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Synthetic and Herbal Drugs Registered in Clinical Trials on COVID-19: a Review on Recent Research

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ABSTRACT

COVID-19 emerged as a widespread worldwide ailment in 2019, with a continued breakdown of novel gamma and lambda variants. Given the high incidence of COVID-19 even in the vaccinated people, research is in progress to develop convenient used drugs to control coronavirus disease. Herein, to review the effectiveness and safety of the recent antiviral, antibacterial, and herbal medication utilized to treat COVID-19, electronic databases including Scopus, PubMed, and Cochrane Library were compiled from papers registered in clinical trials on COVID-19 from January 2021 to February 2022. Oseltamivir, remdesivir, ivermectin, casirivimab, imdevimab, sotrovimab, Tocilizumab, sarilumab, dexamethasone, methylprednisolon, paxlovid, fluvoxamine, molnupiravir, ruxolitinib, tofacitinib, baricitinib, favipiravir, molnupiravir, azithromycin, niclosamide, nitazoxanide, and tetracyclines are the most commonly used antiviral and antibiotics to control mild to severe COVID-19 illnesses in the clinic. Despite the efficacy of drugs solely and in combination, medicinal herbs and natural products were considered in some clinical trials due to the high cost and unwanted side effects. However, no substantial evidence has been reported to confirm the significant anti-COVID-19 impact of synthetic and herbal medicines. This scenario opens an exciting new perspective for the elucidation of convenient therapeutic pipelines.

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Introduction

Coronavirus disease 19 (COVID-19) originated in China's Wuhan City on 31 December 2019, quickly widespread with confirmed cases in almost every country in the world, and became a prime worldwide health problem. As of 21 May 2022, globally, over 521 million confirmed cases, including almost 6.2 million deaths attributed to SARS-CoV2 infection, have been confirmed by the World Health Organization (WHO) (Fig. 1) (Hu *et al*., 2021; WHO, 2022), making it one of the fetal pandemics to date. The majority of new confirmed cases were reported from Europe (219,393,358 cumulative cases). COVID-19 mortality is higher among men than women, which may be attributed to females' X chromosome, which expresses immune-associated genes. Several reports have shown that about 78-85% of transmission occurs during social gatherings or between family members (Capuano *et al*., 2020). While some parts of the world are experiencing a drop in COVID-19 cases and deaths, other parts are seeing a spike in cases. COVID-19 infection is divided by disease severity into mild, moderate, and severe illnesses, ranging from no symptoms to life-threatening. Older people or individuals with chronic health conditions will probably get severe COVID-19 disease (Cascella *et al*., 2022).

SARS-CoV-2, as the seventh subfamily of Coronaviridae, is an enveloped, plus single-stranded RNA (+ssRNA) virus. This subfamily can be assorted into four sub-groupings: Alpha, Beta, Delta, Gamma, and Omicron-Coronaviruses, which cause severe, moderate, and mild maladies (Ko *et al*., 2020). SARS-CoV-2 exhibits about 50% and 79.5% shared homological sequences with SARS-CoV-1 and MERS-CoV, respectively (Lu *et al*., 2020).

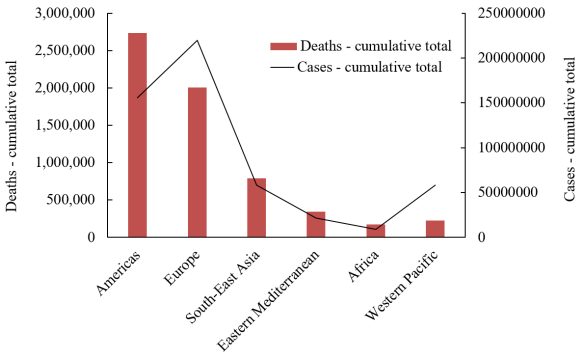

Fig. 1. The cumulative number of COVID-19 cases and mortalities reported worldwide is over 197 million and the number of accumulative deaths is nearly 4.2 million, as of May 21, 2022 (WHO, 2022).

Scientists around the world have developed treatments and vaccines for COVID-19. Worldwide accessibility to COVID-19 vaccines is needed to decrease case numbers and deaths, stop the pandemic, and achieve global population immunity. Limitations in worldwide access to vaccines mean that most of the world's population remains susceptible to this virus (Samimi Nemati *et al.*, 2020). The vaccine effectiveness and duration of protection against new variants of SARS-CoV-2 remain partially understood. In summary, it is still urgent to discover more specific medications for SARS-CoV-2 infection. Until now, according to several lines of verifications, no known herbal or antiviral drugs have been supposed for the treatment of severe COVID-19. In this sense, the appropriate and most straightforward approach to producing pharmaceuticals is to exploit pre-defined and marketed medications whose characteristics, mechanisms, cytotoxicity, dosage, and promised effectiveness have been confirmed. In contrast, these drugs cannot eradicate CoVs (Tarighi *et al*., 2021; Xu *et al*., 2020, Fallah *et al*., 2022).

