Acta Pharm. **73** (2023) 157–173
https://doi.org/10.2478/acph-2023-0014

Mini-review

Pharmaceutical approaches for COVID-19: An update on current therapeutic opportunities

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Accepted November 18, 2022
Published online November 18, 2022

ABSTRACT

SARS-CoV-2, a newly discovered coronavirus, has been linked to the COVID-19 pandemic and is currently an important public health issue. Despite all the work done to date around the world, there is still no viable treatment for COVID-19. This study examined the most recent evidence on the efficacy and safety of several therapeutic options available including natural substances, synthetic drugs and vaccines in the treatment of COVID-19. Various natural compounds such as sarsapogenin, lycorine, biscoclaurine, vitamin B_{12}, glycyrrhizic acid, riboflavin, resveratrol and kaempferol, various vaccines and drugs such as AZD1222, mRNA-1273, BNT162b2, Sputnik V, and remdesivir, lopinavir, favipiravir, darunavir, oseltamivir, and umifenovir, resp., have been discussed comprehensively. We attempted to provide exhaustive information regarding the various prospective therapeutic approaches available in order to assist researchers and physicians in treating COVID-19 patients.

Keywords: COVID-19, SARS-CoV-2, drugs, natural compounds, vaccine, treatment

INTRODUCTION

The Coronavirus disease 2019 (COVID-19) was reported in December 2019 and is responsible for the world pandemic which was announced by WHO in March 2020. COVID-19 is showing a massive global impact in relation to economic disruption and human health (1). Now it affects millions of people globally because of its high prevalence and long incubation time even without having any symptoms (2). Researchers have been debating the origin of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since its discovery. SARS-CoV-2 may be the result of laboratory manipulations, according to certain reports (3). SARS-genomic CoV-2's data, however, does not corroborate this concept and demonstrates that it did not originate from a known virus backbone (4). SARS-CoV-2 has unique

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characteristics that set it apart from other coronaviruses, according to analyses of its genome and comparisons with other coronavirus genomes previously known. It is the infectivity and host range that are determined by the S1/S2 spike junction's polybasic cleavage site's affinity for the angiotensin-converting enzyme 2 (ACE2) receptor (5).

SARS-CoV-2 is a single-stranded RNA (ssRNA) virus with spike-like glycoproteins expressed on the surface, forming a "corona". The genome of SARS-CoV-2 shares 79.6 % genetic similarity with SARS-CoV and contains four main proteins such as spike (S) protein, membrane (M) protein, nucleocapsid (N) protein and envelope (E) protein (6–8). As many as 632,953,782 confirmed cases of COVID-19 worldwide, including 6,593,715 fatalities, had been reported to WHO by November 16, 2022 (9). So, considering the above-mentioned situation as a pandemic, people are looking towards emergency medical treatment with successful antiviral drugs or vaccines to eradicate this pandemic situation by removing this virus as soon as possible. The purpose of this review is to investigate the genesis of COVID-19, as well as its transmission mechanism and various treatment options, including natural substances, pharmaceuticals, and other treatments.

The rationale and design of the study are represented in the form of a flow chart in Fig. 1.

Etiology of COVID-19

There is no effective etiology reported yet and people are depending on the clinical picture and may be discharged from the hospital on the basis of different parameters such as no fever, improvement in respiratory defect, clear lung report, and negative RT-PCR report. Near touch with respiratory droplets, immediate contact with infectious people, or contact with polluted items and surfaces are the most common methods of human-to--human transmission (10). The SARS-CoV-2 virus has genomes that are between 26 and 32 kb in size (11). The incubation time is thought to be between two and fourteen days. Dry cough (67 %), fever (88 %), nausea (38 %), myalgia (14.9 %) and dyspnea (18.7 %) are the most common clinical signs of SARS-CoV-2 infection. Headache, sore throat, rhinorrhea and

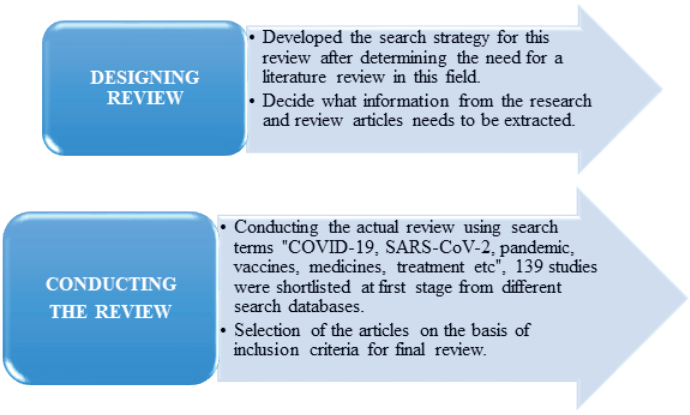


Fig. 1. Flow chart indicating rationale and design of the study.

stomach complaints are among the other symptoms. Pneumonia happens to be the infection's most serious and significant symptom (12, 13). Symptoms that arise after the SARS-CoV infection lasting more than 12 weeks that cannot be attributed to another illness have been identified as post-COVID-19 syndrome.

