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Therapeutic Drug Targets for Covid-19

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Review Article

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Abstract

COVID-19 pandemic is a respiratory disease that has spread in many countries worldwide and has become a significant health problem. Caused by the virus called SARS-CoV-2, this disease typically manifests with symptoms such as fever, cough, shortness of breath, fatigue, and muscle aches. Various approaches are used in the treatment of COVID-19, including antiviral drugs, respiratory support, anti-inflammatory drugs, and antibody therapies. Antiviral drugs like remdesivir, in particular, are used to alleviate the course of the disease and expedite the recovery process. Vaccination programs are also becoming widespread globally, playing a crucial role in controlling the spread of the disease. The treatment of COVID-19 requires a global effort, and health authorities and scientists are continuously working on new treatment options and measures. This review study focuses on potential drug targets in the treatment process of COVID-19. It discusses the effects of some researched drugs as well as certain components derived from natural sources such as plants, microorganisms, and algae with pharmaceutical potential. However, further research and development of effective treatment methods are still needed for the treatment of COVID-19.

Keywords: COVID-19; Drug Targets; SARS-CoV-2; Therapeutic Strategies

Introduction

COVID-19 is known as a highly pathogenic coronavirus belonging to the Coronaviridae family, which was initially detected in December 2019 in the city of Wuhan, China [1]. Coronaviridae family are single-stranded enveloped positive RNA viruses. Among them, the CoV group is divided into two categories: Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2), known as COVID-19, and Middle East Respiratory Syndrome coronavirus (MERS-CoV). These viruses are lethal and can cause respiratory, liver, gastrointestinal, and central nervous system damages in humans and animals [2]. Human coronaviruses (HCoVs) are positive-sense RNA viruses with a genome size of approximately 30 kb. HCoVs are characterized by two types of proteins: structural proteins spike (S), nucleocapsid (N), membrane (M), and envelope (E)) and non-structural proteins, including the RNA-dependent RNA polymerase (RdRp) (nsp12). The viral genome contains four open reading frames (ORFs) at the thirty end, encoding a series of structural proteins including the nucleocapsid (N) protein, spike (S) protein, membrane (M) protein, and envelope (E) protein.

The S protein is a trimeric glycoprotein located on the surface of coronaviruses and plays a crucial role in binding to the host cell by interacting with angiotensin-converting enzyme 2 (ACE2) and facilitating virus-cell membrane fusion during viral infection. Therefore, the S protein is considered an important target for developing vaccines and therapeutics against SARS-CoV-2. Membrane fusion is the initial step for entering host cells and establishing infection for all enveloped

viruses. In the case of coronaviruses, the fusion protein is the S protein, which decorates the virion surface with a crown-like appearance (hence the name "corona"). This protein also induces neutralizing antibody responses, making it a critical target for vaccine development. The S protein is a type I transmembrane protein that is glycosylated and anchored to the viral membrane. It is initially synthesized as a precursor protein. After trimerization, it is believed to be cleaved by a furin-like protease into two subunits: the receptor-binding domain (S1) and the fusion subunit (S2). This cleavage allows the S protein to mediate viral entry into host cells. Both SARS-CoV and SARS-CoV-2 bind to the host cell receptor ACE2 through the receptor-binding domain (RBD) in the S1 region. The nucleocapsid protein is a critical component that protects the viral RNA genome and packages it into a ribonucleoprotein complex. Additionally, it regulates viral RNA replication and transcription, protein translation through the EF1α region, inhibits host cell cycle and apoptosis. The M protein plays a significant role in maintaining the integrity of the viral envelope. It accomplishes this task through interactions with other CoV proteins, incorporating the Golgi complex into newly formed virions, and stabilizing the nucleocapsid protein. The M protein also plays a crucial role in viral intracellular homeostasis through multiple protein-protein interactions. The envelope (E) protein has been shown to participate in the activation of the host inflammasome. After a coronavirus enters host cells, the E protein regulates viral lysis and subsequent viral genome release [2].

SARS-CoV-2, responsible for COVID-19, is more pathogenic than SARS-CoV and MERS-CoV, and it can cause a fatal disease through human-to-human transmission. It can lead to severe respiratory problems with various symptoms such as fever, dry cough, vomiting, fatigue, diarrhea, and shortness of breath. The SARS-CoV-2 virus typically begins to replicate by binding to the epithelial cells in the nasal cavity through the respiratory route. Subsequently, the virus migrates downwards in the respiratory tract, triggering the natural immune response. Recent studies have shown that the initial viral contact occurs through the binding of the viral spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptor on the nasal mucosa of the host organism, followed by cleavage of the S protein by the transmembrane serine protease 2 (TMPRSS2) (Figure 1) [1,2].

