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Journal of Infection and Public Health 14 (2021) 495–503

Contents lists available at ScienceDirect

Journal of Infection and Public Health

journal homepage: http://www.elsevier.com/locate/jiph

Combating COVID-19: The role of drug repurposing and medicinal plants

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ARTICLE INFO

Article history:
Received 11 April 2020
Received in revised form 11 July 2020
Accepted 12 October 2020

Keywords:
COVID-19
Corona virus
Pandemic
Drug repurposing
Medicinal plants

ABSTRACT

Background: A novel corona virus-2 disease has spread to 213 countries and territories across the globe. The corona pandemic has claimed more than 548,934 deaths worldwide till the evening of 8th of July 2020 and the number of confirmed cases is increasing at an alarming rate. Therefore, there is an urgent need to find a treatment or a vaccine for COVID-19 at the earliest. The aim of this mini-review is to give an overview of identified repurposed anti-COVID-19 drugs which are currently under clinical trials.
Methods: A thorough literature survey was done to retrieve relevant information using various web based search engines such as Google, Google scholar, and various other electronic research databases such as PubMed, Medline, MeSh *etc*. The findings of the recently published articles, clinical trials, COVID-19 update by World Health Organization *etc*., and the opinion of the authors is summarized in this brief review. The antiviral medicinal plants were identified based on their use in Chinese/Indian indigenous systems of medicine, traditional use, published scientific phytochemical studies and/or their effectiveness against upper respiratory infections, severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS).
Results: The disease is just over six months old and effective prophylactic or therapeutic agents are yet to be developed for COVID-19. Thus, in the absence of an effective therapy, scientific community has rationally considered the drug repurposing approach for the development of anti COVID-19 drugs. Various studies and clinical trials involving antimalarial drugs, anti-HIV drugs, anti-hepatitis drugs, anti-parasitic drug, anti-inflammatory drugs, the combination of antimalarial and macrolide antibiotic and few other molecules identified through drug repurposing are currently underway to combat COVID-19. Due emphasis is also given to develop novel corona vaccines for the prophylaxis and to identify drugs for adjunct/supportive therapy. Several medicinal plants along with their major phytochemicals exhibiting antiviral activity are identified for further exploration. It is anticipated that these natural products might also play an important role in combating COVID-19.
Conclusions: Use of drug repurposing strategy to develop anti COVID-19 drugs and exploring antiviral medicinal plants as adjunct or supportive therapy appears to be a viable option. Therefore, it is the need of the hour to work in parallel on different strategies such as genetic engineering, *in silico* approach, herbal remedies and drug repositioning to achieve the common goal of finding a safe and effective treatment for COVID-19 at the earliest.
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Introduction

Never before in the history was a corona virus disease declared as a pandemic. However, World Health Organization (WHO) on 11th March 2020 declared the outbreak of a corona virus disease 2019 (COVID-19) pandemic. COVID-19 is caused by a novel corona virus (2019-nCoV) also known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) [1]. Though there is no consensus among scientific community regarding the first transmission of COVID-19 to humans, Guo et al., based on genome sequencing and other analyses have suggested that the enveloped zoonotic virus was originated in bats and then through an unknown intermediate was transmitted to humans [2]. The first case of COVID-19 was detected on 31st December 2019 in Wuhan city of China and since then, it has spread to 213 countries and few territories of the world in just over six months mainly due to human

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https://doi.org/10.1016/j.jiph.2020.10.012
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to human transmission. Almost the entire world has come to a halt as most of the countries were in lock down in order to contain and prevent its transmission. As of 8th July 2020, the outbreak has infected 12,054,157 and caused the death of about 548,934 people around the world [4] and the number is still increasing at an alarming rate. The lockdown is being slowly lifted in phases across globe with preventive measures in place but unfortunately no one knows exactly how long they have to live with it. The COVID-19 has certainly pushed the world towards global economic crisis and recession phase. It has affected all aspects of socio-economic and mental health of human life.

The most important modes of transmission of the COVID-19 include; airborne, droplets, respiratory secretions and direct contact with the infected patient [3]. Like other corona viruses that have previously caused Middle East Respiratory Syndrome (MERS) in 2012 and severe acute respiratory syndrome (SARS-CoV-1) in 2002–2003, COVID-19 produces from mild symptoms of common cold such as dry cough, running nose, high fever, and body ache to pneumonia in severe cases. The mortality rate is higher in elderly and in patients with other underlying co-morbidities such as hypertension, diabetes and other cardiovascular diseases [3,5]. Goldstein et al., reported that some medications like angiotensin receptor blockers (ARBs) and statins, commonly used to treat hypertension and atherosclerosis co-morbidities, may increase the risk of severe pneumonia, acute respiratory distress syndrome and death in COVID-19 patients, in particular elderly [6]. Since the start of the COVID-19 crisis, tremendous research efforts have been invested to develop a vaccine or a treatment for this disease all over the world.

The aim of this mini-review is to provide an overview of identified repurposed anti-COVID-19 drugs which are currently under clinical trials. We have also tried to shed light on some of the potential medicinal plants and the natural products that could be used to fight against COVID-19.