Long-term recovery interventions should focus on patients who have more significant impairments in their pulmonary diffusion capacities as well as aberrant chest imaging symptoms. Neurological/cognitive as well as systemic symptoms tend to be seen in the most persistent symptoms. Because of cognitive dysfunction and other incapacitating symptoms, the patient's ability to work was diminished in comparison to pre-illness levels, which led to a reduction in hours, jobs and overall productivity (14, 15). A number of other sequelae (a condition which is the consequence of a previous disease or injury), such as respiratory system complications, mental health issues, metabolic diseases, cardiovascular issues and gastrointestinal problems are also common (16).

Mechanism of COVID-19 spreading

SARS-CoV-2 uses its S-glycoprotein to bind to ACE2 receptors on cells. S1 and S2 are the two domains of the S protein. S1 binds to the peptidase domain of ACE2 and is thus known as the receptor-binding domain, while S2 catalyzes membrane fusion, allowing genetic material to be released into cells (17). The RNA serves as a basis for structural proteins such as replicase (R1a/ab), E, S, M, N, and many NSPs, as well as uncharacterized protein 14, protein 9b, which are found within the cell. NSPs are thought to play a role in host-protein interactions as well as modulate host-cell signalling pathways (18). By considering these pathways, the future therapeutics for COVID-19 might be based on targeting these proteins. The molecular mechanism is shown in Fig. 2.

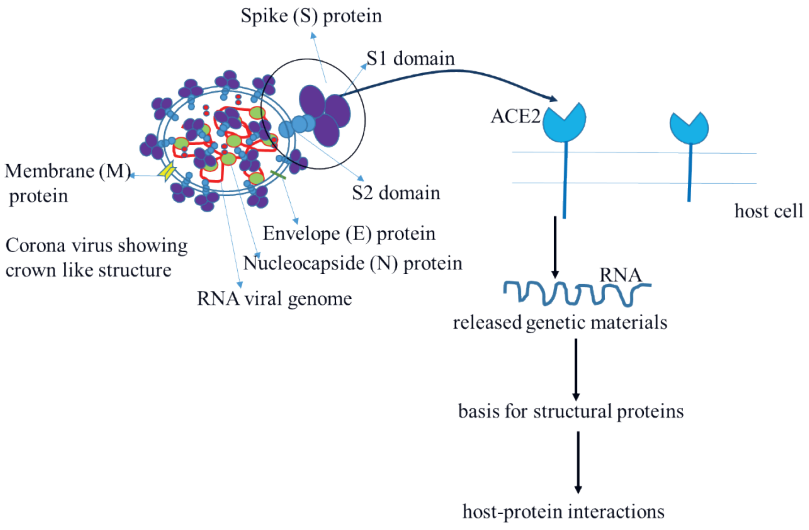


Fig. 2. The molecular mechanism of COVID-19 spreading.

Identification of COVID-19

Currently, the RT-PCR technique is very popular to detect COVID-19 globally. It is based on swabs of the throat and nasopharynx. According to a published report on 4,880 specimens, it showed a positive test rate of 38 % (19). IgM is thought to be the first immunoglobulin produced in response to virus infection, while IgG has the highest opsonization and neutralization processes in the humoral immune response. Seroconversion is the transition from the point of viral infection to when antibodies of the virus become present in the blood. IgM, IgG seroconversion can begin as early as 4 days after the onset of SARS infection, according to previous research (20, 21). So due to the lack of other specific diagnostic tools, emerging techniques may be welcomed to test COVID-19.

COVID-19 main proteins

The spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins are the four main structural proteins found in the corona viral genome. S, E, M and N proteins are major virulence proteins that play a critical role in DNA replication. These proteins bind to the ACE2 receptor as they enter a human cell. As a result, these viral proteins may be used as a drug target to stop trial replication (22). The general feature regarding S, E, M and N proteins was elaborated in Fig. 3.