With the COVID-19 pandemic, scientists have been striving to find urgent treatments for the disease. However, as new variants of the virus rapidly emerge, the need for drugs and vaccines has increased even further. To expedite the identification of drugs that could be effective in preventing COVID-19, researchers have resorted to identifying existing molecules or molecules within approved drugs, driven by the increasing demand for treatment options [2]. The process of discovering and obtaining approval for a new drug is time-consuming. Therefore, in the context of the coronavirus pandemic, efforts have been made to repurpose existing antiviral drugs. Currently, several groups of drugs are being investigated for their effects on COVID-19, including hydroxychloroquine, remdesivir, chloroquine, lopinavir, and ritonavir. These drug groups have been previously used in the treatment of SARS-CoV, MERS-CoV, and other viruses. Redesigning these drugs has been considered an appropriate strategy to identify potential inhibitors that can act within a limited timeframe during the COVID-19 pandemic. During the process of drug repurposing, virtual screening, pharmacophore modeling, various computational methods, and experimental techniques are commonly employed [4].

Antiviral drugs targeting SARS-CoV-2 can be classified into two main categories: those that target virus-host interactions and prevent virus-host fusion. In general, three approaches can be used to investigate antiviral compounds that can inhibit COVID-19 infection. The first approach involves examining existing antiviral compounds and molecules to assess their effects on viral replication and packaging. Molecules such as interferon alpha, beta, and gamma, ribavirin, and chemical inhibitors of cyclophilin A, which are actively used in clinical settings and have well-studied pharmacokinetic and pharmacodynamic properties, can be evaluated for their antiviral activities. However, it should be considered that these drugs may lack specificity against SARS-CoV-2 and therefore could have serious side effects. The second approach involves screening drug-like chemical compounds in databases for molecules with antiviral effects. Screening libraries of existing drugs can also lead to the identification of new functions for many known drug molecules. The third approach may involve the development of specific new agents based on a strong understanding of the genomic and biophysical aspects of the SARS-CoV-2 life cycle derived from fundamental research. siRNA molecules or inhibitors that can inhibit specific viral enzymes involved in the viral replication cycle, or monoclonal antibodies targeting ACE-2 in the host, could serve this purpose [5].

Among the latest pharmacotherapeutic agents used in the treatment of COVID-19 patients are antiviral drugs, certain antibiotics, systemic corticosteroids and anti-inflammatory drugs, neuraminidase inhibitors, and RNA synthesis inhibitors [6]. Below are some of the drugs used for COVID-19 treatment.

Chloroquine (CQ) and Hydroxychloroquine (HCQ)

Chloroquine (CQ) and hydroxychloroquine (HCQ) are substances with a 4-aminoquinoline structure that have been suggested as potential treatments for COVID-19. CQ

and HCQ are drugs with similar chemical structures that are commonly used in the treatment of lupus erythematosus, rheumatoid arthritis, and malaria. The antiviral activities of these drugs have been studied for many years. Both CQ and HCQ are weak bases known to increase the pH of acidic intracellular organelles such as endosomes/lysosomes, which are necessary for membrane fusion. Additionally, it is known that CQ can inhibit the entry of SARS-CoV by altering or preventing the glycosylation of the ACE2 receptor and spike protein [7,8].

CQ primarily inhibits the entry, transportation, and post-entry stages of SARS-CoV-2. It also increases endosomal pH and interferes with the glycosylation of the cellular receptor for SARS-CoV, thereby having the potential to block viral infection. Additionally, CQ inhibits cathepsins, which are involved in autophagosome formation that breaks down the SARS-CoV-2 S protein. CQ inhibits the activity of SARS-CoV-2 in molecular pathways through the inhibition of MAP kinase. It is also known to interfere with the proteolytic processing of the M protein, demonstrating its effects. HCQ, on the other hand, has the same mechanism of action as CQ, except for an additional hydroxyl group at one terminal [9].

Remdesivir

Remdesivir, originally developed for the treatment of Ebola virus infection in 2017, has been identified as an effective antiviral drug for COVID-19 treatment. The antiviral mechanism of remdesivir is attributed to the inhibition of the chain termination of newly synthesized viral RNA. *In vitro* studies have also shown that remdesivir can inhibit coronaviruses [10].

The potential mechanism of action of remdesivir on SARS-CoV-2 is explained as shown in Figure 2. Firstly, the virus binds to the ACE-2 receptor to enter the target cell and releases viral RNA. SARS-CoV-2 utilizes the host cell to convert RNA into RNA-dependent RNA polymerase (RdRp). Subsequently, RdRp facilitates viral replication. When remdesivir enters the host cell, it is converted into remdesivir triphosphate. In this state, it competes with the endogenous ATP, which serves as a source of nucleotide, to be incorporated into RdRp, leading to chain termination. In a study conducted by Beigel et al., hospitalized individuals with lower respiratory tract infection due to COVID-19 were enrolled in a double-blind, randomized, placebo-controlled trial of intravenous remdesivir [11]. The patients were randomly assigned to receive remdesivir (200 mg on day 1, followed by 100 mg daily for a total of 10 days) or placebo. The data obtained showed that remdesivir was superior to placebo in shortening the time to recovery in individuals hospitalized with COVID-19 and evidence of lower respiratory tract infection.