Therapeutic strategies to develop antiviral therapy for COVID-19

At present, infected patients are treated mainly on the basis of symptoms as no effective and approved treatment is available to fight COVID-19. As per the recommendation of WHO and other health authorities, preventive measures such as frequent washing of hands, use of sanitizers, social distancing, use of face mask, personal hygiene, early diagnosis, isolation of the suspected cases and supportive treatments are in place to contain and curb the spread of this deadly virus to flatten the curve of incidences. Focus is also on the development of an effective antiviral therapy and vaccine but this may require months or even years. Hence, in the current situation, the best strategy to combat this dreaded disease is to use the drug repurposing approach for anti-COVID-19 drug discovery. Drug repurposing also called as drug repositioning has high probability of success rates because it explores the existing therapies for new therapeutic purposes and therefore, information related to drug's synthetic methodology, safety and toxicology is available before hand. Thus, drug repurposing potentially reduces the cost and shortens the time for drug discovery in comparison to the conventional *de novo* drug discovery [7]. Researchers have primarily explored the existing antiviral drugs as potential anti-COVID-19 therapy. Several of the tested drugs showed promising results in preclinical studies and therefore moved to clinical trial phases. The other approach included testing repurposed drugs that act on the human immune system and inhibit corona virus replication and infection through interferons and thereby improving and strengthening the patient's own immune system [8].

Potent antiviral drug candidates should be identified capable of interfering with at least one or more stages of the Corona virus replication cycle [9]. The various known antiviral targets includes: (i) inhibition of the virus fusion to human cellular receptors such as serine protease (TMPRSS2) inhibitors, (ii) blockade of virus receptor on to the host cell surface (monoclonal antibodies) (ii) inhibition of virus entry into the host cytoplasm and (iv) inhibition of virus translation and replication by developing RNA dependent RNA polymerase inhibitors, protease inhibitors to block polyprotein processing, budding, exocytosis and virus release inhibitors (Fig. 1) [10]. Working along the same line, researchers have identified few promising anti COVID-19 drugs through repurposing which are currently under clinical trials [11]. These molecules have earlier showed beneficial effects against several viral diseases such as MERS, SARS, Ebola, HIV and/or hepatitis [2]. Antimalarial drugs chloroquine, hydroxychloroquine and an FDA approved antiparasitic drug Ivermectin which possess antiviral activity have also been identified for further testing [11,13].

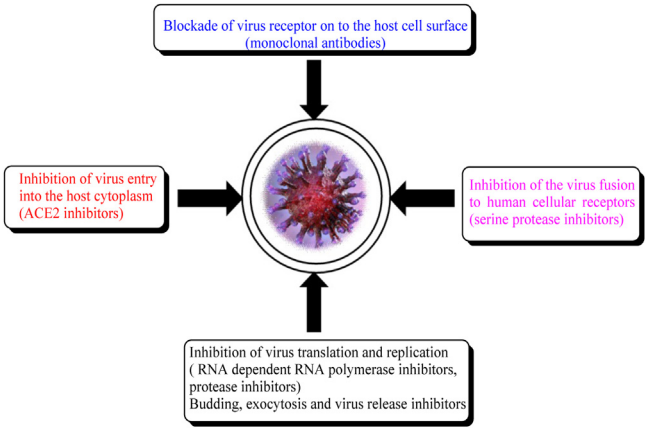

Fig. 1. Potential targets of anti-COVID-19 drugs.

A brief update on the status of potential repurposed drugs and/or combinations currently under clinical trials is given below;

(i) Anti-HIV drugs: the combination of lopinavir–ritonavir (Kaletra®) is used in the USA to treat HIV infections and it has been selected because of its ability to inhibit protease of HIV and other coronaviruses. Lopinavir (400 mg)–ritonavir (100 mg) combination of the two protease inhibitors is currently in Phase III clinical trial. The study will establish the efficacy, safety and antiviral activity of the combination of two antiretroviral drugs against COVID-19 [14]. The above combination of HIV drugs (lopinavir–ritonavir) along with a broad-spectrum antiviral ribavirin has also been selected for further testing and validation of their use in COVID-19. Chu et al., in 2004 reported that combined therapy with lopinavir–ritonavir and ribavirin, a nucleoside analogue had a better clinical outcome in the treatment of SARS in comparison to the ribavirin monotherapy [15]. These drugs are considered as potential candidates for the COVID-19 but the recently published results of a clinical trial did not show much anticipated benefits of lopinavir–ritonavir combination in adults hospitalized with severe Covid-19 in comparison to current standard care [16]. The lopinavir–ritonavir combination therapy was also found to induce nausea and diarrhea (up to 28%) as well as hepatotoxic effects in 2–10% patients. The plausible reason for the ineffectiveness of this combination could be the delayed treatment initiation, the median time from symptoms identification to therapy onset being 13 days [14].

