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Review

COVID-19 pandemic: outbreak, potential vaccines and medications

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Abstract: The outbreak of the current global pandemic caused by the spread of a novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has posed an unprecedented threat to global health and economy across the whole world. As of today, the number of cases diagnosed with SARS-CoV-2 is exceeding 271 million with over 5.32 million deaths globally. Despite the high throughput technology and considerable advances in sciences, the outbreaks of the COVID-19 pandemic present a colossal challenge to scientific community. Scientists and clinicians all over the world are putting tremendous efforts to develop effective treatments to combat this deadly pathogen, at least to contain it momentarily until an adequate treatment regimen is available. Conventionally, vaccines have been developed as one of the therapeutic strategies to restrict infectious diseases. Although several vaccines are in the pipeline, evaluation of efficacy in animals' studies and human are time-consuming. On the other hand, several drugs already in clinical use are being employed to test their efficacy against SARS-CoV-2. Some of these drugs have been already used as anti-viral drugs and others have been used for different therapeutic purposes. In this review, we summarize the ongoing efforts to control the dissemination of SARS-CoV-2 and highlight the potential prophylactic and therapeutic measures including the recently developed vaccines in the foreseeable future. Moreover, we emphasize an importance of having a customized strategy that can be easily and quickly employed to overcome possible future outbreaks.

Keywords: COVID-19 pandemic, SARS-CoV-2, coronavirus, vaccines, S-protein, anti-viral agents.

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Introduction

The emergence of novel virus infections continues to pose a serious threat to global public health with immense economic repercussions. In the last two decades, several viral epidemics have occurred including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2002-2003, H1N1 influenza in 2009 and the Middle East respiratory syndrome coronavirus (MERS-CoV) [1, 2]. Recently, the current outbreak in the city of Wuhan, China is caused by a novel coronavirus (SARS-CoV-2) and designated COVID-19 (Coronavirus-2019) by the World Health Organization (WHO). According to WHO, SARS-CoV-2 continues to represent an unprecedented challenge for public health and the global economy since World War-II [3]. After many countries reported clusters of COVID-19 cases and community transmission, WHO in March 2020, declared that the SARS-CoV-2 outbreak is pandemic [4]. Within a short period, SARS-CoV-2 spread to many countries with high mortality rates around the world. While more than 80% of COVID-19 cases are mild respiratory infections, severe illness and death are more common among people at high risk including in particular immunocompromised patients [3]. There are no safe and effective vaccines available for SARS-CoV-2 and the efficacy of potential anti-viral is still controversial. Therefore, there is an urgent need for the development of novel prophylactic and therapeutic strategies to combat SARS-CoV-2. In this review, we highlight the efforts that have been taken worldwide to control the dissemination of SARS-CoV-2 and potential prophylactic and therapeutic agents being developed.

SARS-CoV-2 survival and dissemination

Environmental factors play a pivotal role in controlling the clinical impact of the human coronaviruses (HCoVs) infection. It is of paramount importance to evaluate the viability and virulence of the HCoVs under different environmental conditions to establish efficient preventive measures. Temperature and humidity are inter-related environmental factors posing a substantial effect on the HCoVs behavior. HCoVs infections have a seasonal predilection and occur mainly in winter with a short incubation period [5, 6]. A recent study concluded that at 20 °C aerosolize HCoV 229 E had a better chance to survive at 50% relative humidity than at 30%. In fact, after 6 days 20% of the virus load was still detectable. A relatively higher humidity (80%) found to be less favorable to the virus. At 6 °C, they noticed a substantial enhancement of the

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survival rate of the HCoV 229E regardless of the humidity rate. This increase in survival rate at high relative humidity and relatively low temperature may give a clue why the coronaviruses' outbreak may occur in winter [7]. It is notable that the outbreak most probably started in November (winter in the northern hemisphere). This geographic zone includes the heavily hit countries by the SARS-CoV-2 such as in China, Iran, Italy, France, Spain and the United states [8]. That being said, a second pandemic wave in the coming winter is a legitimate concern.

Regarding survival it has been confirmed that virus survival in biological fluids such as respiratory secretions or faces is enhanced. Low temperature, high relative humidity, and organic materials provide a relative protection to HCoVs. Antiseptics like ethanol or bleach demonstrates a significant anti HCoVs activity. However, hexamidine, povidone-iodine or chlorhexidine are more efficient specially when associated with ethanol and/or cetrimide [9].

To sum up, social distancing is the cornerstone to mitigate the spread of the COVID-19 pandemic but testing, isolation, and contact tracing are the fundamental triad to fight and overcome COVID-19 pandemic.

Potential vaccine and anti-viral therapy for SARS-CoV-2

Several treatment regimens are being tried currently in SARS-CoV-2 infected patients. There is no currently FDA-approved COVID-19 specific treatment or vaccine. While viral targeting therapies may limit the infection and reduce organ injury, prevention of current and future COVID-19 infections will require methods to safely stimulate the acquired immunity.

