macular retinopathy, cardiomyopathy [15] |
| Hydroxychloroquine | Malaria, rheumatoid arthritis, Dengue Virus, COVID-19 [16,17] | Bind to and modify DNA and cause viral inhibition [16] | Arrhythmias [17] |
| Lopinavir- Ritonavir | HIV [23], SARS [23], MERS [23,24] | Viral replication [23,24,26] | Gastrointestinal adverse effects, hyperlipidemia and glucose intolerance [23,26] |
| Remdesivir | Ebola, COVID-19, SARS and MERS [12] | inhibits viral RNA polymerases [12] | Multiple organ-dysfunction syndrome, septic shock, acute kidney injury, and hypotension [12,17] |
| Favipiravir | Influenza A, B, and C [31], COVID-19 [32] | RNA-dependent RNA polymerase viruses [31] | Teratogenic [36] |
| Oseltamivir | Influenza [37], COVID-19 [39] | Inhibits the neuraminidase enzyme and viral replication [37] | Neuropsychiatric adverse events [37,38] |
| Ribavirin | Respiratory syncytial virus (RSV) and RSV pneumonia [40], COVID-19 [41,42] | Viral replication by stopping RNA synthesis and mRNA capping [40,41] | Hemolytic anemia, teratogenic [40] |
| Sofosbuvir | COVID-19[43], Hepatitis C Virus [43], Zika virus [44] | Viral replication by inhibiting RNA synthesis [39] | Pulmonary arterial hypertension [43,44] |
| Ivermectin | RNA viruses [46], pseudorabies virus (PRV) [46], COVID-19 [47]. | Viral replication [46,47] | Neurological adverse events [46] |
| Interferon Alfa-2B | hepatitis C virus, HIV. AIDS, RSV, and SARS [49–51] | Viral replication [49] | Neuropsychiatric effects [49,50]. |
| Tocilizumab | Juvenile idiopathic arthritis, polyarticular juvenile idiopathic arthritis, rheumatoid arthritis [52] and COVID-19 [53] | Signaling blockage of IL-6 and its inflammatory response [52]. | Allergic-type reaction [52] |

HIV: Human immunodeficiency virus, SARS: Severe acute respiratory syndrome, MERS: Middle East respiratory syndrome, COVID-19: Coronavirus infectious disease-2019, IL-6: Interleukin-6 receptor.

symptoms. However, amid the growing COVID-19 pandemic situation, French Health Minister Olivier Véran called on social media to warn patients not to take anti-inflammatory drugs such as ibuprofen or cortisone because they may worsen the disease and should rely on paracetamol [57]. Additionally, according to a recently published letter in a medical journal hypostasized that ibuprofen may increase the levels of an enzyme called angiotensin-converting enzyme 2 (ACE2) which ultimately increases the severity of COVID-19. The ACE2 enzyme is increased in people with diabetes and also in those who received some hypertension therapy [58]. However, there is presently no scientific proofs to establish a connection between ibuprofen and the worsening of COVID-19. Later on, 19 March 2020, the WHO states that they do not suggest against the use of ibuprofen [59]. More evidence is therefore needed to explore this issue.

#### *Paracetamol*

Paracetamol is also known as acetaminophen and is used in the treatment of fever and pain. It is typically used for mild to moderate relief of pain. Few health care professionals suggest first-line use of paracetamol over ibuprofen [60]. The WHO does not oppose the use of non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen for symptoms [59] and the FDA describes that there is presently no evidence that COVID-19 symptoms worsen with NSAIDs [61].