Herbal remedies have traditionally been used to remedy viruses and infections. Still, one of the biggest problems with using these herbs is that many natural and herbal remedies are of low quality. Some of the approved herbal medicines that, according to the researchers' claim, can alleviate symptoms of COVID-19, only work as immune boosters. They may boost immunity, and the person may not be readily susceptible to infection but everyone still has to take care of themselves (Al-Kuraishy *et al*., 2022).

Among several antiviral prescriptions suggested to treat COVID-19, remdesivir is the first antiviral FDA-approved medication utilized for COVID-19 patients (Yin *et al*., 2020). Glucocorticoids have also shown an improvement in survival for critically ill patients. The advantage of glucocorticoids in severe COVID-19 patients confirms that the different inflammatory response is the leading cause of mortality and severity of COVID-19. More importantly, in line with the recently updated WHO guidelines, interleukin-6 receptor blockers are highly successful in increasing the life span in patients with severe COVID-19, especially when administered in combination with corticosteroids (Angriman *et al*., 2021). In response to infection, interleukin-6 is released and stimulates inflammatory 9. Two monoclonal antibodies, sarilumab, and tocilizumab, have been identified as potential inhibitors of both soluble and membrane-bound interleukin-6 receptors. They are commonly utilized to manage inflammatory diseases, like rheumatoid arthritis and cytokine release syndrome after chimeric antigen receptor (CAR) T-cell therapy (Sujin Kang, 2021).

The network meta-analyses of clinical trials indicated that in critically or severe patients, this drug administration leads to decreased death odds by 13% compared to the standard of care (Hermine *et al*., 2022). It suggests that there will be 15 and 28 fewer deaths, respectively, per thousand patients and every thousand severe COVID-19. Mechanical ventilation odds in severe patients are decreased by 28% compared to the standard of care. This means that 23 fewer patients per thousand require mechanical ventilation (Brown *et al*., 2021). WHO Director (Dr. Tedros Adhanom) explained that these drugs allow people to hope for critical or severe

COVID-19 patients. Currently, IL-6 receptor blockers are unavailable throughout the world; however, it is within the power of governments and manufacturers to change that. This study reviewed treatments registered in clinical trials on COVID-19 from January 2021 to November 2022 to allocate a view of conceivably effective medications.

Synthetic drugs in clinical trials

Antiviral drugs

One of the quick ways to attenuate COVID-19 is drug repositioning, which is a unique approach to investigating the new remedial properties of existing pharmaceuticals. For this purpose, a constructive strategy for Coronavirus (CoV) monitoring is to examine the effectiveness of FDA-approved medications against new viruses (Table 1). Nevertheless, most pharmaceutics to alleviate COVID-19 symptoms were founded on clinical follow-up instead of experimental verification. However, this does not include intense attempts toward vaccine evolution and rational drug design (Mahmoud *et al*., 2020; Pushpakom *et al*., 2019).

Oseltamivir

One of the concerns about developing an antiviral drug compared to an antibiotic agent development is unavoidable toxicity. Viruses are mandatory intracellular organisms that replicate mainly by recruiting a host cell's metabolic machinery present in an uninfected host cell. An antiviral drug that interferes with viral replication is likely to interfere with an essential cell function, resulting in inevitable toxicity. In traditional designing of antiviral drugs, the priority was that the drug is effective on the proteins or genetic material of the virus and has the least interaction with the host system. Oseltamivir is an example of an effective antiviral medication, which inactivates most influenza viruses due to binding to a unique enzyme on a viral protein (neuraminidase) and inhibiting it. Oseltamivir has little inhibitory effect against neuraminidase activity found in uninfected human cells, so toxicity is limited (Laborda *et al*., 2016; Muthuri *et al*., 2014).

Remdesivir

An RNA molecule encodes the genetic information of the coronaviruses. RNA-dependent RNA polymerase is a unique enzyme in some RNA viruses, such as SARS-CoV-2. The viral replication and disease occur by the viral RNA polymerase that constructs multiple copies of the viral RNA, which are necessary for viral particle assembly (Jiang *et al*., 2020). Inhibition of this enzyme causes little toxicity in humans. Remdesivir is an inhibitor that binds viral polymerase and prevents viral replication. This inhibitor has homology to adenosine nucleotide structure and produces truncated RNA transcripts. In multiple clinical trials, remdesivir has been used to manage COVID-19. The FDA authorized remdesivir for in-hospital adult and child COVID-19 patients (Jiang *et al*., 2020). The prescription of remdesivir concomitant corticosteroids has not been thoroughly studied for safety and efficacy in clinical trials; however, the combination treatment seems to be theoretically effective in severe COVID-19 (Lee *et al*., 2021).

Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine earned emergency use authorization (EUA) for oral control of COVID-19 infections in hospitalized juveniles and adults on March 28. Clinical evidence in China, Italy, and France demonstrated a swift decline in COVID-19 viral load in patients who took these medications with azithromycin than in patients who did not take these drugs (Ebina-Shibuya *et al*., 2021). When chloroquine and hydroxychloroquine received EUA for application in COVID-19 patients, it revealed these drugs might provide benefits and that the potential benefit overcomes the potential risks of adverse side effects (Abd-Elsalam *et al*., 2020; Zou *et al*., 2020). The EUA is distinct from FDA approval for an investigational drug. The EUA is approved following an assertion by the Secretary of Health and Human Services related to an emergency condition.