Vaccine-development for SARS-CoV-2 (2020-2021)

Vaccines in clinical trials

mRNA-1273 (NCT04283461, Phase I): The first US clinical trial of a SARS-CoV-2 vaccine initiated by Moderna using mRNA-1273. A novel lipid nanoparticle (LNP)-encapsulated mRNA-based vaccine that encodes a full-length stabilized S-protein which is necessary for membrane fusion and host cell infection and has been the target of vaccines against the MERS-CoV and SARS-CoV. This vaccine has shown a promising immune response in animal models and expected to show effective immune response against SARS-CoV-2.

Ad5-nCoV (ChiCTR2000030906, Phase I): Ad5-nCoV is the first novel coronavirus vaccine for COVID-19 in Phase 1 clinical trial in China. The vaccine candidate is built upon CanSinoBIO's adenovirus-based viral vector vaccine technology platform, which has also been successfully applied to develop the vaccine against Ebola virus [10]. The Ad5-nCoV vaccine candidate is a genetically engineered vaccine candidate with the replication-defective adenovirus type 5 as the vector to express SARS-CoV-2 S-protein.

COV001 (NCT04324606, Phase I/II): ChAdOx1 nCoV-19 is a chimpanzee adenovirus [11] developed at the University of Oxford (UK) as a viral vector and investigated as a potential vector for vaccines against MERS-CoV [12]. The ChAdOx1 nCoV-19 vaccine consists of an attenuated adenovirus capable of producing the S-protein of SARS-CoV-2, allowing for the formation of endogenous antibodies against these proteins and, consequently, against the virus [13]. The vaccine will be administered intramuscularly (IM).

INO-4800 (NCT04336410, Phase I): MERS. INO-4700 (GLS-5300) developed by Inovio Pharmaceuticals (USA) is a DNA plasmid vaccine that expresses the MERS CoV S-glycoprotein (NCT03721718, Phase I/II, Korea). Using modern DNA medicines platform, the DNA vaccine INO-4800 was designed in three hours after the publication of the genetic sequence of the novel coronavirus that causes COVID-19. This vaccine will be administered intradermally [14].

BCG vaccine for COVID-19: The Bacillus Calmette-Guerin (BCG) is a live-attenuated vaccine that has been implicated to combat infections other than TB by boosting the immune system to fight similar infections. In Australia, a Phase 3 clinical trial was started and aimed to recruit 4,170 healthcare workers to receive BCG vaccine (NCT04327206, Phase III). Researchers in Netherlands launched phase 3 BCG-CORONA trial and plan to enroll 1,500 healthcare workers (NCT04328441, Phase III). The Faustman Laboratory (Massachusetts General Hospital, USA) is currently evaluating the BCG vaccine's effectiveness in type 1 diabetes [15] and seeking a fund to launch trials to assess whether the vaccine helps to prevent COVID-19 in healthcare workers. In 2017, the WHO reported that the BCG vaccine may be effective against leprosy [16] and other non-tuberculous mycobacteria such as Buruli ulcer disease [17]. Other studies have posited the vaccine as an effective treatment in acute respiratory tract infections in elderly patients [18, 19]. It is based on previous findings that BCG decreases the level of virus in patients infected by viruses similar to SARS-CoV-2.

Vaccines in preclinical phase

PittCoVacc: Scientists from University of Pittsburgh School of Medicine (USA) developed a vaccine for SARS-CoV-2 that is effective in mice and can be delivered through a fingertip patch. The vaccine creates antibodies in mice that are sufficient to neutralize the virus. This array is a fingertip-sized patch of needles that deliver S-protein pieces into the skin using micro-needle array, where the immune reaction is the strongest [20]. The patch goes on like a Band-Aid, and the needles, which are made entirely of sugar and protein pieces, simply dissolved into the skin.

Ii-Key peptide SARS-CoV-2 vaccine: Generex Biotechnology (Canada) is working to develop a peptide vaccine against the SARS-CoV-2 using the Ii-Key immune system activation technology. The Ii-Key technology uses synthetic peptides that mimic essential protein regions from a virus that are chemically linked to the 4-amino acid Ii-Key to ensure the activation of robust immune system [21]. The Ii-Key ensures potent activation of CD4+ T cells, which in turn facilitates antibody production against the infection. This Ii-Key modification can be applied to any protein fragment of any pathogen to increase the potency of immune system.

BNT162: Pfizer (USA) and BioNTech (Germany) agreed to develop and distribute a potential mRNA-based coronavirus vaccine. BNT162, an mRNA-based vaccine expressing codon-optimized SARS-CoV-2 S-protein encapsulated in lipid nanoparticles. The companies had previously agreed to develop an mRNA-based influenza vaccine in 2018 [22].

Nanoparticle COVID-19 vaccine: Novavax biotech (Rockville, MD) announced that several recombinant S-proteins are produced as nanoparticle vaccines for COVID-19 and they are vetted for animal testing.