(ii) Anti-Ebola drug: remdesivir (2-ethylbutyl-L-alaninate phosphoramidate prodrug) is a novel nucleotide analogue originally developed by GILEAD Sciences to treat Ebola virus. It acts by

inhibiting the RNA-dependent RNA polymerase to stop the virus replication [17].Two independent studied conducted by Wang et al., and Holshue et al., obtained promising results with remdesivir in COVID-19 patients. The drug was found to have high selectivity (EC_{50} = 0.77 μM) and blocked the SARS-CoV-2 at low μM concentrations [18,19]. On 25th March 2020, US-FDA granted remdesivir an Orphan drug status and Gilead Sciences® began testing it in Phase III in five COVID-19 clinical trials [20]. The drug was subsequently been given Expanded Access, or "compassionate use" status to address the pandemic [21]. China in February 2020 has also initiated the randomized, placebo-controlled, double-blind, multicenter, phase III clinical trial on remdesivir [9]. It is a leading drug candidate in clinical trials race among COVID-19 antiviral drugs. Recently on 1st May 2020, the US-FDA based on the results of a phase III clinical trial, further granted Gilead Sciences® Emergency Use Authorization (EUA) of intravenous ramdesivir in hospitalized patients with severe symptoms though it has yet to be approved for market use [22]. The FDA also warned that remdesivir should not be used along with Chloroquine (CQ) or Hydroxychloroquine (HCQ) as the antimalarial drugs may reduce its antiviral potency [23]. Another study reported that remdesivir seems to work better if given for 5 days rather than 10 days. Galidesivir, another nucleoside RNA polymerase inhibitor and structural analog of remdesivir, active against Zika and Ebola is also under evaluation. It inhibits viral replication (EC_{50} = 100 μM) in Vero E6 cells against SARS-CoV-2 [24]. A clinical placebo-controlled, randomized study (NCT03891420) is evaluating galidesivir administered intravenously at 12 h intervals for 7 days in COVID-19 patients [25].

(iii) Antimalarial drugs (CQ/HCQ): more than 20 studies conducted in China and France till early March 2020 reported the beneficial effects of repurposed drugs CQ/HCQ in the treatment of COVID-19. Zhou et al., recommended HCQ clinical trials to investigate its effect in both COVID-19 infection and progression [26]. Based on the outcome of clinical studies conducted in Beijing, in central China's Hunan Province and South China's Guangdong Province, Chinese medical advisory board has suggested including CQ in the SARS-CoV-2 treatment guidelines [11,27]. However, Sahraei et al., in a letter to editor of *Int J Antimicrobial* agents have recommended use of HCQ over CQ to treat COVID-19 because of former's lower ocular toxicity. Also, CQ can interact with lopinavir–ritonavir combination and may result in prolongation of the QT interval [28]. Yao et al., also found HCQ to be more potent than CQ at inhibiting SARS-CoV-2 *in vitro* and recommended 400 mg HCQ-BID for 1 day followed by 200 mg twice daily for 4 more days to treat SARS-CoV-2 infection [29]. Devaux et al., proposed the multiple mechanism of action of CQ in SARS-CoV-2, in 2020. They hypothesized that CQ: (i) interferes with angiotensin converting enzyme type II (ACE2) receptor glycosylation and thus prevents binding of SARS-CoV-2 to the target cells; (ii) may act indirectly to reduce the production of pro-inflammatory cytokines and/or by activating anti-SARS-CoV-2 CD^{8+} T-cells [30]. Wang et al., reported CQ to exhibit good activity against SARS-CoV-2 (1.13 μM at half maximal concentration) and was shown to act by increasing the endosomal pH required for viral fusion [18]. However, both CQ and HCQ have been discontinued in June 2020 from the WHO and UK sponsored Solidarity and UK Recovery trials due to lack of data regarding their safety, efficacy and as "having no clinical benefit in hospitalized patients with COVID-19 trials" [31,32].

(iv) Anti-HIV and anti-hepatitis drugs combination: the Ritonavir and Danoprevir combination is approved for the treatment of HIV and hepatitis C. Ascletis Pharma Inc., a Chinese manufacturer is evaluating this combination with or without Interferon nebulization for the treatment of COVID-19 Pneumonia *via* a small sample, open Phase 4 clinical trial [33]. Interferon-beta is an immune system messenger and is involved in the regulating inflammation in the body is included in the trials because of its encouraging results in the treatment of MERS.

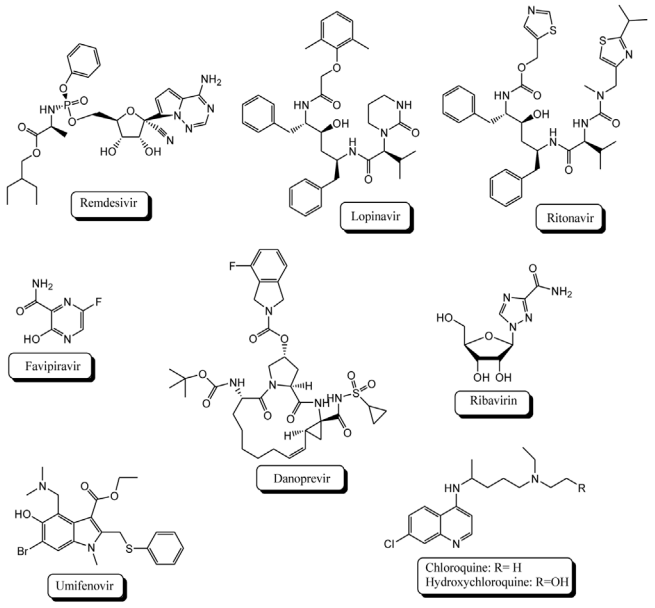

Fig. 2. Chemical structure of some of the most important repurposed drugs currently being evaluated for COVID-19 therapy.