Spike (S) protein

Spike (S) protein allows viral entry into target cells in the host (23). Since it forms the crown-like structure on the virus's outer surface, the S protein is responsible for the virus's

N	M
• Most abundant viral protein • Bind to viral RNA to form a core of a ribonucleoprotein • 90 % similarity with N protein of SARS-CoV • C-terminal domain is hydrophobic • Rich in helix	• Present in high amounts • Contains 220–260 amino acids • The tyrosine at 211 may be essential in the stability of the long form of M protein • Organized in a 2D lattice and provides a scaffold in viral assembly • Showing N-terminal ectodomain and C-terminal endodomain • Therapeutic option to inhibit the virion formation
E	**S**
• Tiny integral membrane protein • Composed of an N-terminal domain, hydrophobic domain, and a chain at C-terminal • 76–109 amino acids • Weighing 8–12 kDa • N terminal stretches from 1^{st}-9^{th} amino acids • Hydrophbic region ranges from 10^{th}-37^{th} position • C-terminal from 38^{th}-76^{th} position	• Molecular weight ia about 141178 kDa • Contains 1237 amino acids • Consists of an ectodomain element transmembrane moiety and a short-intracellular C fragment • Promoting adhesion of infected cells • Plays a crucial role in viral entry into the host cells

Fig. 3. The function of S, E, M, and N proteins.

distinctive function. S1 and S2 are the two subunits that make up the S protein. The S1 subunit is further divided into three domains, with A, B and C being the most common. SARS-CoV-2 and SARS-CoV join the target cell by interacting directly with domain B. The ACE2 receptor is then attached to this. Surprisingly, the S protein structure of all SARS-CoV and novel SARS-CoV-2 viruses is almost identical, with only minor differences (24–27). The S protein is responsible for the virus's binding to the host cell's surface receptors, resulting in fusion and viral entry (10). S protein S1 subunit encourages membrane fusion while the S2 subunit enables ACE2-mediated virus binding. SARS-CoV-2 contains amino acids, glutamine, asparagine, leucine, phenylalanine and serine, which increase ACE2 binding (28).

Membrane (M) protein

The M protein is the most abundant protein in the viral envelope, and it determines the form of the envelope (13, 29). The *C*-terminal of the M protein is hydrophilic, while the *N*-terminal is amphipathic. Its long form encourages the introduction of spikes, and its association with E encourages virion development (28). The M protein is arranged in a two-dimensional lattice and serves as a scaffold during viral assembly. They are translated on membrane-bound polysomes in the ER, fused in the Golgi complex, and brought to the Golgi complex, where they interact with E proteins to form virions (30, 31).

Nucleocapsid (N) protein

The E protein is the tiniest of the main structural proteins, and it helps viruses assemble and bud (13). A serine-rich linker region is sandwiched between the *N*- and *C*-terminal domains in the N protein. These terminals are involved in viral entry and post-entry collection. The *N*-terminal binds to the viral genome and forms orthorhombic crystals. The linker region has phosphorylation sites that control how it works. The *C*-terminal encourages the formation of nucleocapsids (28). It is known to bind to viral RNA to form a ribonucleoprotein centre, which aids in virus entry and association with cellular processes after virus fusion (32). Replication transcription complexes formed by NSP are crucial for viral genome synthesis (33).

The N protein in SARS-CoV stimulates cyclooxygenase-2 activation, resulting in lung inflammation (34). It also plays a role in the inhibition of phosphorylation of B23 phosphoprotein, which is needed for cell cycle progression during centrosome replication (35). It also prevents type I interferon (IFN), limiting the body's immune responses in response to viral infections (36). The N protein binds to the p42 proteasome subunit, which is in control of viral protein degradation (37). According to cell line studies it was displayed that due to the inhibitory action of N protein on the cyclin-cyclin-dependent kinase complex (C-CDK) the progression of the S-phase was reduced (38). It was also reported that cell line study showed reduced proliferation of cells due to inhibition of cytokinesis and protein translation (39).

Envelope (E) protein

The E protein is a small integral membrane protein with an *N*-terminal domain, hydrophobic domain, and *C*-terminal chain (40) with 76–109 amino acids (41) and a size of 8–12 kDa (42). N is the only protein that binds to the RNA genome and is active in viral

assembly and budding. Attachment and entry are the first steps of coronavirus replication (13). The *N*-terminal, hydrophobic domain, and *C*-terminal of the E protein combine to form viroporins, which are needed for viral assembly (28).