One of the drugs recommended by the WHO for the treatment of COVID-19 is nirmatrelvir-ritonavir. Nirmatrelvir, an orally administered drug, functions as an inhibitor of the SARS-CoV-2 3-chymotrypsin-like cysteine protease enzyme and has received emergency use authorization in numerous nations. However, availability of nirmatrelvir is more limited. As previously mentioned, remdesivir is also a recommended drug for COVID treatment. However, it needs to be administered intravenously, which which has hindered its extensive utilization throughout the pandemic. Due to this reason, some analogs of remdesivir have been developed, and VV116 is one of these analogs. In a study performed by Cao et al., VV116 or nirmatrelvir–ritonavir was administered to adult COVID-19 patients at high risk of progression [13]. The administration of oral VV116 was found to be not less effective than nirmatrelvir-ritonavir in shortening the time to clinical recovery. This result has also demonstrated that VV116 could be a potentially effective option for the treatment of COVID-19.

Favipiravir

Favipiravir is an antiviral drug developed in 2014 for the treatment of novel influenza strains resistant to neuraminidase inhibitors or avian influenza. It has been used to treat infectious diseases caused by RNA viruses such as Ebola, norovirus, neurovirus, and influenza. In addition to in vitro studies, human trials have shown that Favipiravir has a strong antiviral effect in the treatment of COVID-19. Favipiravir is a purine-based analog that undergoes intracellular phosphoribosylation to form active favipiravir ribofuranosyl-5'-triphosphate (favipiravir-RTP). It acts as a selective and potent inhibitor of RNA-dependent RNA polymerase (RdRp) of RNA viruses [14]. Sada et al conducted a study in which the active form of favipiravir, F-RTP, was found to directly bind to the SARS-CoV-2 RdRp protein with a binding energy of -6.6 kcal/mol. Asp760 has been identified as a critical amino acid residue that facilitates this interaction [15]. F-RTP was also found to bind to Ser679 in the active site of the SARS-CoV RdRp protein with an energy of -6.4 kcal/mol.

Ribavirin and Corticosteroids

The combination of ribavirin and corticosteroids as a drug mixture was initially used during the SARS outbreak in 2003. However, subsequent reports have shown that ribavirin has high toxicity and lacks the ability to control the spread of the infection [5].

Lopinavir and Ritonavir (LPV/RTV)

LPV/RTV are a drug combination used for the treatment of HIV-1 infection. Lopinavir inhibits the CYP3A isoenzyme,

resulting in increased plasma levels of lopinavir. Therefore, lopinavir is always used in combination with ritonavir. It has been reported that lopinavir inhibits the main protease of SARSCoV-2, thereby halting viral replication. Due to this, it has been investigated for the treatment of COVID-19 [6,16]. The combination of the viral protease inhibitors ritonavir 400 mg and lopinavir 100 mg has shown promising results in clinical trials conducted during the SARS pandemic when administered orally at 12-hour intervals for 10 to 14 days as standard treatment. Clinical trials of the same drug combination have also been conducted for COVID-19 [5]. However, in a study conducted in China with patients diagnosed with COVID-19, the administration of ritonavir (100 mg) and lopinavir (400 mg) did not show any positive effects. Both of these drugs are claimed to inhibit the SARS-CoV 3C-like protease, a key enzyme involved in coronavirus polyprotein processing [17].

In a study by Choy et al., it was suggested that lopinavir could have a therapeutic effect against SARS-CoV-2 at a concentration of 26.63 μM in Vero E6 cells [18]. However, ritonavir alone did not show any effect against SARS-CoV-2. Therefore, it was proposed that the combination of these drugs could enhance their effectiveness against SARS-CoV-2 when used at lower concentrations. The same study found that ribavirin or favipiravir did not show any inhibitory effect at a concentration of 100 μM. Another study by Kang et al. demonstrated a significant antiviral effect of the lopinavir-ritonavir combination against SARS-CoV-2 [19].

In another study it was observed that a combination of three different drugs against the SARS-CoV-2 protease more effective results [20]. According to this study, lopinavir, oseltamivir, and ritonavir drugs individually exhibited binding energies of -4.1 kcal/mol, -4.65 kcal/mol, and -5.11 kcal/mol, respectively. However, when the three drugs were treated together, the binding energy was determined to be -8.32 kcal/mol.

In addition to these studies in a study carried out by Bramante et al. the effect of metformin, ivermectin, or fluvoxamine on the risk of long COVID in outpatient treatment immediately after SARS-CoV-2 infection was evaluated [21]. At the end of the study, it was observed that ivermectin and fluvoxamine did not have a significant effect on the incidence of long COVID, while in patients treated with metformin, the incidence of long COVID was reduced by approximately 41% compared to the placebo.