Ribavirin ((1-β-D-ribofuranosyl-1,2,4-triazole-3-carbox amide) is another broad spectrum antiviral drug. It is approved by FDA in the treatment of hepatitis C which acts by competing for the active site of RNA-dependent RNA polymerase (RdRp). It is generally used in combination with interferon α (IFN). It has been shown to exhibit 109.5 μM of half maximum concentration in Vero E6 cells against SARS-CoV-2 [18].

(v) Anti-influenza drugs: favipiravir (6-fluoro-3-hydroxy-2-pyrazinecarboxamide) (Fig. 2) was approved in China for the treatment of novel influenza on February 15, 2020. It is a new type of RdRp inhibitor which is currently undergoing clinic trials for the treatment of COVID-19 [9]. Clinical Medical Research Center of the National Infectious Diseases and the Third People's Hospital of Shenzhen in February 2020 conducted a clinical trial on favipiravir for the treatment of COVID-19 and reported promising results [34]. Russian Ministry of Health (MOH) on 30th May 2020 approved the use of Avifavir© (a generic version of favipiravir) as the first anti-COVID-19 drug produced by JV of RDIF and ChemRar. The final stage of Avifavir© clinical trials involving 330 patients is currently underway [35]. Similarly, India also approved the use of a generic version of favipiravir called FabiFlu©, developed by Glenmark Pharmaceuticals, in the treatment of mild to moderate cases of COVID-19 [36].

Umifenovir (Arbidol©) is an indole carboxylic acid derivative (Fig. 2). It is approved in Russia and China for the prophylaxis of influenza A and B. It acts by blocking the virus-cell membrane fusion as well as virus-endosome fusion through incorporation into cell membranes and by interfering with the hydrogen bonding network of phospholipids [37]. A retrospective cohort study conducted by Deng et al. has reported that combination of Arbidol©

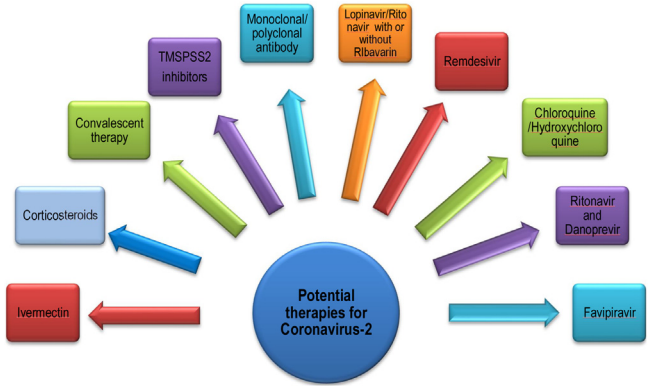

Fig. 3. Therapeutic interventions/repositioned drugs which are currently being explored for the treatment of COVID-19.

and lopinavir–ritonavir drugs increased negative conversion rate of SARS-CoV-2 and improved chest CT scan results [38].

Other possible approaches for supportive/adjunctive therapy and vaccines development against COVID-19

Supportive or adjunctive therapies are primarily aimed to prevent severe morbidity and mortality in COVID-19 patients. Various therapeutic interventions and investigation of supportive or adjunctive therapy currently underway to fight COVID-19 include development of mesenchymal stem cell therapy, monoclonal antibody therapy, polyclonal antibody therapy, type II transmembrane serine protease (TMSPSS2) inhibitors, antirheumatoid arthritis drugs (JAK-STAT inhibitors) and combination therapy of HCQ and azithromycin *etc.*, (Fig. 1) [15]. Convalescent therapy which involve using plasma from recovered COVID-19 patients had been earlier used a strategy to induce passive immunity in MERS patients [39].

An FDA approved anti-parasitic drug Ivermectin with known antiviral activity has also been reported to inhibit the replication of SARS-CoV-2 *in vitro* only in 48 h. Ivermectin deserves further *in vivo* exploration to investigate its anti-COVID-19 spectrum [13]. Till June 4, 2020, Ivermectin is being evaluated in 10 ongoing and 14 planned clinical trials [40].

Corticosteroids such as methylprednisolone and dexamethasone are potent steroidal anti-inflammatory drugs which can prevent an extended cytokine response. Huang et al., demonstrated that corticosteroids could decrease the viral clearance in COVID-19 patients [41]. The results of a multicenter, randomized controlled trial has shown that dexamethasone use decreases ventilator days and mortality on severe acute respiratory distress syndrome in patients without COVID-19 [42]. Monoclonal antibodies (mAbs) such as sarilumab, tocilizumab, lenzilumab *etc.*, are capable of contrasting cytokine storm by targeting and binding to IL-6 in severe COVID-19 patients [43]. The mAbs reduce the replication of the virus and its spread through passive immunization and possess a strong potential in combating highly pathogenic viral diseases.