Role of nonstructural proteins (NSP)

There are several NSPs present in SARS-CoV-2 which are playing a crucial role in early drug design (43) and these NSPs are taking part in the different functions of the virus such as the formation of replicase transcriptase complex (10). These NSPs along with their functions are listed in Table I. Among these known NSPs, Nsp15 is a nidoviral RNA uridylate-specific endoribonuclease (NendoU) with a *C*-terminal catalytic domain. It is one of the mysterious enzymes that precisely belong to the EndoU family (44). Nsp15 was thought to simply participate in viral replication at first, but it was later discovered that Nsp15-deficient coronaviruses were also viable and capable of replication, raising questions about its biological role (45). Another recent research stated that Nsp15's NendoU behaviour is to account for proteins interfering with the innate immune response (46). By considering the above-mentioned information Nsp15 may be a crucial target for the treatment of COVID-19.

Role of natural compounds for the treatment of COVID-19

Natural ingredients and their molecular structures have a long history of serving as important starting points for medicinal chemistry and drug development (52). These items pave the way for the development of successful antiviral drugs to fight COVID-19 (53).

Table I. The different known non-structural proteins (NSP) and their function

Type of NSP	Function	Ref.
NSP1 and NSP2	Suppression of host gene expression	47
NSP3	Formation of a multi-domain complex	
NSP4	Transmembrane (TM) proteins	48
NSP5	Role in replication	47
NSP6	Transmembrane (TM) proteins	48
NSP7 and NSP8	Act as a primase	49
NSP9	RNA-binding protein, the dimeric form which is important for viral infection	50
NSP10	Acts as a co-factor for the activation of the replicative enzyme	51
NSP12	RNA-dependent RNA polymerase activity	48
NSP13	Shows helicase activity	
NSP14	Shows exoribonuclease activity	
NSP15	Shows endoribonuclease activity	
NSP16	Has methyl-transferase activity	

Table II. Different natural compounds against NSP

Compound(s)	Target	Function	Ref.
Sarsasapogenin, ursonic acid, curcumin, ajmalicine, novobiocin, silymarin, aranotin, piperine, gingerol, rosmarinic acid, alpha terpinyl acetate	Nsp15	Inhibiting SARS-CoV-2 replication	60
Diosmetin-7-*O*-beta-d-apiofuranoside, 3′-epi-afroside, 3-*O*-alpha-l-arabinopyranosyl-echinocystic acid, genkwanin 8-C-beta-glucopyranoside	RNA-dependent RNA-polymerases (RdRp)	Therapeutic candidates against the coronaviruses	61
Lycorine, silvestrol, homoharringtonine, ouabain, tylophorine	Viral proteins	Antiviral activity at nanomolar concentration	62
Biscoclaurine, norreticuline, umifenovir-umifenovir	3CLpro, spike protein and PLpro	Anti-COVID-19 candidates	63
Ribavirin, telbivudine, vitamin B_{12}, nicotinamide	Viral Mpro	Potential use in COVID-treatment	64
Glycyrrhizic acid, limonin, 7-deacetyl-7-benzoylgedunin, maslinic acid, corosolic acid, obacunone and ursolic acid	3CLpro, PLpro, SGp-RBD, RdRp, and ACE2	Effective against the target proteins of SARS-CoV-2	65
Luteolin	Main protease	Key role in fighting against virus	66
Riboflavin, absinthin, schaftoside, oleanolic acid	Mpro, ACE2	Used to develop effective antiviral drugs	67
Resveratrol	ACE2	Anti-COVID-19	68
Kaempferol, quercetin, luteolin-7-glucoside, naringenin and oleuropein	Mpro	Potential inhibitors of the SARS-CoV-2 Mpro	68

Botanical medications and supplements have been prescribed for SARS-CoV-2 prevention, adjuvant therapy, and treatment following exposure. Traditional Chinese herbal medicine (TCM) is allegedly effective when combined with conventional Western medicine. Based on observed modes of action and *in silico* experiments, natural extracts and compounds of possible therapeutic significance have been established, but clinical studies have remained to be conducted (54–59). Several natural compounds have been explored against different targets of COVID-19 to combat this disease. These compounds are mentioned in Table II.