Intranasal COVID-19 vaccine: Altimmune biotech (Rockville, MD) has developed a COVID-19 vaccine using the same technology they used to build their influenza vaccine, NasoVAX (NCT03760549, Phase IIa). The COVID-19 vaccine developed using

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adenovirus vector incorporating SARS-CoV-2 S-protein and delivered intranasal as a single dose.

Ad26Vac for COVID-19: Johnson & Johnson (Janssen, Belgium) are developing a COVID-19 vaccine using recombinant adenovirus 26 (Ad26Vac) vaccine incorporating SARS-CoV-2 S-protein using human retinal cell line (Per.Co6), which were also used to develop Ebola vaccine [23, 24]. This vaccine administered intranasal as a single-dose.

DNA-based vaccine for COVID-19: Takis biotech (Rome, Italy) announced that a COVID-19 vaccine is ready to be tested on pre-clinical models. This vaccine contains only a fragment of DNA and will be administered via intramuscular injection [25].

Oral recombinant COVID-19 vaccine: Vaxart (South San Francisco, CA) focused on developing oral recombinant adenovirus vaccines expressing SARS-CoV-2 S-protein. Each of the COVID-19 vaccine constructs is based on a different coronavirus antigen combination [26].

Plant-based COVID-19 vaccine: Medicago (Quebec, Canada) recently developed a seasonal recombinant quadrivalent virus-like particle (VLP) influenza vaccine [27, 28], and reported that they have been created a coronavirus VLP 20 days after working with the SARS-CoV-2 gene encoding S-protein [29].

Vaccines in research stage

mRNA-based vaccine: BIOCAD (Russia) and Sanofi (Paris) and Translate Bio (Lexington, MA) announced to create an mRNA vaccine candidate for COVID-19. It is a recombinant vaccine made from SARS-CoV-2 S-protein expressed in baculovirus system using DNA platform made from previous SARS vaccine. In addition, Arcturus Therapeutics (San Diego, CA) and Duke-NUS Medical School (Singapore) are partnering to develop a COVID-19 vaccine that uses Arcturus' self-replicating RNA and nanoparticle non-viral delivery system. Furthermore, Fudan University and Shanghai JiaoTang University with RNACure (China) had partnered to develop a SARS-CoV-2 mRNA vaccine. They are using two methods to develop an mRNA-based vaccine, mRNA to express the receptor binding domain (RBD) of the S-protein of COVID-19 to induce neutralizing-antibodies, and developing mRNAs that can instruct the host to produce virus-like particles (VLP) similar to SARS-CoV-2.

COVID-19 S-Trimer: Clover Pharmaceuticals (Sichuan, China) and GlaxoSmithKline (GSK, Brentford, United Kingdom) are developing a vaccine using recombinant SARS-CoV-2 S-protein trimer subunit vaccine.

Heat's gp96 vaccine: Heat Biologics (HTBX, Morrisville, NC) and University of Miami Miller School of Medicine utilize a heat-shock protein gp96 backbone to develop COVID-19 vaccine [30]. Heat's gp96 platform is generating open docking sites for the insertion of multiple SARS-CoV-2 antigens. Heat's approach inducing a multi-epitope specific memory CD8 T-cell response that protects against multiple, distinct coronavirus strains and against potential future mutations of SARS-CoV-2 and other coronavirus [31].

RBD protein vaccine: Researchers at the Baylor College of Medicine (Texas) are developing an S1 or RBD protein vaccine as a targeted vaccine for COVID-19.

MVA encoded VLP: Geovax and Bravovax (China) announced they would collaborate to create a modified Vaccinia ankara virus-like particles (MVA-VLP) vaccine candidate for COVID-19. This vaccine developed from a recombinant MVA-VLP and employed for Ebola virus [32, 33].

Adenovirus-based vector vaccine for COVID-19: Greffex (Houston, Texas) is developing an adenovirus-based vector vaccine for COVID-19.

Modified avian coronavirus vaccine: MIGAL Galilee Research Institute (Qiryat Shemona, Israel) plans to create a new COVID-19 vaccine by adapting its research in developing a vaccine for the genetically-similar avian coronavirus Infectious Bronchitis Virus (IBV) [34, 35].

Horsepox vaccine with percutaneous administration: Tonix Biopharmaceuticals (New York) and Southern Research are planning to develop a live-attenuated modified horsepox vaccine expressing SARS-CoV-2 S-protein (TNX-1800) [36, 37].

Gene-encoded antibody vaccine candidate: Sorrento Therapeutics (San Diego, CA) with SmartPharm Therapeutics (Cambridge, MA) are utilizing monoclonal antibodies against SARS-CoV-2 virus generated by Sorrento and encode a gene utilized by SmartPharm's non-viral nanoparticle platform for delivery [38].