Apart from the development of antiviral drug therapy, due emphasis is also given to develop preventive COVID-19 vaccines [44]. On this front, clinical trials for mRNA-1273 by Moderna and COVID-19 vaccine (CanSinoBio) have already begun and the results are expected to be available by summer 2020 [45]. The human clinical trials for 14 potential COVID-19 vaccines are currently going on in countries *viz.*, USA (3), China (5), United Kingdom (2), Russia (1), Germany (1), India (1), US and Europe (1). In addition to these, several other vaccines are in the pre-clinical stages of development [46] Fig. 3.

Major clinical trials

SOLIDARITY clinical trial

WHO launched the global mega trial called "SOLIDARITY" in March 2020 to test effectiveness and safety of the four most promising Corona virus treatments namely, remdesivir, CQ and HCQ, ritonavir–lopinavir combination and ritonavir–lopinavir combination with interferon-beta [47]. The Solidarity trial is implemented in coordination with thousands of hospital sites in over 100 countries on 5 continents. The WHO in June 2020 has discontinued the use of HCQ for the treatment of COVID-19 in the Solidarity trial as it failed to show benefits in the COVID-19 therapy [32].

RECOVERY clinical trial

RECOVERY (Randomised Evaluation of COVid-19 thERapY) is a randomized clinical trial which was launched in April 2020 in 132 hospitals across UK to evaluate anti-COVID-19 medications (lopinavir–ritonavir, HCQ, azithromycin and low-dose dexamethasone [48]. In mid of April, it expanded to include 5400 infected COVID patients receiving treatment at 165 UK hospitals [49]. In mid June, the trial group reported that "Low-cost dexamethasone reduces death by up to one third in hospitalized patients with severe respiratory complications of COVID-19". In this controlled trial, low and daily dose of dexamethasone was given to 2000 hospitalized COVID patients and the results were compared with more than 4000 patients who did not receive the drug. The dexamethasone given either po or IV injection, appeared to be very helpful for patients on ventilators (1/3rd lower death rate) or in need of oxygen support (1/5th lower death rate) [50].

Potential of medicinal plants against COVID-19

Health authorities in several countries are also exploring the role of antiviral medicinal plants, either alone or as supplement to the antiviral therapy to fight against COVID-19 [51]. Bioactive natural products have played a key role in discovery of many important drug molecules and medicinal plants are still considered as potential sources of New Chemical Entities (NCE) including anti-COVID19 drugs. In fact, several antiviral herbal drugs have been used in the past for SARS, MERS, influenza and dengue virus-related symptoms [52,53]. Secondary plant metabolites could act at one or multiple stages of virus replication [54,55]. The herbal drugs with potent antioxidant and antiviral activity might help in alleviating the anxiety and other upper respiratory related symptoms associated with COVID-19.

Researchers have investigated the potential of medicinal plants and natural products *via* computational, *in vitro* and *in vivo* studies in a hope to defeat the SARS-CoV-2 pandemic. Wang et al., in January 2020 carried out a retrospective study on four confirmed COVID-19 patients at Shanghai Public Health Clinical Center, China to evaluate the effect of combined traditional Chinese medicine, Shufeng Jiedu Capsule (SFJDC) with lopinavir/ritonavir and arbidol [18]. SFJDC is also recommended for treating COVID-19 infection in the latest version of Diagnosis and Treatment of Pneumonia Caused by 2019-nCoV (version 5) [56]. The results were encouraging and warrant further exploration. Zhang et al. performed the rational *in silico* screening of some potential Chinese herbal medicines with an aim to identify phytochemicals and medicinal plants that might directly inhibit the SARS-CoV-2. They identified 13 natural products, which occur in traditional Chinese medicines and could exert antiCovid-19 activity. 125 herbs contained at least two of these phytoconstituents while only 26 herbs are categorically used to treat viral respiratory infections [57]. The identified chemicals

Table 1
List of potential medicinal plants possessing antiviral activity.

S. No	Name of the plant	Common name	Important phytoconstituents(s)	Antiviral activity [Reference]
1.	*Nigella sativa* Family: Ranuncluceae	Black seed	Thymoquinone, nigellimine	Influenza virus (H9N2) [59] Cytomegalovirus (MCMV) [60] Hepatitis C virus [61,62] HIV [63].
2.	*Cinchona succirubra* Family: Rubiaceae	Cinchona	Quinine Quinidine, cinchonidine Cinchonine	Herpes simplex virus-1 (HSV-1) influenza A virus (IAV) [64]
3.	*Sambucus nigra* Family: Caprifoliaceae	Elderberry	Ursolic acid Oleanolic acid	Herpes virus [65]
4.	*Withania somnifera (L.) Dunal* Family: Solanaceae	Winter cherry (Ashwagandha)	Withanolides Withaferins Isopelletierine Anaferine Sitoindoside	Herpes simplex virus [66] Influenza virus H1N1 [67]
5.	*Prunella vulgaris* Fam: Lamiaceae	Self heal	Betulinic acid hyperoside Delphinidin Lupeol	HIV-1 and Ebola virus [68] Herpes simplex virus-1 & 2 [68]
6.	*Glycyrrhiza glabra* Family: Fabaceae	Licorice	Glycyrrhizin Glycyrrhetic acid liquiritin Isoliquiritin	HCV [69,70] Influenza virus [71] HSV1 [72]
7.	*Caesalpinia pulcherrima* Family: Leguminosae	Peacock flower	Lupeol β-Amyrin, peltoginoids Homoisoflavonoide	Herpes viruses, adenovirus [73]
8.	*Curcuma longa* Family: Zingiberaceae	Turmeric	Curcumin	HSV-1 [74] HIV [75] HCV [76]
9.	*Zingiber officinale* Family: Zingiberaceae	Ginger	Gingerol Shogaols Zingerone	Avian influenza virus H9N2 [77]
10.	*Punica granatum* Family: Lythraceae	Pomegranate	Punicalagins ellagitannin	SARS-CoV [78]
11.	*Andrographis paniculate* Family: Acanthaceae	Creat or green chireta	Andrographolide	Antiviral properties [79,80] HSV, HBV, HCV, Chikungunya virus, HPV, HIV [81]