Besides the mentioned antiviral drugs, some antibody-based treatments have also been shown to be effective in COVID-19 treatment. It is emphasized that the main target group for these treatments is individuals with compromised immune systems. One example of such treatment is bamlanivimab (LY-CoV555), an anti-SARS-CoV-2 monoclonal antibody. In a study conducted by Westendorf et al., bamlanivimab was found to effectively neutralize SARS-CoV-2 and variants including B.1.351, B.1.1.7 and B.1.617.2 [22]. These results suggest that bamlanivimab has the potential to be an effective therapeutic agent to treat all known variants. Experimental and *in silico* analyses of approved drugs have been conducted targeting viral proteins. Additionally, studies investigating the potential use of naturally derived metabolites as new drugs for the treatment of COVID-19 have also been conducted.

The Plant, Animal and Microorganisms Metabolites against COVID-19

Plant metabolites, both primary and secondary, are considered potential drugs for inhibiting different types of coronaviruses. Studies have shown that plant metabolites often have fewer side effects compared to traditional antiviral drugs and are readily available from inexpensive sources. These metabolites exert their effects by disrupting enzymatic activities in viruses. They participate in the replication cycle of coronaviruses, including proteins such as papain-like protease and 3CL protease, thereby preventing the binding of the S protein and ACE2 receptors. Additionally, it has been suggested that metabolites can also inhibit intracellular transduction pathways [23].

Research conducted on cell cultures and animal models has identified several potential antiviral drug candidates that can prevent virus entry into the host or reduce viral replication. Among these antiviral candidates, various medicinal plants containing glycosides, saponins, flavonoids, proanthocyanidins, terpenoids, phenylpropanoids, tannins, resins, lignans, sulfites, polyphenolics, coumarins, furan compounds, alkaloids, and essential oils have been suggested to have potential effects against COVID-19. Some of these components have demonstrated strong antiviral activity against different viruses, while others have shown potential as phytoantiviral agents for various diseases caused by coronaviruses.

In a research investigation conducted by Lestari and colleagues in 2020, they found that chloroquine, hydroxychloroquine, and quinine have the ability to engage with the amino acid residues located in the peptidase domain of the ACE2 receptor [24]. Among these substances, quinine exhibited the most robust binding energy to the ACE2 receptor, registering at -4.89 kcal/mol. Hydroxychloroquine and chloroquine, on the other hand, displayed binding energies of -3.87 kcal/mol and -3.17 kcal/mol, respectively, when interacting with the ACE2 receptor. To reduce the side effects of chloroquine and hydroxychloroquine, the metabolite of artemisinin produced by the Artemisia annua

plant is used as an adjunct treatment. *A. annua* is a plant with antiviral activity against humans. During COVID-19 infection, a chymotrypsin-like protease (CLPro) enzyme is produced. It has been suggested that the pharmacological mechanism of Artemisia annua inhibits the activity of this enzyme. The effects or interactions of artemisinins on the ACE2 receptor of SARS-CoV-2 are not yet known. A. annua can reduce the expression of ACE2 and TMPRSS2 proteins, which can slow down the entry of viruses into human host cells [25]. Additionally, *A. annua* may slow down the transmission of infection in the human body, thereby reducing the adverse effects of COVID-19 symptoms. Due to these advantages, artemisinin has been considered a potential drug candidate and treatment for the COVID-19 pandemic [26]. Another study conducted by Choy et al investigated the antiviral effect of the alkaloid Homoharringtonine obtained from *Cephalotoxus fortunei* plant [18]. The study found an IC_{50} value of 2.10 μM, indicating inhibition of SARS-CoV-2. It was noted that the antitumor activity of Homoharringtonine alkaloid is exhibited by binding to the ribosomal A site to inhibit protein translation.

A study performed by Hassan et al utilized certain natural plant metabolites to inhibit SARS-CoV-2 Omicron BA.1 variant [27]. Fifteen compounds obtained from *Echium angustifolium* and *Prunus persica* plants were analyzed using various *in silico* techniques. Molecular dynamics (MD) simulations over 200 ns were performed to estimate binding energies, followed by molecular mechanics Poisson-Boltzmann surface area calculations (MM/PBSA). Data obtained from molecular docking indicated that five compounds out of the 15 exhibited good potential with scores higher than -9.0 kcal/mol. Compound 1 derived from *E. angustifolium* showed a binding energy of -49.02 KJ/mol, compound 2 derived from *P. persica* exhibited -48.07 KJ/mol, and compound 4 exhibited -67.47 KJ/mol binding energy, indicating the highest stability in binding to the active binding region of Omicron BA.1. The findings highlighted the promising nature of these discovered phytochemicals as anti-Omicron BA.1 drugs and emphasized the need for further investigation *in vitro* and *in vivo* studies.