Vaccines used in COVID-19 treatment

Vaccines produce the same germs that cause sickness, but they have been destroyed or damaged so that they do not cause illness. Just a portion of the disease germ is contained in certain vaccines. The immune system is stimulated to develop antibodies by a vaccine. Vaccination services helped to reduce the death and morbidity associated with a variety of infectious diseases (69). Several vaccine candidates to protect against SARS-CoV-2 infection or COVID-19 have entered (70). There are several types of vaccine technology

Table III. Different types of known vaccines and their function

Name of vaccine	Producing company	Country	Type of vaccine	Function	Ref.
AZD1222	AstraZeneca	UK	DNA-based, viral vector	High antibody response	72
mRNA-1273	Moderna	USA	mRNA-based vaccine	Immune response in a greater number of individuals	73, 74
BNT162b2	Pfizer (BioNtech)	Germany	mRNA-based vaccine	Participants show increased IgG levels	75
Sputnik V	Gamaleya	Russia	Viral vector	Preventing COVID-19 in an interim efficacy analysis report	76

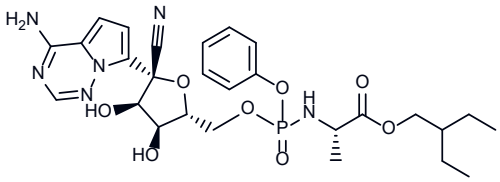
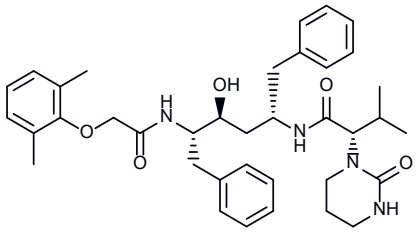
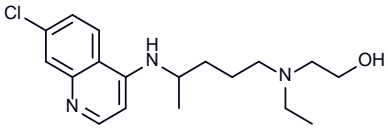
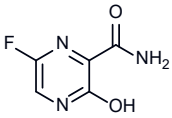
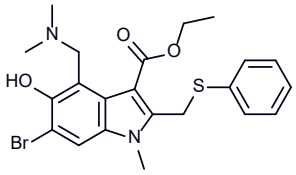
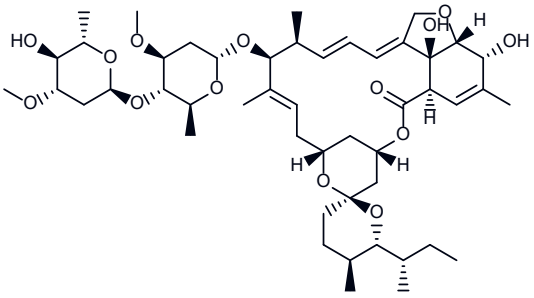
used to combat the COVID-19 such as mRNA-based and DNA-based, peptide-based, live attenuated virus, and inactivated virus-based technology (71). In various nations throughout the world, the use of AZD1222 (AstraZeneca, UK) and Sputnik V (Russia) have been allowed for emergency use. In addition, in August 2021 and January 2022, the US FDA approved the clinical use of the BNT162b2 and mRNA-1273 vaccines, resp., to prevent COVID-19 after initially approving a EUA (72). The list of some emerging and known vaccines is listed in Table III.

Drugs for COVID-19 treatment

In the lack of a scientifically validated therapeutic plan, COVID-19 is managed and treated mostly supportively, with the sole goal of lowering mortality. To prevent the spread of the infection, good sanitation, social distancing, and quarantine procedures are recommended around the world. Several repurposed medications, including antiviral and antimalarial drugs, are being used as tactical therapies to reduce the negative effects of viral pathogenesis. Antiviral drugs interfere with different stages of viral growth by targeting certain proteins required for viral survival (72, 77). The majority of drugs in clinical trials are repurposed drugs that were originally developed to cure various diseases (78, 79). Several clinical trials are also being conducted to assess the suitability and effectiveness of repurposed antiviral medications for treating COVID-19, including remdesivir, ribavirin, galidesivir, favipiravir, darunavir, oseltamivir, and umifenovir (78, 80, 81). Among the mentioned drugs remdesivir is a broad-spectrum antiviral drug that has been repurposed for single-stranded RNA viruses. It is the most promising antiviral drug currently being used to treat COVID-19 (82).