include; quercetin, kaempferol, betulinic acid, coumaryl tyramine, crytptotanshinone, sugiol *etc.* The potential Chinese herbal plants containing these constituents and possibly be used to treat respiratory syndromes are *Forsythiae fructus*, Liquorice, *Mori cortex, Eriobotryae folium, Ardisia japonicae herba etc.*

Qamar et al., screened a medicinal plant database containing 32,297 potential anti-viral phytochemicals/traditional Chinese medicinal compounds and selected the top nine hits that may inhibit SARS-CoV-2 $3CL^{pro}$ activity and hence virus replication. Top ranked phytochemicals 5,7,3′,4′-tetrahydroxy-2′-(3,3-dimethylallyl)isoflavone from *Psorothamnu sarborescens*, myricitrin from *Myrica cerifera*, methyl rosmarinate from *Hyptisa trorubens Poit*, Calceolarioside B from *Fraxinus sieboldiana*, licoleafol from *Glycyrrhiza uralensis* showed better binding affinity and docking scores than positive control drugs, Nelfinavir and Prulifloxacin. They concluded that these phytochemicals might serve as potential anti-COVID-19 lead molecules for further optimization and drug development process to combat COVID-19 [58].

Given below is a brief description of some potential ethnomedicinal plants which are known to exhibit antiviral activity and are used in Chinese traditional system of Medicine, Ayurvedic system of medicine, Unani and as Prophetic medicine. These plants could be explored further for the drug discovery and development of anti-COVID-19 drugs (Table 1).

The roots of a Chinese medicinal plant *Scutellaria baicalensis* Georgi (Family: Lamiaceae) is known to exhibit potent antiviral activity against the family of corona virus. The traditional antiviral Chinese medicine Huang-Qin contains the roots of this plant. The antiviral activity of this plant is attributed to Baicalein (5,6,7-trihydroxyflavone) and its glycoside baicalin (5,6-dihydroxyflavone 7-*O*-β-D-glucuronide) present in the plant. These two natural products exhibit beneficial effect against dengue virus by preventing its entry into the host and by inhibiting virus replication [37]. Zhang and Liu suggested that baicalin could be used as a therapeutic alternative to improve the immunity in the COVID-19 patients and to fight against the viral infection [82]. Quercetin, another flavonoid with five hydroxyl groups, found in *Allium cepa, Ginkgo biloba, Hypericum perforatum, and Sambucus canadensis* was demonstrated to inhibit the entry of the H5N1 virus in the early stages [83]. It inhibits Angiotensin-Converting Enzyme more strongly than rutin, kaempferol, rhoifolin, and apigenin K flavonoids and indicated by their IC_{50} (43 < 64 < 178 < 183 < and 196 μM, respectively) [84].

Nigella sativa is a miraculous remedy with a wide range of pharmacological properties. Its seeds have been mentioned as the cure for every disease except death by the last prophet of Islam. It may possess the desired potency to be used as a complementary and alternative medicine for COVID-19 treatment. Its bioactive constituents especially thymoquinone has been reported to possess antiviral activity. Sommer et al., argued that antiviral mechanism of action of thymoquinone is similar to CQ/HCQ but antiviral spectrum of thymoquinone is superior to HCQ as it is devoid of adverse effects which are associated with the use of CQ/HCQ. They further added that thymoquinone being a smaller size hydrophobic molecule can bind to the lipophilic envelope of the SARS-CoV-2 and is capable of killing the deadly virus by oxidizing it [85]. In contrast to this, Rahman hypothesized that thymoquinone and nigellimine may block the entry of SARSCoV-2 *via* angiotensin converting enzyme 2 (ACE2) in pneumocytes. He also mentioned that the antiviral action of black seed against COVID-19 could further be augmented by Zinc supplement. The uptake of Zinc into the pneumocytes will be enhanced in the presence of thymoquinone and other bioactive compounds functioning as ionophores which in turn could inhibit the replication of novel corona virus by blocking