Polyphenols derived from certain medicinal plants have been found to exhibit effects such as suppressing the S protein of SARS-CoV-2 that binds to host cell ACE2 receptors, preventing the entry of the virus into host cells, inhibiting the replication of viral RNA, and preventing protein synthesis. A study carried out by Singh et al investigated the effects of polyphenols against the RdRp protein of SARS-CoV-2 [28]. Following molecular docking, the binding energies of control compounds GTP and remdesivir were found to be -7.9 and -7.7 kcal/mol, respectively. Eight polyphenols, namely TF3, TF2b, TF1, TF2a, hesperidin, EGCG, myricetin, and quercetagetin, exhibited the highest binding energies of -9.9, -9.6, -9.6, -9.3, -8.8, -7.3, -7.2, and -7.0 kcal/mol, respectively. In another study by Mahmoud, molecular docking was performed using a polyphenol-rich extract from Cuphea ignea plant against the main protease of SARS-CoV-2 [29]. Among the 15 studied compounds from the plant, rutin, myricetin-3-O-rhamnoside, and rosmarinic acid demonstrated the best antiviral activity.

The therapeutic properties of metabolites derived from algae against COVID-19 have been investigated through various studies. Algae are common plant-like organisms found in aquatic environments that perform photosynthesis. Algal metabolites encompass a wide range of compound classes, including polyphenols, lipids, phytols, terpenes, pigments, sterols, free fatty acids, vitamins, amino acids, peptides, polysaccharides, chitooligosaccharides, and halogenated compounds, similar to other plant-derived molecules. These compounds exhibit diverse pharmacological activities, such as antibacterial, analgesic, antiviral properties, among others. Moreover, the variety and structural characteristics of compounds like alkaloids, terpenes, polyphenols, sterols, and lactones present in algae offer new opportunities in the field of bioactivity and drug development [30].

Studies have identified some bioactive metabolites derived from algae with therapeutic effects, including antiviral activity. For instance, bioactive metabolites obtained from seaweeds have demonstrated strong antiviral activity against *Cytomegalovirus (HCMV), Enterovirus, Influenza virus, Immunodeficiency virus type-1 (HIV-1), Herpes simplex virus (HSV), Hepatitis B virus, Norovirus, and Respiratory Syncytial virus (RSV).* Due to these findings, it has been suggested that algae metabolites could inhibit SARS-CoV-2 and therapeutically interfere with the progression of COVID-19 [31].

Studies have reported that alg-based nutraceuticals, especially *Spirulina,* can enhance immunity against viral diseases. Spirulina-based nutraceuticals boost both adaptive and innate immunity. Certain bioactive compounds found in algae, such as ACE inhibitor peptides, phycobiliproteins, sulfated polysaccharides, and calcium-spirulan, can also act as antiviral agents [32]. Phycocyanobilins (PCBs), also known as blue phycobilins, are tetrapyrrole chromophores found in cyanobacteria and rhodophytes. These pigments have been extensively studied for their light-capturing properties and antioxidant, antiviral, and NADPH-oxidase inhibitory activities. *In silico* studies have explored the potential of PCBs obtained from *Spirulina* sp. as inhibitors of SARS-CoV-2 infection. It has been found that PCBs show strong binding energy to two potential targets, RNA-dependent RNA polymerase (RdRp), and Main protease (Mpro) [30].

In an *in silico* research conducted by Petit et al., it was discovered that components obtained from *Arthrospira* sp.

exhibit effective antiviral properties against SARS-CoV-2 [33]. The identified phycocyanobilin, phycoerythrobilin, phycoerythrobilin, and folate exhibited binding energies ranging from -6.95 to -7.45 kcal/mol using Autodock Vina and between -9.285 to -10.35 kcal/mol using SwissDock.

Microbial metabolites are utilized as important therapeutic agents in the fields of health and agriculture for infection treatment. Due to their advantages over chemically synthesized products, researchers consistently embrace studies based on microbial products for the development of new drugs. Microbial metabolites serve as reliable and useful sources for the production of novel pharmaceutical and therapeutic substances against various types of pathogens. These resources play a significant role in the development of effective treatments against different pathogens such as viruses, bacteria, fungi, and parasites. Various microorganisms including bacteria, fungi, actinomycetes, and microalgae produce diverse secondary metabolites such as quinones, terpenoids, lignans, alkaloids, peptides, polysaccharides, lactones, polyketides, xanthones, and esters, which possess antiviral effects. These metabolites exhibit numerous antiviral activities and serve as important therapeutic agents in the field of healthcare. Microbial metabolites can target viral factors associated with viral pathogenesis, including viral proteins involved in cell binding, viral proteases, viral translation, among others [34].