### Antihypertensive drugs

The angiotensin-converting enzyme inhibitors (ACE inhibitor) and angiotensin II receptor blockers (ARBs) are used mainly for the treatment of high blood pressure and heart failure. Some scientists are hoping that these drugs may be beneficial for patients with COVID-19. The University of Minnesota has performed two clinical trials using the inexpensive generic (losartan) drug. The trials will assess and explain whether losartan can prevent multi-organ failure and control prolonged hospitalization in COVID-19 patients with pneumonia [62]. Losartan works by blocking the receptor or gateway to the cells which are used by the chemical called angiotensin II to penetrate the cells and raise blood pressure. COVID-19 binds to the receptor of angiotensin-converting enzyme 2 (ACE2), and it may be assumed that because losartan can block these receptors, it can prevent the virus from infecting cells. The recently published study raised complicating issues and mentioned the possibility that specific hypertension drugs (ACE inhibitors and ARBs) specifically losartan may cause the body to generate more ACE2 and thus increase the ability of the virus to infiltrate cells [58]. Furthermore, a recent analysis of 355 COVID-19 patients in Italy found that hypertension existed in three-quarters of the patients who died and suggested that this was one of the reasons for their increased sensitivity [63]. Although theoretical questions about ACE inhibitors, ARBs and ibuprofen have been raised, but there is no convincing evidence that either ACE inhibitors, ARBs or ibuprofen facilitate or worsen COVID-19 infection in any type of patient [64].

#### *Corticosteroid*

Corticosteroid medication used to suppress the immune system and reduce inflammation. These are not recommended for COVID-19 until the disease is complicated [65].

#### *Ozone treatment*

Ozone is considered a natural killer of viruses and has been widely used by people for disinfection, sterilization, deodorization, detoxification, and bleaching for more than 100 years. Ozone kills viruses by disseminating the protein coat into the nucleic acid core and causing viral RNA damage. At higher concentrations, ozone destroys the capsid or outer protein layer and damages either the microorganism's DNA or RNA (virus/bacteria) structure [66]. Ozone has three main attributes such as full coverage (reach to every corner of the environment), high detergency with no toxic residues, convenience (produced by simple equipment). Ozone should be adopted as a weapon in the global fight against COVID-19 due to the above-mentioned features [67].

#### *Plant-derived antivirals drugs*

Plants are the main traditional source of biologically active substances and compounds extracted from plants have gained the attention for their antiviral therapy. An ample amount of literature is available on the antiviral plant-derived compounds [68,69]. Some plants have reputedly been successful against respiratory viral infection, including, *Allium satimum*, *Mentha pipertia*, *Zinger officinale* and *Lianhua Qingwen* [69–71]. *Diammonium glycyrrhizinate* (liquorice root extract) is a herbal remedy recruited to control COVID-19. *Glycyrrhiza glabra* has long been used against coughs and colds as well as to alleviate disrupted digestion, while *Diammonium glycyrrhizinate* has anti-inflammatory properties and is used to treat liver damage caused by hepatitis B. Extracts from *Lycoris radiata*, *Artemisia annua*, *Lindera aggregate*, *Isatis indigotica*, *Torreya nucifera,* and *Houttuynia cordata* showed effectiveness against SARS [71]. The plant *Flavone baicalein* is capable of preventing the entry of dengue virus into the host and inhibiting post-entry viral replication [72]. The natural products from *Pelargonium sidoides* roots and *Dandelion* have an anti-influenza effect by inhibiting virus entry and enzyme activities [73,74].

There is no clear information about the effectiveness of plant-derived drugs in COVID-19. Still, it is possible, that various herbs combined with western medicines can improve symptoms, quality of life and pulmonary infiltration absorption. Many antiviral drugs in most developing countries are costly and beyond the reach of the common man. There are many viral diseases that we keep battling constantly and they prove deadly and contagious. While some may be curbed by the use of antiviral drugs, others have become worse over some time by developing resistance to these drugs. Compounds obtained from plants

need to be marketable and made available at a low cost. Plants are not only essential for food but also as medicinal products. Knowing the pathways of secondary metabolite synthesis are also essential for the production of plant drug products [71].

## Conclusion

Until now, it is still unclear which drug can successfully fight against the disease. While studies are underway and different countries try different combinations to treat their patients. It is too early to be sure about them as safe treatments and studies appear to indicate some troubling side effects. There are currently no complete data available from large RCTs to provide clinical advice on the use, dosing or duration to validate the effective role, safety profile and adverse effects of all of the above-mentioned drugs for prophylaxis or treatment of COVID-19. There is a desperate need for new drugs to treat COVID-19 and, meanwhile, scientists are working hard to develop effective treatments. However, a lot of work needs to be done to achieve a better treatment outcome and it will take some time to establish the complete safety and efficacy of the trial drugs. Therefore, further clinical studies and large randomized control studies are needed for the better treatment option and safety of COVID-19 patients. Collaborative efforts around the world are needed to achieve this goal.

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