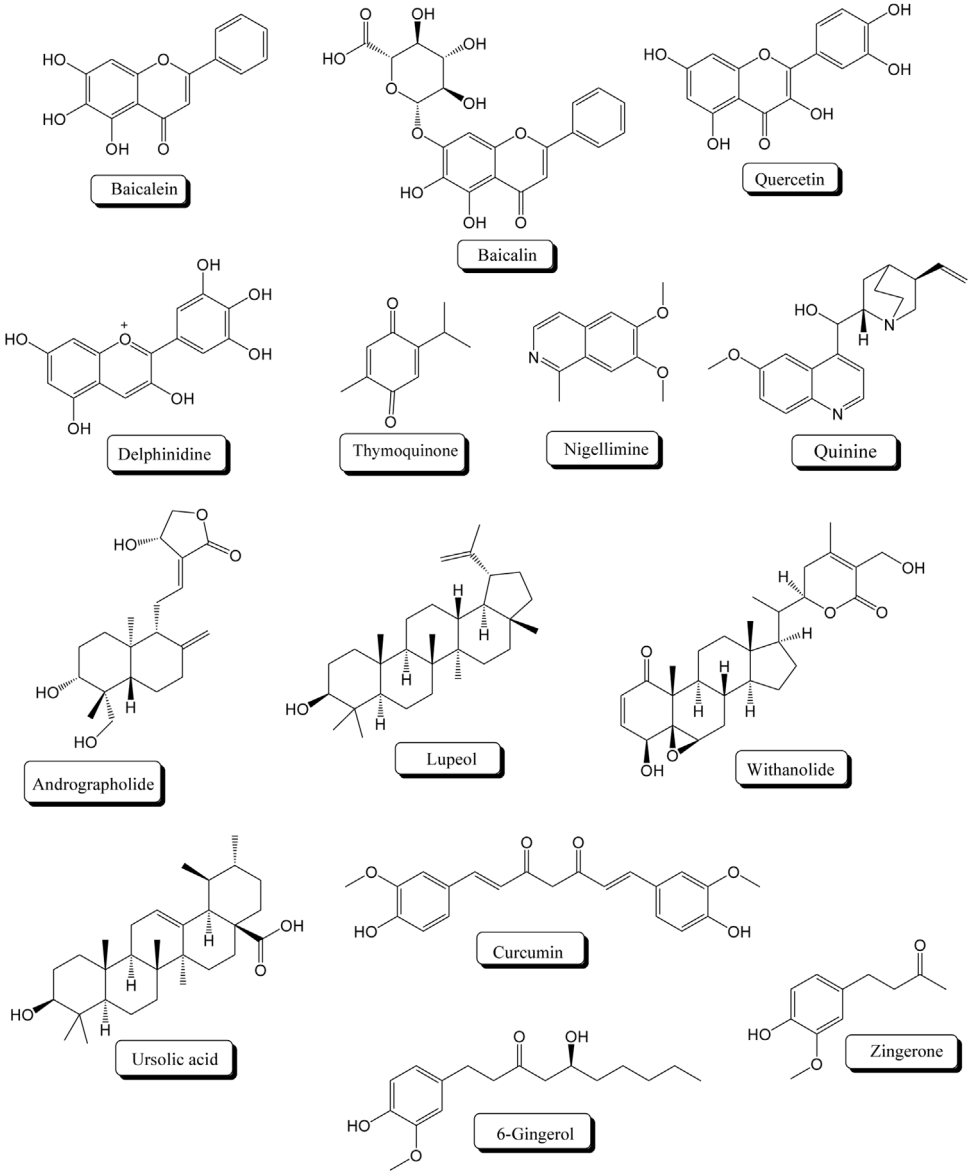

Fig. 4. Chemical structure of some selected natural products known to exhibit potent aniviral activity.

RdRp and also boost the host immunity [86]. Al-Noaemi and Chayad also suggested the use of co-administration of *Nigella sativa* as an adjuvant therapy with HCQ to reduce the toxicity and to potentiate the antiviral actions of HCQ against COVID-19 [87].

Ahmad et al., used molecular docking, molecular dynamics and MM-PSBA computational approaches on *Nigella sativa* compounds to identify the potential antiviral compounds for SARS-COV-2 infectious disease. They found dithymoquinone (−8.6 kcal/mol) to be more effective than CQ 9–7.2 kcal/mol) in disrupting the SARS-CoV-2:ACE2 interface *i.e.* viral-host interaction through formation of various hydrophobic and hydrophilic bonding [88].

A Randomized controlled, Open-label, add on, clinical trial (Phase 3) in Pakistan is currently evaluating the effectiveness of combination of honey (30 mL BID) and *Nigella sativa* seed powder (1 gm BID) in the management of COVID-19. The results of the interventional study are expected to be available by the end of August 2020 [89]. Another clinical trial phase 2 (initiated in May 2020) utilizing Saudi FDA licensed *Nigella sativa* seed oil is studying its role in the treatment of upper respiratory tract infection (URTI) in 200 hospitalized adult COVID-19 patients through a Prospective, Randomized Open-label, controlled clinical study. The results will be available after the completion of study on 31 December 2020 [90].