In a study performed by Sayed et al., over 24,000 natural microbial compounds were examined, and components such as Citriquinochroman, Holyrine B, Proximicin C, Pityriacitrin B, (+)-Anthrobenzoxoconone, and Penimethavone A were found to have potential anti-SARS-CoV-2 properties [35]. Fu et al. conducted another study where a microbial metabolite called lopetinib demonstrated inhibitory effects against the SARS-CoV-2 main protease with an IC50 value of 127.2 μM [36]. Additionally, lopetinib inhibited SARS-CoV-2 in Vero cells with an IC_{50} value of 42.34 μM.

Source	Drug (Metabolite)	References
Honeybee and propolis	3-phenyllactic acid, caffeic acid phenethyl ester (CAPE), lumichrome, galangin, chrysin, and caffeic acid	Hashem, et al. [37]
Moringa oleifera	apigenin-7-O-rutinoside, isoquercetin, Mudanpioside, isoquercitrin, quercetin, dihydroquercetin	Athira Nair and James [38]
Propolis	caffeic acid, caffeic acid phenethyl ester, chrysin, galangin, myricetin, rutin, hesperetin, pinocembrin, luteolin and quercetin	Guler, et al. [39]
Holy Basil (Tulsi)	Eugenol	Paidi, et al. [40]
Hypericum perforatum	hypericin/isohypericin, Pseudohiperisin, Protopseudohyperisin, Protohypericin, Hyperoside, Hiperforine etc..	Yalçın, et al. [41]
Passiflora	Luteolin, Lucenin, Olealonic acid, Isoorientin, Isochaphoside, Saponarin, Schaftoside etc..	Yalçın, et al. [42]
-	Curcumin, quercetin, and vitamin D3 supplements	Khan, et al. [43]
-	Chlorhexidine (CHX) and flavonoids	Tatar, et al. [44]
Olive leaves	Oleuropein	Hussain, et al. [45]
-	Oleuropein, Ganoderic acid A, and Conocurvone	Le, et al. [46]

Table 1: Studies on metabolites investigated for use in SARS-CoV-2 treatment.

Conclusion

The COVID-19 pandemic has been a significant global public health issue, and the search for effective treatment methods continues. This review focuses on potential drug targets for the treatment of COVID-19. Studies have shown that there are several therapeutic drug targets that could be effective at different stages of the SARS-CoV-2 virus. Targets such as the ACE2 receptor, S protein and TMPRSS2 protease play an important role in the viral entry phase. In the viral replication process, RNA polymerase (RdRp) and proteases involved in viral protein processing can be targeted. Particularly, drugs such as remdesivir, lopinavir/ritonavir combination, and chloroquine/hydroxychloroquine have been evaluated as potential treatments targeting SARS-CoV-2 infection. However, further research and clinical trials are needed.

Identifying therapeutic drug targets for COVID-19 can lead to the development of effective treatment strategies. It is important to conduct more studies and safety tests for each drug target and treatment method. Additionally, multidisciplinary approaches and drug combinations should be considered. In conclusion, it is of great importance to

identify potential therapeutic drug targets for the treatment of COVID-19 and continue drug development efforts towards these targets. By building on these efforts, effective treatment strategies can be developed, and progress can be made in combating the effects of the pandemic.

References

1. Gil C, Ginex T, Maestro I, Nozal V, Barrado-Gil L, et al. (2020) COVID-19: Drug Targets and Potential Treatments. Journal of Medicinal Chemistry 63(21): 12359-12386.

2. Khataniar A, Pathak U, Rajkhowa S, Jha AN (2022) A Comprehensive Review of Drug Repurposing Strategies against Known Drug Targets of COVID-19. Covid 2(2): 148-167.

3. Kuba K, Yamaguchi T, Penninger JM (2021) Angiotensin-Converting Enzyme 2 (ACE2) in the Pathogenesis of ARDS in COVID-19. Frontiers in Immunology 12: 732690.

4. Elfiky AA (2020) Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19 . The COVID-19 resource centre is hosted on Elsevier Connect , the company ' s public news and information.

5. Saxena A (2020) Drug targets for COVID-19 therapeutics: Ongoing global efforts. Journal of Biosciences 45(1): 87.

6. Eroğlu E, Balcı H, Baskın V, Aktuna Z (2021) COVID-19 Tedavisine Yönelik Güncel Farmakolojik Yaklaşımlar. YIU Saglik Bil Derg 2: 1-15.

7. Savarino A, Di Tranii L, Donatelli I, Cauda R, Cassone A (2006) New insights into the antiviral effects of chloroquine. Lancet Infect Dis 6(2): 67-69.

8. Liu J, Cao R, Xu M, Wang X, Zhang H, et al. (2020) Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. Cell Discovery 6(1): 6-9.

9. Salvi R, Patankar P (2020) Emerging pharmacotherapies for COVID-19. Biomedicine and Pharmacotherapy 128: 1-11.

10. Al-Tawfiq JA, Al-Homoud AH, Memish ZA (2020) Remdesivir as a possible therapeutic option for the COVID-19. Travel Medicine and Infectious Disease 34: 101615.