DPX-COVID-19: IMV, a biotech company (Canada) developed a vaccine for COVID-19 based on DPX-Survivac, a T-cell activating immunotherapy antigen vaccine using sequences of the virus and immunoinformatics to predict and identify several hundred epitopes. Of which 23 were selected for their biological relevance to the virus and their potential to generate neutralizing antibodies against SARS-CoV-2. The DPX platform formulated with peptide antigens with unique mechanism of action allows antigen presenting cells (APCs) to be attracted to the injection site, facilitating a robust and sustained immune response within lymph nodes.

DNA and/or live attenuated recombinant COVID-19 vaccine: Zydus Cadila (India) announced a DNA vaccine targeting the viral entry of membrane protein and a live attenuated recombinant measles virus targeted SARS-CoV-2.

Formalin-inactivated and alum-adjuvant candidate vaccine for COVID-19: Sinovac biotech (China) is working on the development of a formalin-inactivated and alum-adjuvant vaccine for COVID-19.

Molecular clamp vaccine for COVID-19: Researchers at the University of Queensland (Australia) developed a recombinant subunit vaccine of SARS-CoV-2 S-protein locked in prefusion conformation by polypeptide moiety (molecular clamp).

Anti-COVID-19 vaccine approved and currently in use (2021)

Multiple vaccines against COVID-19 were authorized for use by the end of 2020. Currently, there are three main types of COVID-19 vaccines that have been authorized for use worldwide.

1. mRNA based vaccines: mRNA vaccines contain mRNA encoding spike protein of SARS-CoV 2 virus delivered as lipid-based nanoparticle carrier technology. After the translation takes place in the cells, the host recognize that the protein and this activates T-lymphocytes and B-lymphocytes which generates antibodies that will protect against the virus in case of future infection.

2. Protein subunit vaccines include spike proteins of SARS-CoV 2, Once vaccinated, the host recognizes the foreign protein and generates T-lymphocytes and antibodies against the future virus infection.

3. Vector vaccines contain a modified version of a different virus other than SARS-CoV2 . comprising a "viral vector." Once the viral vector is inside the cells, the genetic material gives cells instructions to make spike protein SARS-CoV 2. Using these instructions, the cells make copies of the protein resulting in a strong T- and B-lymphocytes mediated cellular response. [39-41].

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Here, we discuss currently used vaccines for immunization against COVID-19 with special reference to Sputnik V. The comparison between different vaccines has been shown in *Table* 1.

COVID-19 mRNA:

1. Pfizer-BioNTech COVID-19: Pfizer-BioNTech vaccine has been authorized in individuals 16 years of age and older. The Pfizer–BioNtech uses a lipid-based nanoparticle carrier system that prevents the rapid enzymatic degradation of mRNA and facilitates in vivo delivery. Pfizer and BioNTech have reported that phase III results of BNT162b2, demonstrated an efficacy of 91.3% against the COVID-19 disease, measured after seven days through up to six months after the second dose. Safety data followed up for six months after the second dose, showed a favourable safety and tolerability profile of the vaccine. The reported side effects, lasting few days included pain at the injection site, tiredness, headache, muscle pain, chills, joint pain, and fever[42, 43].

2. Oxford–AstraZeneca COVID-19 vaccine (AZD1222): Also marketed under the brand names Covishieldand Vaxzevria is a viral vector vaccine using the modified chimpanzee adenovirus ChAdOx1for COVID-19 developed by Oxford University and AstraZeneca. The vaccine showed an efficacy of 76.0% at preventing symptomatic COVID-19 following the first dose, increasing to 81.3% with the second dose given 12 weeks or more later. The vaccine has a promising safety profile, with side effects including pain, headache, and nausea, resolving within a few days. In few rare cases, reported mostly from Europe, the vaccine increased the risk of blood clots but it is still undetermined whether it is directly caused by the vaccine [44].

3. Moderna COVID-19 vaccine: It is manufactured by Moderna TX, Inc. for the prevention of COVID-19 for individuals 18 years of age and older. Based on evidence from clinical trials, the Moderna vaccine was 94.1% effective at preventing COVID-19 disease in people who received two doses. The reported side effects, typically lasting few days, included pain at the injection site, tiredness, fever, headache, muscle pain, chills etc at the site of the injection. The side effects after the second dose were more than after the first dose [45].

4. Janssen COVID-19 Vaccine: This vaccine is manufacture red by Janssen Biotech Inc. and authorized for use in individuals 18 years of age and older. The Janssen vaccine was 66.3% effective in clinical trials at preventing COVID-19 disease. People had the most protection 2 weeks after getting vaccinated with Janssen vaccine. The vaccine had high efficacy at preventing hospitalization and death in people who did get infected with COVID 19. The side effects were mild to moderate in severity including pain at the injection site, headache, fatigue, muscle aches and nausea after 1-2 days following vaccination and were mild to moderate in severity [46].