Lopinavir and/or ritonavir

It is necessary for SARS-CoV-2 replication that a polyprotein cleaves into a helicase and an RNA-dependent RNA polymerase (Zumla *et al*., 2016). Papain-like protease (PLpro) and 3-chymotrypsin-like protease (3CLpro) are in

charge of this splitting. Lopinavir and/or ritonavir as well-known protease inhibitors are used for HIV viral disease. Nevertheless, these protease inhibitors are not recommended to treat COVID-19 infections; because results from randomized trials in patients hospitalized with COVID-19 treated with protease inhibitors darunavir/cobicistat and lopinavir/ritonavir have not demonstrated clinical efficacy in patients (Cao *et al*., 2020; Chen *et al*., 2020b; Consortium, 2020; Horby *et al*., 2020).

Ivermectin

Ivermectin is one of the FDA-approved antiparasitic drugs applied for the therapy of several ancient tropical disorders including scabies, onchocerciasis, and helminthiases (Ōmura and Crump, 2014). The weight of evidence supports that ivermectin inhibits importin alpha/beta-1 nuclear transport proteins in the host involved in intracellular uptake of the virus to increase infection by repressing the host's antiviral response (Arevalo *et al*., 2020; Yang *et al*., 2020). Furthermore, ivermectin anchoring seems to suppress the interaction of the SARS-CoV-2 spike protein with the host cellular membrane (Lehrer and Rheinstein, 2020). Ivermectin has been reported as a broad-spectrum antiviral agent against a dozen of viruses that develop dengue, yellow fever, HIV, and Zika (Barrows *et al*., 2016; Tay *et al*., 2013; Wagstaff *et al*., 2012; Yang *et al*., 2020). However, no reports have been published to indicate the clinical utility of ivermectin in patients with these viruses. According to some research, potential anti-inflammatory characteristics of ivermectin have also been illustrated to be effective in people with COVID-19 (Ci *et al*., 2009; DiNicolantonio *et al*., 2020; Zhang *et al*., 2008). WHO Solidarity trial investigators reported that clinical trials of four reused antiviral medications including lopinavir, hydroxychloroquine, remdesivir, and interferon, indicate their inefficiency in hospitalized patients with COVID-19 (Consortium, 2020).

Sotrovimab , imdevimab and casirivimab

Sotrovimab, a recombinant monoclonal antibody, as a sole therapy and/or combination therapy of imdevimab and casirivimab, has been shown to reduce hospitalization and mortality rates in people with COVID-19 symptoms (Gupta *et al.* 2021; Horby *et al.*, 2021). Therefore, these medications have gained Emergency Use Authorizations (EUAs) from the FDA for COVID-19 treatment in these people. Sotrovimab and imdevimab plus casirivimab remain effective against Gamma (P.1) and Beta (B.1.351) variants (Gupta *et al.*, 2021).

Tocilizumab and sarilumab

Recent evidence reveals that immunomodulatory approaches such as inhibition of IL-6 and IL-6Rα signaling with tocilizumab and sarilumab are promising treatments for hospitalized COVID-19 patients (Matthay and Luetkemeyer, 2021). This treatment is based on the supposition that SARS-CoV-2 induces lung lesions through the secretion of proinflammatory cytokines. The preliminary analysis demonstrates that mortality was decreased up to 28 days after hospitalization of COVID-19 patients exposed to sarilumab and tocilizumab (as blockers of IL-6rα) compared to sufferers exposed upon usual care or placebo. More importantly, the coadministration of blockers of IL-6rα with glucocorticoids is associated with significant mortality benefits. IL-6rα blockers are accomplished for hospitalized patients who are severely or acutely sick with COVID-19 but are not yet deserved for pervasive use in patients with mild and/or severe disorders (Gordon *et al*., 2021; Matthay and Luetkemeyer, 2021).

In a retrospective report, Vecchie *et al.* discovered that high-dose dexamethasone improves mortality and worsening respiratory function in hospitalized patients with COVID-19-related acute respiratory distress syndrome (ARDS) (Vecchié *et al*., 2021). A well-known glucocorticoid, methylprednisolone (MP) has been reported as a convenient therapeutic strategy for hospitalized patients with COVID-19 and it is expected to have a better performance than dexamethasone in patients with hypoxic COVID-19 (Jeronimo *et al*., 2021; Ranjbar *et al*., 2021).