The Food and Drug Administration (FDA) has approved 100 mg/20 mL intravenous remdesivir for the treatment of COVID-19 in adult and pediatric patients (≥ 12 years old and ≥ 40 kg bm). It is authorized for the treatment of COVID-19 in hospitalized patients as well as high-risk, non-hospitalized individuals with mild to moderate COVID-19 (*i.e.*, a 3-day course started within 7 days of symptom onset) (*i.e.*, a 5-day course) (83). Usually, low booster doses of ritonavir are used along with lopinavir to improve the pharmacokinetics of lopinavir by inhibiting the cytochrome P450 3A4 enzyme, which slows the hepatic metabolism of lopinavir. Adults should generally take 800 mg of lopinavir daily

Table IV. Known drugs used for the prevention of COVID-19 and their dose

Name of drug	Chemical structure	Dose
Remdesivir		100 mg in 20 mL, intravenous
Lopinavir		800 mg lopinavir + 200 mg of ritonavir
Hydroxy-chloroquine		400 mg *per os* BD followed by 200 mg BD for 4 days
Favipiravir		1600 mg twice a day on day 1, and a maintenance dose of 1200 mg twice daily for nine days
Umifenovir		200 mg kg^{-1} per day
Ivermectin		150–200 μg kg^{-1} twice daily

together with 200 mg of ritonavir, typically in two separate doses (84). The therapeutic dose of hydroxychloroquine can be determined based on the EC_{50} values. For the treatment of COVID-19, a physiologically based pharmacokinetic modelling study suggested a loading dose of hydroxychloroquine of 400 mg which is taken by mouth twice a day (PO BD), followed by 200 mg BD for 4 days. There are no dose guidelines available for patients with systemic comorbidities identified as COVID-19, pregnant women, obese patients, children, or patients in the paediatric community (85). According to Pertinez *et al*. (86), the intracellular active metabolite of favipiravir may be reached at therapeutic concentrations with a loading dose of 1600 mg twice a day on day 1 and a maintenance dose of 1200 mg twice daily for nine days. Umifenovir (registered as Arbidol) is an RNA polymerase inhibitor that is only approved in Russia and China to treat flu. Because of how the medicine works, it has been seen as a possible treatment for the new SARS-CoV-2 infection. Umifenovir has been shown to be safe, even for pregnant women, and has not been shown to cause birth defects. Umifenovir has a broad therapeutic index, hence, it is likely that it is well tolerated. The oral administration of 200 mg to volunteers was found to be extremely tolerable. No adverse events of vital signs or laboratory tests were noticed in this study (87). One of the potential repurposed drugs that exhibit an *in vitro* inhibitory activity on SARS-CoV-2 replication is ivermectin. For ivermectin, 150–200 μg kg^{-1} twice daily is the dosage most frequently suggested for the treatment of COVID-19. FDA issued a caution regarding the use of ivermectin during the pandemic as its use for COVID-19 increased (88).

CONCLUSIONS

The SARS-CoV-2 virus and its variations are still wreaking havoc on the global healthcare system and economies of many nations. This review examined the most recent evidence on the efficacy and safety of several therapeutic options available including natural substances, synthetic drugs and vaccines in the treatment of COVID-19. Medications targeting the spike, membrane, nucleocapsid and envelope proteins are currently in use. In addition, the spike protein is an important target for vaccine production. People are looking towards emergency medical treatment with successful antiviral drugs or vaccines to eradicate this pandemic situation. Clinical trials are being conducted to assess the suitability and effectiveness of repurposed antiviral medications for treating COVID-19. The FDA has approved remdesivir for the treatment of COVID-19 in adult and pediatric patients. Umifenovir has been shown to be safe, even in pregnant women.

With the introduction of possibly drug-resistant strains, COVID-19 will continue to be a threat to global public health until the majority of the world's population receives full vaccination (including booster injections). In addition, the most recent clinical guidelines regarding the diagnostic and therapeutic options available in the management of COVID-19 should be regularly reviewed by clinical providers caring for COVID-19 patients on the front lines, especially in light of the emergence of new SARS-CoV-2 variants that have the potential to significantly increase morbidity and mortality.

Acronyms, abbreviations, symbols. – ACE2 – angiotensin-converting enzyme 2, RT-PCR – reverse transcriptase-polymerase chain reaction, NSPs – non-structural proteins, EC_{50} – half maximal effective concentration, PO BD – taken by mouth twice a day, IgM – immunoglobulin M, IgG – immunoglobulin G.

Conflict of interest. – The authors declare no conflict of interest.

Funding. – This research received no external funding.

Author's contributions. – SF and HW: Conceptualization, methodology and investigation, DW and LL: original draft preparation, review and editing. All the authors have read and agreed to the published version of the manuscript.

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