Aloe vera plant has been considered as a source of highly potential candidate for the SARS-CoV-2 therapy in Democratic Republic of the Congo Several studies have shown it's extract as well as its bioactive constituents anthraquinones to possess excellent broad spectrum virucidal activities [91–93]. *Aloe vera* also contains zinc, which has the ability to inhibit the replication of retroviruses including SARS-CoV-1 [94]. Mpiana et al. are convinced that *Aloe vera* extract rich in zinc and its secondary bioactive metabolites could be used in the management of COVID-19 owing to their ability to attenuate expression of pro-inflammatory factors that induce acute respiratory distress and by strengthening the immune system [95]. Gyebi et al. screened 62 alkaloids and 100 terpenoid bioactive natural products derived from the native African medicinal plants as potential inhibitors of coronavirus 3-chymotrypsin-like protease ($3CL^{pro}$) using *in silico* approach. More than ten alkaloids and terpenoids were found to be superior than lopinavir and ritonavir in terms of binding affinities to the active site of $3CL^{pro}$. They recommended to evaluate the

clinical efficacy of 10-hydroxyusambarensine, cryptoquindoline, 6-oxoisoiguesterin and 22-hydroxyhopan-3-one against SARS-CoV-2 $3CL^{pro}$ through *in vivo* experimental studies [96]. Isothymol, a major volatile constituent (51.2%) of *Ammoides verticillata* plant harvested from Western Algeria was found to be an inhibitor of angiotensin converting enzyme 2 (ACE2) receptor *via in silico* study. Molecular docking study revealed it to form a stable interaction with ACE2 receptor. Based on the results of the study, authors suggested that *Ammoides verticillata* essential oil components could slow down the spread of infection by blocking the entry of the virus in to the cell [97].

Liquorice, ginger, turmeric, green chireta and winter cherry are widely used in Indian system of medicine for upper respiratory infections since ancient time. Glycyrrhizin and glycyrrhetinic acid, the bioactive constituents of licorice (*Glycyrrhiza glabra),* can induce nitrous oxide synthase which in turn blocks viral replication. The licorice root may provide symptomatic relief to COVID-19 patients experiencing breathlessness because of its expectorant and antitussive actions [98]. *Zingiber officinale* and its biologically active metabolites also possess potent antiviral spectrum. Chen et al. showed that curcumin exhibit anti-influenza activity by inhibiting virus replication and its haemagglutinating activity [99]. They reported that curcumin has promising potential as an anti-influenza drug. Curcumin has also been proven to be effective against a non-enveloped virus, human norovirus (HuNoV) [100]. Andrographolide present in *Andrographis paniculata* has anti-inflammatory properties and has also shown broad spectrum antiviral activity against Influenza A virus (H9N2, H5N1 and H1N1), Hepatitis B and C virus, Herpes simplex virus, Epstein–Barr virus, Human papillomavirus, Human immunodeficiency virus, and Chikungunya virus [81]. Bioactive compounds like quercetin, curcumin, andrographolide, glycyrrhizin, withanolide from Indian medicinal plants could be used for designing COVID-19 trials [101].

Various research studies focusing on plant species such as *Coriandrum sativum, Coscinium fenestratum, Cynara scolymus, Punica granatum* and *Cassia occidentalis* have demonstrated them to inhibit the virus entry significantly *via* ACE inhibition A lot of research trials has been conducted regarding ACE inhibition thus locking virus entry [78,102]. Some plants like *Ocimum sanctum* (Holy basil)) *Solanum nigrum (*Black nightshade*) and Vitex negundo* (Chinese chaste tree) possess anti-reverse transcriptase activity of HIV could also be used for the screening and development of COVID-19 drug [103]. Elderberry, Self heal and Peacock flowers are used in Chinese traditional system of medicine for cold, cough and flu symptoms. These plants deserve further exploration and some of these could prove to be a panacea against COVID-19 owing to their antioxidant, immune-stimulant and anti-inflammatory activities in addition to antiviral activity. The outcome of well designed research studies on these holistic medicines will provide the scientific evidence; improve the public awareness and perception towards the indiscriminate use and promotion of fake herbal medicines [104] (Fig. 4).

Conclusion and future direction

A number of repurposed drugs are currently being studied in various phases of clinical trials but till date the mainstay treatment for COVID-19 has been largely supportive. Drugs like CQ, HCQ did not show any benefits in reducing the mortality rate of hospitalized patients in large studies and thus WHO has recommended suspending their further use to treat SARS-Cov-2 infections. Some mega clinical trials are currently underway to identify a safe and effective therapy for combating COVID-19. Complementary efforts need to be put by health authorities, non-governmental organizations, funding bodies all over the world to combat this COVID-19 pandemic. Accelerated methods of drug/vaccine approval taking into account both efficacy and safety needs to be put in place to help in flattening the curve of COVID-19 incidence in the world.

We believe that natural products might play an important role and contribute to antiviral drug development. Exploring antiviral medicinal plants as adjunct or supportive therapy appears to be a viable option to manage this medical crisis. Natural products could be used to treat symptoms such as fever, coughing, as well as for boosting immunity in COVID-19 patients. Detailed studies should be carried on potential natural products alone or in combination with the antiviral therapy to investigate their role in combating COVID-19. Therefore, it is the need of the hour to work in parallel on different strategies such as genetic engineering, *in silico* approach, herbal remedies and repositioning of drugs to achieve the common goal of finding a treatment for COVID-19 at the earliest.

Authors' contributions

SAK and KB carried out literature review and wrote the manuscript.

Funding

No funding sources.

Competing interests

None declared.

Ethical approval

Not required.

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