Paxlovid

Pfizer Inc.'s Paxlovid is an experimental SARS-CoV-2 protease inhibitor antiviral medication. Pfizer's oral antiviral medication, a combination of Paxlovid (PF-07321332) and ritonavir, was

given alongside molnupiravir, which is another antiviral for COVID-19. According to recent studies, Paxlovid lowered the plausibility of hospitalization or death by 89 percent. Paxlovid is intended to inhibit the action of SARSCOV-2-3Cl protease, which is required for coronavirus replication. In conjunction with a modest dosage of ritonavir, Paxlovid slows the breakdown rate of PF-07321332, allowing it to last longer throughout the body with a higher dose against the virus (Pfizer). Paxlovid does not operate as effectively when taken alone and is more effective for the coronavirus than molnupiravir since it was recognized with a novel and unique coronavirus-specific protease inhibitory activity (Wen *et al*., 2022).

Fluvoxamine

Fluvoxamine is a selective inhibitor of serotonin reuptake (SSRI) with a high tendency to sigma-1 receptor (Calusic *et al*., 2022). The research work led by Reis *et al.* (Reis *et al*., 2022b) assessed 9803 prospective trial participants. In the preliminary analysis, 17 fatalities and 25 deaths were in the fluvoxamine and placebo groups, respectively. There were one and twelve fatalities, respectively, in the fluvoxamine and placebo groups with no remarkable distinction in some adverse events between the fluvoxamine and placebo groups. Fluvoxamine palliates hospitalization in high-risk outpatients with preliminary SARS-CoV2 infection. Fischer *et al.* investigated that molnupiravir is one of the earliest oral antiviral medications with an approved safety that is extremely effective at bringing down the nasopharyngeal infection of SARS-CoV-2 (Mahase, 2021a, 2021c).

Ruxolitinib

Iastrebner and colleagues conducted the study of ruxolitinib which belongs to the Janus kinase inhibitors drugs (JAK Inhibitors) that operate by competitively inhibiting the ATP-binding catalytic site on JAK1 and JAK2. The primary goal was to appraise the safety and effectiveness of ruxolitinib in SARS-CoV2 infection (Iastrebner *et al*., 2021). Ruxolitinib had an immediate anti-inflammatory impact, and while it did not substantially diminish the ratio of pneumonia in patients with ICU and MV, the death rate was reduced (p= 0.24). The side effect profile was moderate, and the study medication produced no direct organ harm. Another study examined if inhibition of cytokine signaling with ruxolitinib mediated by Janus kinase targeting led to improved hyperinflammation in ARDS progressed by SARS-CoV-2 in a non-randomized phase II multicenter research (Iastrebner *et al*., 2021).

Tofacitinib

Guimares et al. (Guimarães *et al*., 2021) Tofacitinib was discovered to be a medication with selective inhibition of Janus kinase (JAK) 1, JAK2, and JAK3 that disrupts related signaling pathways when a cytokine binds to its receptor. As a result, no cellular reaction is elicited, and cytokine production is reduced indirectly. Tofacitinib also affects the activity of IL-6 and interferons, reducing the production of cytokines by TH-1 and TH-17 cells, both of which are entailed in the pathophysiology of the ARDS. Thus, tofacitinib's effect on numerous vital pathways of the inflammatory pathways seems to relieve intensifying, lung damage derived from inflammation in hospitalized COVID-19 sufferers. Tofacitinib had a reduced risk of mortality or respiratory failure than placebo in hospitalized COVID-19 persons with pneumonia. Kalil *et al.* (Kalil *et al*., 2021b) showed that a combination of baricitinib and remdesivir was secure and incomparable to remdesivir alone for the therapy of hospitalized individuals with COVID-19 pneumonia.

Baricitinib

Baricitinib, developed by Marconi et al., is a selective inhibitor of JAK 1/2 with anti-inflammatory effects that is orally administered (Marconi *et al*., 2021a). This trial looks at the effectiveness and safeness of baricitinib in conjunction with the standard of care (systemic corticosteroids and remdesivir) for treating COVID-19 in hospitalized patients. In the meantime, the disease progressed in some of them to a low oxygen concentration, invasive mechanical ventilation, and/or death after about one month. Although there was no substantial decrease in the overall incidence of disease advancement, therapy with baricitinib showed the same tolerability to the standard of care alone

and was linked with lower morbidity in COVID-19 hospitalized people.

Antibiotic

A main discrimination of antibiotics from viral drugs is that antibiotics can target unique metabolic pathways in bacteria that do not interfere with eukaryotic cells.

Penicillin

Some antibiotics, such as penicillin, bind to special enzymes responsible for synthesizing the bacterial cell wall (peptidoglycan); these enzymes are also named penicillin-binding proteins. The tight peptidoglycan protects bacteria against osmotic pressure (Scheffers and Pinho, 2005). Throughout the last stages of bacterial cell wall synthesis, penicillin forbids the proper formation of peptidoglycan cross-links. Loss of peptidoglycan causes lysis of the bacterium and stops its replication. Penicillin is selectively toxic to bacteria because peptidoglycan does not exist in human cells (Liu and Breukink, 2016). Furthermore, antibiotics are only effective against bacterial infections. Moreover, doctors may prescribe antibiotics for infections to fight prospective resultant bacterial infections such as bacterial pneumonia (Cox *et al*., 2020). Concerning the WHO, antibiotics are not efficient in fighting SARS-CoV-2 infection. The inappropriate use of antibiotics for COVID-19 will intensify microbial resistance and cause more deaths throughout the disaster and ahead (Table 1).