Table 1. Major COVID-19 vaccines

Vaccine	*Country of origin*	*Phase clinical trials*	*Efficacy*	*Storage*	*Dosage*
Sputnik-V/Gam-COVID-Vac	Gamaleya research Institute, Russia	3	91.6% efficacy	storage at 2 to 8°C	two doses, 21 days apart.
ChAdOX1-S	University of Oxford/AstraZeneca	3	95% effective at preventing symptomatic COVID-19 infection	2 to 8°C (36 to 46°F).	Two shots are required, delivered 21 days apart
BNT162b2	Pfizer/BioNTech vaccine, USA/Germany	3	95% effective at preventing symptomatic COVID-19 infection	-80°C to -60°C (-112°F to -76°F)	Two shots are required, delivered 21 days apart.
Ad26CoVS1	Janssen pharmaceutical companies, Belgium	3	66.9% effective at preventing moderate to severe COVID-19 infection	2 to 8°C (36 to 46°F).	One shot is required.
LNP-encapsulated mRNA	Moderna/N1 AID, USA	3	94.1% effective at preventing symptomatic COVID-19 infection	2° to 8°C (36° to 46°F)	Two shots are required, delivered 28 days apart.
mRNA vaccine	Curevac, Germany	3	- No data	- No data	No data
DNA-vaccine (GX-19)	Genexine-consortium, South Korea	1	- No data	- No data	No data
Inactivated vaccine (COVID-19 vaccine)	Wuhan Institute of biological products/Sinopharm, China	3	- No data	No data	No data

Table 2. Major proposed anti-viral drugs to COVID-19

Drug	*Country of origin*	*Direct*	*Indirect*	*Target Mechanism*	*FDA approved*
EIDD-2801	USA	√		viral replication	In process
Ivermectin	Australia	√		viral replication	In process
APN01	Europe	√		Inhibits the entrance	In process
Remdesivir	USA	√		viral replication	Approved
Lopinavir and ritonavir		√		viral replication	No data
N-sulfonylanthranilic acid		√		viral replication	
Natural products (flavonoids and tannin)	Variable	√	√	Not determined	No data
Chloroquine and hydroxychloroquine			√	-Host immunity -Host zinc -Host heme -Host alkalinization	Approved but not for COVID-19
Azithromycin			√	Immunomodulatory	Approved but not for COVID-19
Tocilizumab			√	Immunomodulatory	Approved for COVID-19
Brilacidin			√	defensin mimetic drug	In process

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5. Sputnik V anti COVID-19 vaccine: Russia's first approved vaccine was developed in early March 2020 at the Gamaleya National Center of Epidemiology and Microbiology in Moscow using two different adenovirus vectors (rAd26 and rAd5) encoding SARS-CoV-2 spike protein delivered separately two doses, 21 days apart. Phase I and II clinical trials on 76 participants of an open, non-randomized trial, were published in the Lancet in September.2 demonstrated that all participants developed SARS-CoV-2 antibodies. The trials showed promising safety results and the immune response was at a level consistent with protection and the recipients generated robust antibody and T cell responses to the spike protein, included neutralizing antibodies. Most side effects were mild, with just over half experiencing local pain at the site of injection and no adverse effects were recorded. Interim phase III randomized, double blind, placebo-controlled trial included nearly 22 000 adults aged 18 years or older indicated that the vaccine is 91.6% effective, and no cases of moderate or severe covid-19 in the vaccinated group were observed. In 94% of subjects, very mild (grade 1) side effects were reported. Approximately 3.5 million Russians have already received both doses of Sputnik V vaccine as of March 15, 2021. Russian researchers are currently working on two versions of the initial Sputnik V vaccine22: (storage at -18°C), and another lyophilized one (storage at 2 to 8°C). It was reported recently that Sputnik V vaccine is set to expand its global roll-out, including Middle East and Asian countries [46-49].

Potential therapeutic agents and drugs for COVID-19

Plasma from recovered COVID-19 patients

The FDA approved plans for nationwide trials to use plasma from recovered patients to treat patients infected with the SARS-CoV-2. The treatment, called convalescent plasma, is based on the fact that recovered patients have antibodies [50]. The results showed that the patients' conditions improved after a transfusion [51]. The same strategy has been employed for the treatment of SARS [52] and Ebola [53].

Potential drugs for COVID-19

Several drugs are reviewed for anti-viral activities as a quick response to the outbreak of COVID-19. Accordingly, we classified these drugs into those are directly and indirectly affecting the virus (*Table* 2).

Direct anti-COVID-19 drugs

In general, anti-viral drugs classified into inhibitors for the viral attachment and entry [54], release [55], replication polymerase [56], nucleoside reverse transcriptase, non-nucleoside reverse transcriptase and RNA synthesis inhibitors [57], inhibitors for viral protein synthesis protease [58], and integrase inhibitors [59] and inhibitor for viral exit [60].

On March 2020, Emory University announced the potential activities of "EIDD-2801" against SARS-CoV-2. The drug showed *in-vitro* and *in-vivo* activities against multiple coronaviruses, including SARS and MERS. EIDD-2801 has been known to inhibit a broad range of RNA viruses. It has been reported that the virus incorporates the drug into its RNA when it replicates, instead of cytosine, leading to a cascade of mistakes called "error catastrophe" causing accumulation of mutations in the virus genome, blocks the viral RNA polymerase, an essential component in viral replication. EIDD-2801 is able to overcome the coronavirus proofreading function. The virus does not develop resistance when it exposed to sub-lethal doses of the drug. EIDD-2801 shows excellent oral bioavailability, a feature that favors its use widely [61].