11. Beigel JH, Tomashek KM, Dodd LE, Mehta AK, Zingman BS, et al. (2020) Remdesivir for the Treatment of Covid-19-Final Report. New England Journal of Medicine 383(19): 1813-1826.

12. Aleissa MM, Silverman EA, Acosta LMP, Nutt CT, Richterman A, et al. (2021) New Perspectives on Antimicrobial Agents : Remdesivir Treatment for COVID-19. ABRMS 65(1).

13. Cao Z, Gao W, Bao H, Feng, H, Mei S, et al. (2023) VV116 versus Nirmatrelvir–Ritonavir for Oral Treatment of Covid-19. The new england journal of medicine 388(5): 406-417.

14. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, et al. (2021) Role of favipiravir in the treatment of COVID-19. International Journal of Infectious Diseases 102: 501-508.

15. Sada M, Saraya T, Ishii H, Okayama K, Hayashi Y, et al. (2020) Detailed molecular interactions of favipiravir with SARS-CoV-2, SARS-CoV, MERS-CoV, and influenza virus polymerases in silico. Microorganisms 8(10): 1610.

16. Bhatnagar T, Murhekar MV, Soneja M, Gupta N, Giri S, et al. (2020) Clinical & immunological erythematosus patients characteristics in systemic lupus Maryam. Indian J Med Res 151: 184-189.

17. Patel TK, Patel PB, Barvaliya M, Saurabh MK, Bhalla HL, et al. (2021) Efficacy and safety of lopinavir-ritonavir in COVID-19: A systematic review of randomized controlled trials. Journal of Infection and Public Health 14(6): 740-748.

18. Choy K-T, Wong AY, Kaewpreedee P, Sia SF, Chen D, et al. (2020) Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Research 178: 104786.

19. Kang CK, Seong M-W, Choi S-J, Kim TS, Choe PG, et al. (2020) In vitro activity of lopinavir/ritonavir and hydroxychloroquine against severe acute respiratory syndrome coronavirus 2 at concentrations achievable by usual doses. Korean Journal of Internal Medicine 35(4): 782-787.

20. Muralidharan N, Sakthivel R, Velmurugan D, Gromiha MM (2021) Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 protease against COVID-19. Journal of Biomolecular Structure and Dynamics 39(7): 2673-2678.

21. Bramante CT., Buse JB, Liebovitz DM, Nicklas JM, Puskarich MA, et al. (2023) Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicenter, randomized, quadruple-

blind, parallel-group, phase 3 trial. Lancet Infect Dis.

22. Westendorf K, Žentelis S, Wang L, Foster D, Vaillancourt P, et al. (2022) LY-CoV1404 (bebtelovimab) potently neutralizes SARS-CoV-2 variants. Cell Reports. 39(7): 110812.

23. Mohammadi M, Yahyapour Y, Nasrollahian S, Tayefeh-Arbab MH, Javanian M, et al. (2022) A Review on Herbal Secondary Metabolites Against COVID-19 Focusing on the Genetic Variants of SARS-CoV-2. Jundishapur Journal of Natural Pharmaceutical Products 17(4): e129618.

24. Lestari K, Sitorus T, Instiaty I, Megantara S, Levita J (2020) Molecular docking of quinine, chloroquine and hydroxychloroquine to angiotensin converting enzyme 2 (ACE2) receptor for discovering new potential COVID-19 antidote. Journal of Advanced Pharmacy Education and Research 10(2): 1-4.

25. Poisson-Benatouil C, Galabert J-L (2020) Assessing the potential of Artemisia annua in the fight against COVID-19 Scientific justification for research. Scientific justification for research, pp: 1-19.

26. Orege JI, Adeyemi SB, Tiamiyu BB, Akinyemi TO, Ibrahim YA, et al. (2023) Artemisia and Artemisia-based products for COVID-19 management: current state and future perspective. Advances in Traditional Medicine 23(1): 85-96.

27. Hassan HA, Hassan AR, Mohamed EAR, Al-Khdhairawi A, Taha HE, et al. (2022) Targeting Natural Plant Metabolites for Hunting SARS-CoV-2 Omicron BA.1 Variant Inhibitors: Extraction, Molecular Docking, Molecular Dynamics, and Physicochemical Properties Study. Current Issues in Molecular Biology 44(10): 5028-5047.

28. Singh S, Sk MF, Sonawane A, Kar P, Sadhukhan S (2021) Plant-derived natural polyphenols as potential antiviral drugs against SARS-CoV-2 via RNA-dependent RNA polymerase (RdRp) inhibition: an in-silico analysis. Journal of Biomolecular Structure and Dynamics 2020: 1-16.

29. Mahmoud DB, Ismail WM, Moatasim Y, Kutkat O, ElMeshad AN, et al. (2021)Delineating a potent antiviral activity of Cuphea ignea extract loaded nano-formulation against SARS-CoV-2: In silico and in vitro studies. Journal of Drug Delivery Science and Technology 66: 102845.