Azithromycin

At present, azithromycin is an investigational antibiotic used by researchers as a conventional curative option for COVID-19. Azithromycin can modulate the immune response against COVID-19 by inhibiting the inflammatory system. Research also demonstrated that azithromycin has beneficial effects against Zika and Ebola viruses in vitro. Moreover, Azithromycin has positive effects in preventing vigorous respiratory tract bacterial complications in children infected by viruses (Gyselinck *et al*., 2021; Venditto *et al*., 2021).

Hydroxychloroquine

It has been suggested that examining azithromycin in combination with Hydroxychloroquine may be more effective than single therapy. In a small-scale study, the effects of azithromycin and hydroxychloroquine were investigated in persons hospitalized for COVID-19 in France. The viral load of the coronavirus was dramatically decreased by hydroxychloroquine. The concomitance of azithromycin increased the potency of hydroxychloroquine (Gyselinck *et al*., 2021; Venditto *et al*., 2021).

However, Rosenberg et al. have manifested that the use of Azithromycin with Hydroxychloroquine did not ameliorate results and increased the risk of a heart attack. This trial was accomplished on 1,438 in-hospital COVID-19 patients in New York. All contributors had homogeneous ages, races, and time to start the intervention (Rosenberg *et al*., 2020). Accordingly, the FDA has repealed the emergency use authorization for hydroxychloroquine, so it is no longer used to remedy COVID-19.

Niclosamide and Nitazoxanide

In another study, some FDA-approved antimicrobial drugs, including niclosamide, nitazoxanide, and azithromycin, were found to have a hopeful capacity to prevent SARS-CoV-2 replication. Besides, they present the idea that several anti-inflammatory and antihistamine medications could relatively decrease SARS-CoV-2 replication (Mahmoud *et al*., 2020; Mostafa *et al*., 2020). Moreover, according to a docking analysis, niclosamide, nitazoxanide, and azithromycin can interact with the prime protease of SARS-CoV-2 and the binding peptide moiety of the spike protein active site, verifying that piroxicam and azithromycin co-treatment should be administered for COVID-19 patients (Mostafa *et al*., 2020). New formulations of niclosamide including Niclosamide–Clay Intercalate Coated with Nonionic Polymer and Bovine Serum Albumin-Coated Niclosamide-Zein Nanoparticles were also associated with high efficiency in COVID-19 patients (Rejinold N *et al*., 2021; Yu *et al*., 2021).