A group of scientists from Australia announced the use of an FDA-approved ivermectin, anti-viral, against SARS-CoV-2 *in-vitro* [62]. They proposed the mechanism of anti-viral activity is through the inhibition of importin α/β (IMPα/β1)-mediated nuclear import of viral proteins, similar to the drug activities on other RNA viruses including Dengue [63, 64], West Nile [65], Venezuelan equine encephalitis [66] and influenza viruses [67].

On April 2020, Austria-based Apeiron Biologics has approved to start Phase II clinical trials on drug called APN01 [68]. APN01 is a recombinant form of human ACE2 let the virus to bind APN01 and hence inhibits the entry of the virus to the lung cells [69].

Other anti-viral drugs were revisited in responses to the outbreak of SARS-CoV-2 included remdesivir, lopinavir and ritonavir [70]. Lopinavir and ritonavir may bind to M^{pro}, a key enzyme involved in coronavirus replication [71]. Remdesivir (GS-5734), a nucleoside analog pro-drug developed by Gilead Sciences (USA) [72]. Remdesivir is a monophosphoramidate pro-drug of remdesivirtriphosphate (RDV-TP), an adenosine analog that acts as an inhibitor of RNA-dependent RNA polymerases (RdRps). The drug also interferes with the proofreading mechanism by viral exoribonuclease [73-75]. Although the phase III clinical trial (NCT04280705) of remdesivir against COVID-19 was launched in Wuhan on February 2020, remdesivir is not expected to cover all patients in a timely manner [76]. Remdesivir was originally developed to treat Ebola and Marburg virus disease but was ineffective [77]. Early May 2020, remdesivir was approved by FDA against COVID-19 and issued an Emergency Use Authorization in the U.S. for hospitalized patients with severe disease.

Of interest, high throughput screening of one million compounds revealed that N-sulfonylanthranilic acid derivatives are allosteric inhibitors of Dengue virus RdRp with no toxicity [78]. Therefore, structure modification of N-sulfonylanthranilic acid may be a target to develop effective anti-viral drugs particularly against SARS-CoV-2.

Other than the conventional medications, traditional Chinese medicines were employed in the potential treatment of patients with COVID-19, while still require more investigations [79]. Plant flavonoids including quercetin, hespertin and catechin and tannins have proved to be effective against several viruses [80-82]. Herbacetin, rhoifolin and pectolinarin flavonoids can efficiently block the enzymatic activity of C-like protease (3CLpro), a cysteine protease required in viral replication [83]. Furthermore, in silico-based approach showed that hydrolysable tannins including pedunculagin, tercatain, and punicalin can inhibitory bind the closed sites of SARS-CoV-2 main protease enzyme (3-chymotrypsin-like cysteine enzyme) [84]. Since 3-Chymotrypsin-like cysteine enzyme controls the duplication and life cycle process of SARS-CoV-2, therefore it can be considered as a good target for anti-viral drug discovery [85]. Identification of natural products or daily use food supplements that contains such components with potential anti-viral activities particularly against SARS-CoV-2 may be helpful in controlling the spread of the virus. For examples, fruits, cereals and vegetables such as apples, pears, berries, broccoli, bran, citrus, tea, and grapes are among the dietary

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sources of flavonoids and tannins that have proven safe for human use [86-88].

Indirect anti-COVID-19 drugs

Several drugs have been proposed following the outbreak of COVID-19 but with unusual anti-viral activities, instead they benefit from initiating a host condition that is adverse the existence of the virus. A much-highlighted drug in this regard included chloroquine (CQ) and hydroxychloroquine (HCQ). The Chinese authorities have listed HCQ, a less toxic derivative of CQ, as effective anti-COVID-19 after positive preliminary clinical data [90]. Although the mechanism of CQ and HCQ as anti-COVID-19 is not fully understood, several reports showed that the mechanism of HCQ and CQ as anti-COVID-19 involved both direct and indirect anti-viral activities.

The indirect activity of CQ and HCQ is mainly depending on their immune-modulatory activities and decrease the production of pro-inflammatory cytokines [90]. While CQ can alkalize the phagolysosome, stopping the acidic pH-dependent viral replication [91], enhance interferons release by the host cell [92] and zinc uptake by the virus [93]. Several studies have reported broad-spectrum anti-viral activity of zinc [94]. A recent study showed that SARS-CoV-2 can attack the 1-beta chain of hemoglobin and dissociate the iron from porphyrin. This leads to a significant decrease in the hemoglobin and hence alters the oxygen-carbon dioxide exchange, causing significant lung poisoning [95]. This result suggests that CQ could help to prevent this attack in an anti-malarial-like mechanism. If the CQ and HCQ can kill the virus in-vitro, a direct anti-viral activity should be involved. However, the direct mechanisms of anti-viral activity are still unclear. Regardless, the direct anti-viral activities of CQ and HCQ may include inhibition of viral enzymes or processes such as viral DNA and RNA polymerase, viral protein glycosylation, virus assembly, new virus particle transport, and virus release. It is of important note that an overdose of CQ can cause acute poisoning and death [96]. It has been confirmed by France and Canadian health authorities that CQ and HCQ is toxic and caused very serious cardiovascular complications to over 80% of patients.