30. Kumar A, Singh RP, Kumar I, Yadav P, Singh SK, et al. (2022) Algal Metabolites Can Be an Immune Booster against COVID-19 Pandemic. Antioxidants 11(3): 452.

31. Pradhan B, Nayak R, Patra S, Bhuyan PP, Dash SR, et al. (2022) Cyanobacteria and Algae-Derived Bioactive Metabolites as Antiviral Agents: Evidence, Mode of Action, and Scope for Further Expansion; A Comprehensive Review in Light of the SARS-CoV-2 Outbreak. Antioxidants 11(2): 354.

32. Ratha SK, Renuka N, Rawat I, Bux F (2021) Prospective options of algae-derived nutraceuticals as supplements to combat COVID-19 and human coronavirus diseases. Nutrition 83: 111089.

33. Petit L, Vernès L, Cadoret J-P (2021) Docking and in silico toxicity assessment of Arthrospira compounds as potential antiviral agents against SARS-CoV-2. Journal of Applied Phycology 33(3): 1579-1602.

34. Raihan T, Rabbee MF, Roy P, Choudhury S, Baek K-H, et al. (2021) Microbial Metabolites: The Emerging Hotspot of Antiviral Compounds as Potential Candidates to Avert Viral Pandemic Alike COVID-19. Frontiers in Molecular Biosciences 8: 732256.

35. M S-MP, Sayed AM, Alhadrami HA, El-gendy AO, Shamikh YI, et al, (2020) Microbial Natural Products as Potential Inhibitors of SARS-CoV-2 main protease (Mpro). UWS University of the west of scotland, pp: 1-14.

36. Fu L, Shao S, Feng Y, Ye F, Sun X, et al. (2021) Mechanism of Microbial Metabolite Leupeptin in the Treatment of COVID-19 by Traditional Chinese Medicine Herbs. mBio 12(5): e0222021.

37. Hashem HE (2020) IN Silico Approach of Some Selected Honey Constituents as SARS-CoV-2 Main Protease (COVID-19) Inhibitors. Eurasian Journal of Medicine and Oncology 4(3): 196-200.

38. Nair DA, James TJ (2020) Computational screening of phytocompounds from Moringa oleifera leaf as potential inhibitors of SARS-CoV-2 Mpro. Research Square, pp: 1-14.

39. Guler HI, Tatar G, Yildiz O, Belduz AO, Kolayli S (2021) Investigation of potential inhibitor properties of ethanolic propolis extracts against ACE-II receptors for COVID-19 treatment by molecular docking study. Archives of Microbiology 203(6): 3557-3564.

40. Paidi RK, Jana M, Raha S, McKay M, Sheinin M, et al. (2021) Eugenol, a Component of Holy Basil (Tulsi) and Common Spice Clove, Inhibits the Interaction Between SARS-CoV-2 Spike S1 and ACE2 to Induce Therapeutic Responses. Journal of Neuroimmune Pharmacology 16(4): 743-755.

41. Yalçın S, Yalçınkaya S, Ercan F (2021) Determination of

Potential Drug Candidate Molecules of the Hypericum perforatum for COVID-19 Treatment. Current Pharmacology Reports 7(2): 42-48.

42. Yalçın S, Yalçınkaya S, Ercan F (2021) In silico detection of inhibitor potential of Passiflora compounds against SARS-Cov-2(Covid-19) main protease by using molecular docking and dynamic analyses. Journal of Molecular Structure 1240: 130556.

43. Khan A, Iqtadar S, Mumtaz SU, Heinrich M, Pascual-Figal DA, et al. (2022) Oral Co-Supplementation of Curcumin, Quercetin, and Vitamin D3 as an Adjuvant Therapy for Mild to Moderate Symptoms of COVID-19-Results From a Pilot Open-Label, Randomized Controlled Trial. Frontiers in Pharmacology 13: 898062.

44. Tatar G, Salmanli M, Dogru Y, Tuzuner T (2022) Evaluation of the effects of chlorhexidine and several flavonoids as antiviral purposes on SARS-CoV-2 main protease: molecular docking, molecular dynamics simulation studies. Journal of Biomolecular Structure and Dynamics 40(17): 7656-7665.

45. Hussain T, Habib AH, Rafeeq MM, Alafnan A, Khafagy ES, et al. (2022) Oleuropein as a Potent Compound against Neurological Complications Linked with COVID-19: A Computational Biology Approach. Entropy 24(7): 881.

46. Le QH, Far BF, Sajadi SM, Jahromi BS, Kaspour S, et al. (2023) Analysis of Conocurvone, Ganoderic acid A and Oleuropein molecules against the main protease molecule of COVID-19 by in silico approaches: Molecular dynamics docking studies. Engineering Analysis with Boundary Elements 150: 583-598.