Table 1. The FDA-approved medications against new virus

Anti-viral drugs	Mechanism of action	References
Remdesivir	Inhibition of viral RNA-dependent RNA polymerase	Ader *et al.*, 2022; Hamilton *et al.*, 2021
Lopinavir/ritonavir	Protease inhibitors	Cao *et al.*, 2020; Di Castelnuovo *et al.*, 2021; Horby *et al.*, 2020
Darunavir/cobicistat	Protease inhibitors	Chen *et al.*, 2020b; Di Castelnuovo *et al.*, 2021
Ivermectin	Inhibiting the host importin alpha/beta-1 nuclear transport proteins; interferes with the attachment of the SARS-CoV-2 spike protein	Abd-Elsalam *et al.*, 2021; Bryant *et al.*, 2021; Buonfrate *et al.*, 2022; DiNicolantonio *et al.*, 2020; Mohan *et al.*, 2021; Yadav *et al.*, 2021
REGEN-COV (Casirivimab plus imdevimab)	Active against Beta (B.1.351) and Gamma (P.1) variants	Horby *et al.*, 2021; O'Brien *et al.*, 2021; Weinreich *et al.*, 2021
Sotrovimab	Active against Beta (B.1.351) and Gamma (P.1) variants	Gupta *et al.*, 2021a; Gupta *et al.*, 2021b; Nagy-Agren & Vasudeva, 2021
Tocilizumab and sarilumab	Inhibition of interleukin 6 (IL-6) receptor-α subunit (IL-6Rα) signaling and	Parums, 2021; Zeraatkar *et al.*, 2021
Baricitinib plus Remdesivir	Janus kinase (JAK) inhibitor and Inhibition of viral RNA-dependent RNA polymerase	Kalil *et al.*, 2021b
Baricitinib plus standard of care	Janus kinase (JAK) inhibitor and anti-inflammatory	Marconi *et al.*, 2021b
Tofacitinib	Inhibitor of the JAK-STAT pathway to lower the inflammatory response	Guimarães *et al.*, 2021
Ruxolitinib	Janus kinase inhibitors (JAK Inhibitors) and fast anti-inflammatory effect	Iastrebner *et al.*, 2021
Dexamethasone	A synthetic glucocorticoid with anti-inflammatory and immunosuppressant properties	Group, 2021; Vecchié *et al.*, 2021
Methylprednisolone	anti-inflammatory steroid	Jeronimo *et al.*, 2021; Ranjbar *et al.*, 2021
Interferon beta-1a plus remdesivir	Boosting expression and concentration of anti-inflammatory agents and decreasing the expression of pro-inflammatory cytokines and Inhibition of viral RNA-dependent RNA polymerase	Kalil *et al.*, 2021a
Favipiravir	The antiviral drug competitively inhibits RNA-dependent RNA polymerase (RdRp).	Chen *et al.*, 2020a
Molnupiravir	antiviral medicine that inhibitor of the replication of certain RNA viruses	Fischer *et al.*, 2021; Mahase, 2021a, 2021c
Paxlovid (combination of PF-07321332 and ritonavir, alongside 480 000 courses of another antiviral for COVID-19, molnupiravir)	Antiviral medicine and orally active 3C-like protease inhibitor	Mahase, 2021b
Fluvoxamine	Selective serotonin reuptake inhibitor (SSRI)	Calusic *et al.*, 2022; Lenze *et al.*, 2020; Reis *et al.*, 2022; Seftel & Boulware, 2021
Azithromycin	It prevents the replication of a COVID-19 isolate; and attaches to the main protease of COVID-19 (Protein data bank (PDB) ID: 6lu7)	Echeverría-Esnal *et al.*, 2021; Gautret *et al.*, 2021; Rosenberg *et al.*, 2020
Niclosamide; Niclosamide–clay intercalate coated with nonionic polymer; Bovine serum albumin-coated niclosamide-zein nanoparticles	It prevents the replication of a COVID-19 isolate; and attaches to the main protease of COVID-19 (Protein data bank (PDB) ID: 6lu7); hydrogen bond (HB) interaction with the key peptide moiety GLN: 493A of the spike glycoprotein active site	Pindiprolu & Pindiprolu, 2020; Rejinold N *et al.*, 2021; Romani *et al.*, 2020; Yu *et al.*, 2021
Nitazoxanide	It prevents the replication of a COVID-19 isolate; and attaches to the main protease of COVID-19 (Protein data bank (PDB) ID: 6lu7)	Mendieta Zerón *et al.*, 2021; Rocco *et al.*, 2021
Tetracyclines	Inhibitory effects on matrix metalloproteinases (MMPs); decrease the levels of inflammatory cytokines	Gironi *et al.*, 2021; Mosquera-Sulbaran & Hernández-Fonseca, 2021; Sodhi & Etminan, 2020
Lianhua Qingwen exert	Block binding of the virus with the receptor, inhibit cytokines storm, and improve clinical applications	Khan *et al.*, 2020; Liu *et al.*, 2020; Runfeng *et al.*, 2020; Shen *et al.*, 2021
Jinhua Qinggan granule	Regulation of genes co-expressed with ACE2 and immune-related signaling pathways	Liu *et al.*, 2020; Zhang *et al.*, 2021
Qingfei Touxie Fuzheng Recipe	Antiviral activity	Ding *et al.*, 2020; Jin *et al.*, 2020
Withania somnifera (isolated bioactive including withanone, withanoside V, withanolide A and D, withaferin A)	Blocking Mpro protease; modulation of cytokine storm and interaction with S protein	Dhawan *et al.*, 2021
Myrrha gummi-resina, *Hederae helicis folium*, *Liquiritiae radix*, *Sambuci fructus*	Modulation of inflammatory response	Silveira *et al.*, 2020
Rheu officinale Baill and Polygonum multiflorum Tunb (emodin)	Modulating the angiotensin-converting enzyme 2 (ACE2) expression	Ho *et al.*, 2007
Polysaccharide and arabinogalactan fractions from medical fungi and plants	Management of immune systems	Sen *et al.*, 2021
Kabasura Kudineer (KSK)	Reducing viral load and preventing the disease progression	Natarajan *et al.*, 2021
Nigella sativa oil (NSO)	Antiviral and immunomodulatory activities	Koshak *et al.*, 2021
Zufa syrup (a combination of herbal medicines: *Nepetabracteata*, *Ziziphus jujube*, *Glycyrrhiza glabra*, *Ficus carica*, *Cordia myxa*, *Papaver somniferum*, Fennel, *Adiantumcapillus-veneris*, Viola, Viper's-buglosses, Lavender, Iris, and sugar)	Treatment of respiratory infections	Borujerdi *et al.*, 2022

Tetracycline

Tetracycline derivatives such as doxycycline are zinc-chelating agents with inhibitory effects on matrix metalloproteinases (MMPs). Coronavirus infection processes, including replication, correlate with the host MMPs complex (Humar *et al*., 2004; Zakeri and Wright, 2008). Accordingly, this property of tetracyclines may help prevent SARS-CoV-2 infections in humans by restraining its replication within the host. Tetracyclines might also decrease inflammatory cytokines derived by SARS-CoV-2 via downregulation of the NF-κB pathway. Furthermore, tetracyclines have been considered potential inhibitors of the main protease of SARS-CoV-2 (Wang, 2020). In this context, several researchers have recommended using tetracyclines as possible curative agents for COVID-19 therapy (Sargiacomo *et al*., 2020; Sodhi and Etminan, 2020; Wang, 2020).