The azithromycin (macrolide antibiotic) may have immune-modulatory properties in pulmonary disorders by down regulate the inflammatory responses and reduces the excessive cytokine production associated with respiratory viral infections. However, their direct effects on viral clearance are uncertain.

Tocilizumab, a recently FDA-approved anti-COVID-19, inhibits IL-6-mediated signaling by competitively binding to both soluble and membrane-bound IL-6 receptors. IL-6 is a pro-inflammatory cytokine that is involved in T-cell activation, immunoglobulin secretion, initiation of hepatic acute-phase protein synthesis, and stimulation of hematopoietic cell proliferation and differentiation [97].

Currently, Innovation Pharmaceuticals is evaluating Brilacidin, a defensin mimetic drug, as a potential candidate in the treatment of COVID-19. Brilacidin is known as anti-infective agent [98] that shows anti-bacterial, anti-inflammatory and immune-modulatory properties in several clinical trials [99].

Future prospective and challenges

In order to combat the current and possible future outbreaks, two major strategies need to be addressed including prevention and treatment of the disease. Regarding the prevention of disease spreading, the best proposed practices included keep social distance and use of sanitizers. But these two practices are impractical to continue our daily busy life. Excessive use of sanitizers was also alerted, since it may cause health complications. Therefore, a strategy based on proper vaccination and availability of efficient anti-viral drugs is required. While the mutation of the virus is unexpected, the response to develop a treatment strategy should be quick.

Herd immunity proposed by few countries is a group protection that happens when a large number of populations are immune to a disease and can help stop or slow the spread of infectious diseases. However, the safest way to get immunity is through vaccination. There is very limited information about the cellular and humoral immune response of the human to SARS-CoV-2. These aspects need to be addressed by basic research for the successful development of a vaccine.

Seasonal changes in SARS-CoV-2 pandemic should be taken into account for future monitoring of the global transmission. The onset of spring and summer season could, for example, give the impression that SARS-CoV-2 infection will be dramatically eliminated. It should be noted, however, that SARS-CoV-2 can transmit in tropical climates, and not necessarily restricted to winter. Recent trends in regions across East-Asia suggest that seasonality alone is unlikely to end SARS-CoV-2 spread [87]. On the other hand, it is known that winter conditions favor the transmissibility of different viruses. Winter season provides a proper conducive condition for virus survival and spreading including dampen the humans' innate immunity. Low humidity can impair the innate defense mechanism of the body and reduce the capacity of cilia cells in the airway to remove virus particles. Low humidity can also cause dryness of the nasal mucus and make the upper respiratory tract vulnerable to virus invasion [88].

The risk of SARS-CoV-2 infection will continue to remain for a long time as it is present in human communities and in wild nature. Therefore, adequate precautions must be taken for safe-guarding against future pandemics of SARS. The prevention can be achieved by adopting a multi-facet system that considers both natural and social aspects of the SARS epidemiology. Regular surveillance of viral status in nature should be carried out to monitor the seasonal mutations and localization of the virus. This information may serve as an early warning and used for preparation of potential vaccines.

The BCG vaccine has received recent attention for being a control option for SARS-CoV-2. A recent study found that countries with universal BCG coverage had statistically less SARS-CoV-2 cases than countries without mass BCG vaccination program. However, the data supporting this hypothesis is sparse. Experimental proof of such association or protection conferred by BCG is lacking. To test the validity of such hypothesis is to compare the epidemiological data from BCG vaccinated and non-vaccinated populations in such countries and relating it to the prevalence of SARS-CoV-2 infection in such individuals. Interestingly, the WHO is currently analyzing this theory with clinical trials on selected cohorts.

Development of drug therapy is urgent and designing a platform to occupy most of the important characteristics that have been identified to overcome the virus viability is required. Such platform should be designed to have anti-viral properties including the prevention of replication, attachment and entry to the host

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cell. It may also occupy properties that can enhance the host environment to disfavor the existence of the virus. Such platform can be easily modified on spot in order to overcome any possible future outbreaks. Further, collaborative efforts of researchers are highly desirable to develop an efficient cost-effective vaccine or drug to control COVID-19 pandemic. The continuous effort of research in this direction might be helpful in producing high-value biologics and pharmaceuticals on a large scale in a short time, especially during epidemics.

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Conflict of Interest

The authors declare no conflicts of interest.