Non-steroidal anti-inflammatory drugs (NSAIDs) are frequently used for symptom relief in COVID-19. Nevertheless, there are concerns that steroidal anti-inflammatory (SAID) and non-SAID (NSAID) drugs are associated with the potential for increased harmful effects when prescribed in patients with COVID-19 (Little, 2020; Russell *et al*., 2020). However, there have been no reports of severe damaging events in COVID-19 patients (Giollo *et al*., 2020).

Currently, no drugs are approved by the FDA for the selective remedial way of COVID-19. Therefore, researchers are trying to find convenient pre-existing drugs and antivirals for effective therapy during the COVID-19 pandemic to get around this problem.

Herbal drugs in clinical trials on Covid-19

Owing to the severe pandemic outbreak of COVID-19 worldwide and the lack of a suitable therapeutic strategy targeting SARS-Cov2, several drugs were proposed to combat the severity of the disease (Table 1). In this line, several antivirals, anti-inflammatory, inhibitors, corticosteroids, and antibiotics, including remdesivir, lopinavir, favipiravir, hydroxychloroquine, nitric oxide, IL-6 antagonists, azithromycin as well as supplements such as ascorbic acids, zinc, and vitamin D, were prescribed in clinics (Wu *et al*., 2020). However, reported clinical trials have not underpinned the eventual effects of mentioned drugs in the repertoire of SARS-CoV2 infections and symptoms (Martinez, 2020).

Although the first evidence of COVID-19 was reported from China, success in the control of the disease was achieved by the middle of March 2020. In addition to the movement restrictions and social distancing, the weight of evidence supports that with standard therapies against COVID-19, multiple Chinese herbal medicines were developed and nominated by the National Health Commission (NHC, 2020). As indicated in Chinese cohort studies, patients treated with herbal and medicine standard care had a much better remission than patients exposed to solely standard care (Fang *et al*., 2020; Shi *et al*., 2020; Tian *et al*., 2020; Zhang *et al*., 2020). Purportedly, Chinese medical herbs were used as decoction and extract capsules. Most of them fall in Lianhua Qingwen exert and capsules, Jinhua Qinggan granule, and Qingfei Touxie Fuzheng Recipe (Kageyama *et al*., 2020; Li *et al*., 2020; Liu *et al*., 2020; Runfeng *et al*., 2020; Xiaojuan DING, 2020). Despite the verified efficacy and safety of Chinese herbal drugs, limited side effects such as liver dysfunction and diarrhea were reported in patients treated with Chinese medical herbs (Javorac *et al*., 2020). In one study from Wuhan, among 293 COVID-19 inpatients, the patients treated with traditional Chinese medical herbs showed efficiency relative to only approved medical care (Wang *et al*., 2021).

Silveira et al. reported several used medicinal herbs and their main ingredients for alleviation of Flu in clinical trials, including Commiphora molmol/gum (Myrrha gummi-resina), Hedera helix/leaves (Hederae helicis folium), Glycyrrhiza glabra/roots (Liquiritiae radix), and Sambucus nigra/fruits (Sambuci fructus), possess high overall benefit and safety (Silveira *et al*., 2020). Consistent with herbs' vital role in improving COVID-19 as adjutant and single therapy, their safety and efficacy were studied in clinical trials. For instance, one of the potential herbal drugs, Lianhuaqingwen, was reportedly assessed in case-control studies, case series, and RCTs (randomized clinical trials). According to Liu *et al*., 924 patients with COVID-19 were exposed to Lianhuaqingwen, and the effective

rate of adjuvant therapy (RR=1.16, 95%; p=0.01) was higher than patients treated with conventional administration and single Lianhua Qingwen therapy (Liu *et al*., 2020). In a pilot, RCT with 42 patients, the efficacy of combined treatment of Xuan fei Baidu decoction with traditional medicine was confirmed in inpatients compared to patients with convenient therapy ($p<0.05$). They concluded that Xuan fei Baidu decoction through modulation of inflammatory response improves patients' immunity to COVID-19 (Xiong *et al*., 2020). *Withania somnifera* as a standard component of the Indian Ayurveda system was implied to be the most functional versus the pathogenesis of SARS-CoV-2. In addition, several steroidal lactones isolated from *W. somnifera*, including withananone and withanoside V through blocking Mpro protease, withanolide A and D via modulation of cytokine storm, and withaferin A by interaction with S protein, can treat COVID-19 (Dhawan *et al*., 2021).

In the case of COVID-19, some phytochemicals such as emodin from Rheu officinale Baill and Polygonum multiflorum Tunb have been indicated to modulate the expression of angiotensin-converting enzyme 2 (ACE2), implying their proposed capacity in the curation of SARS-COV2 (Ho *et al*., 2007). Other natural products such as polysaccharide and arabinogalactan fractions from medical fungi and plants can be considered other potential agents against COVID-19 patients due to their involvement in managing immune systems. Furthermore, it seems that some anti-thromboembolic medical herbs, including A. satium L. and M. glomerata spreng, are effectively used drugs to improve the well-being of COVID-19 in patients (Silveira *et al*., 2020). It is well-documented that the interaction between medical herbs and synthetic drugs can accelerate the recovery process of patients with COVID-19 (Farooq *et al*., 2021). In line with the potential evidence from the known efficacy of 17 of 39 likely proposed medical herbs, it is suggested to use them as adjuvant therapy in COVID-19 clinical trials. It seems that they possess the potential curative impact of the SARS-Cov2 pandemic. However, other proposed herbs have not been reported evidence of their convincing in the remedy of COVID-19 and are considered herbs with unknown effects (Silveira *et al*., 2020).

Natarajan et al. investigated the potency of Kabasura Kudineer (KSK) in lowering viral loads and halting disease in asymptomatic COVID-19 patients. KSK, a polyherbal compound, has historically been used to treat clinical manifestations comparable to COVID-19. KSK effectively decreased the SARS-CoV-2 viral load in asymptomatic COVID-19 cases and had no side effects, indicating that KSK should be used in the COVID-19 strategy (Natarajan *et al*., 2020).

Koshak and colleagues conducted a clinical trial to explore the anti-COVID-19 efficacy of Nigella sativa oil (NSO). NSO is a natural immunomodulatory and antiviral herb recommended for the treatment of COVID-19. For individuals with mild COVID-19 infection, NSO additives led to a faster betterment of symptoms than conventional therapy alone (Koshak *et al*., 2021).

Between March and April 2020, another study examined the efficacy of Zufa syrup (a combination of herbal medicines, including Papaver somniferum, Ziziphus jujube, Glycyrrhizaglabra, Adiantumcapillus-veneris, Ficuscarica, Fennel, Nepetabracteata, Viola, Viper's-buglosses, Cordia myxa, Lavender, and Iris) in the medication of suspected COVID-19. This trial enrolled patients with signs of COVID-19 on chest computed tomography who did not require hospitalization. Anxiety, dyspnea, headache, insomnia, anorexia, Cough, and myalgia steadily improved in both groups over time, with no difference between the two groups. Throughout the follow-up period, oxygen saturation and pulse rate remained steady and were comparable between study arms. Compared to the placebo, Zufa syrup did not affect symptomatology in patients with COVID-19 symptoms throughout 10 days (Borujerdi *et al*., 2022).

Conclusions

A world pandemic of SARS-CoV2 infection has been quickly spreading, especially by developing new high pathogenic variants. As a vehicle for managing COVID-19, several effective and safe vaccines were approved to provide a high degree of protection against getting severe illness and

dying. However, by developing new variants of SARS-CoV-2 with faster spreading and more infection than earlier ones, even vaccinated people are also in danger. In addition, there are still many people who have not been vaccinated till now. Accordingly, novel therapeutic pipelines should be developed to ameliorate COVID-19 mortality. In this line, several antiviral, antibiotics, and herbal drugs were examined for COVID-19 ailment. Amid the course of clinical trials, antivirals such as remdesivir and Favipiravir as RNA polymerase inhibitors, lopinavir/ritonavir, darunavir/cobicistat, and Paxlovid as viral protease inhibitors, molnupiravir as an inhibitor of the replication of certain RNA viruses and ivermectin by inhibition of importin α/β1 nuclear transport protein are used in COVID-19 trials. Various small molecules such as baricitinib, tofacitinib, and ruxolitinib have been used as Janus kinase (JAK) inhibitors and fluvoxamine selective serotonin reuptake inhibitor (SSRI) in COVID-19 clinical trials (Limen *et al*., 2022). Antiviral monoclonal antibodies such as casirivimab, imdevimab, and sotrovimab are active against beta and gamma variants. Tocilizumab and sarilumab via inhibition of IL6Rαs signaling were also prescribed for COVID-19 patients with invasive ventilation. Among antibiotics, azithromycin, niclosamide, and nitazoxanide through blockade of SARS-CoV-2 replication and blockade of proteases, tetracyclines by inhibition of host MMPs and downregulation of inflammatory cytokines are effective in the prevention of coronavirus infection. However, no drugs received approval from the FDA for the selective remedy for COVID-19, and more evidence is needed to check out the clinical and cost-usefulness of drugs. Prescription of COVID-19 patients with Chinese medicinal herbs combined with standard care has revealed much better improvement than standard care therapy. Lianhua Qingwen exerts and capsules, Jinhua Qinggan granule, Qingfei Touxie Fuzheng Recipe, from Rheu officinale Baill, Polygonum multiflorum Tunb, Withania somnifera ingredients, A. satium L., and M. glomerata spreng were the practical herbal therapeutics in clinical trials. It is suggested that medicinal herbs as adjuvant therapy are helpful in the treatment of COVID-19. Despite abundant endeavors during recent months in the case of COVID-19 treatment, high-throughput screening is required to combat this global pandemic.

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Conflict of Interest

The authors declare no conflicts of interest.

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