Authors' contributions

Sameh Soliman, Rauf Bhat, Magdy Ahmed and Mohamed Husseiny: Conceptualization, methodology, data collection and interpretation, draft preparation, reviewing and approval of the final version for submission.

References

1. de Wit E, van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. *Nat Rev Microbiol* 2016;14(8):523-534. https://doi.org/10.1038/nrmicro.2016.81.
2. Song Z, Xu Y, Bao L, Zhang L, Yu P, Qu Y, et al. From SARS to MERS, Thrusting Coronaviruses into the Spotlight. *Viruses* 2019; 11(1): 59. https://doi.org/10.3390/v11010059.
3. Li Q, Guan X, Wu P, Wang X, Zhou L, Tong Y, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med* 2020; 382(13): 1199-1207. https://doi.org/10.1056/nejmoa2001316.
4. Zheng J. SARS-CoV-2: an Emerging Coronavirus that Causes a Global Threat. *Int J Biol Sci* 2020; 16(10): 1678-1685. https://doi.org/10.7150/ijbs.45053.
5. Gerna G, Percivalle E, Sarasini A, Campanini G, Piralla A, Rovida F, et al. Human respiratory coronavirus HKU1 versus other coronavirus infections in Italian hospitalised patients. *J Clin Virol* 2007; 38(3): 244-250. https://doi.org/10.1016/j.jcv.2006.12.008.
6. Esposito S, Bosis S, Niesters HG, Tremolati E, Begliatti E, Rognoni A, et al. Impact of human coronavirus infections in otherwise healthy children who attended an emergency department. *J Med Virol* 2006; 78(12): 1609-1615. https://doi.org/10.1002/jmv.20745.
7. Ijaz MK, Brunner AH, Sattar SA, Nair RC, Johnson-Lussenburg CM. Survival characteristics of airborne human coronavirus 229E. *J Gen Virol* 1985; 66(12): 2743-2748. https://doi.org/10.1099/0022-1317-66-12-2743.
8. Sajadi MM, Habibzadeh P, Vintzileos A, Shokouhi S, Miralles-Wilhelm F, Amoroso A. Temperature, Humidity, and Latitude Analysis to Estimate Potential Spread and Seasonality of Coronavirus Disease 2019 (COVID-19). *JAMA Netw Open* 2020; 3(6): e2011834. https://doi.org/10.1001/jamanetworkopen.2020.11834.
9. Geller C, Varbanov M, Duval RE. Human coronaviruses: insights into environmental resistance and its influence on the development of new antiseptic strategies. *Viruses* 2012; 4(11) 3044-3068. https://doi.org/10.3390/v4113044.
10. Zhu FC, Hou LH, Li JX, Wu SP, Liu P, Zhang GR, et al. Safety and immunogenicity of a novel recombinant adenovirus type-5 vector-based Ebola vaccine in healthy adults in China: preliminary report of a randomized, double-blind, placebo-controlled, phase 1 trial. *Lancet* 2015; 385(9984): 2272-2279. https://doi.org/10.1016/s0140-6736(15)60553-0.
11. Dicks MD, Spencer AJ, Edwards NJ, Wadell G, Bojang K, Gilbert SC, et al. A novel chimpanzee adenovirus vector with low human seroprevalence: improved systems for vector derivation and comparative immunogenicity. *PLoS One* 2012; 7(7): e40385. https://doi.org/10.1371/journal.pone.0040385.
12. Alharbi NK, Padron-Regalado E, Thompson CP, Kupke A, Wells D, Sloan MA, et al. ChAdOx1 and MVA based vaccine candidates against MERS-CoV elicit neutralizing antibodies and cellular immune responses in mice. *Vaccine* 2017; 35(30): 3780-3788. https://doi.org/10.1016/j.vaccine.2017.05.032.
13. University of Oxford Commences Clinical Trial for Vaccine Candidate (ChAdOx1 nCoV-19) Targeting COVID-19. *TrialSiteNews* 2020. https://trialsitenews.com/university-of-oxford-commences-clinical-trial-for-vaccine-candidate-chadox1-ncov-19-targeting-covid-19-2/.
14. Carlson R. INO-4800 COVID-19 Vaccine. *Precision Vaccinations* 2021. https://www.precisionvaccinations.com/vaccines/ino-4800-covid-19-vaccine.
15. Kuhtreiber WM, Tran L, Kim T, Dybala M, Nguyen B, Plager S, et al. Long-term reduction in hyperglycemia in advanced type 1 diabetes: the value of induced aerobic glycolysis with BCG vaccinations. *NPJ vaccines* 2018; 3: 23. https://doi.org/10.1038/s41541-018-0062-8.
16. Coppola M, van den Eeden SJF, Robbins N, Wilson L, Franken K, Adams LB, et al. Vaccines for Leprosy and Tuberculosis: Opportunities for Shared Research, Development, and Application. *Front Immunol* 2018; 9: 308. https://doi.org/10.3389/fimmu.2018.00308.
17. Phillips RO, Phanzu DM, Beissner M, Badziklou K, Luzolo EK, Sarfo FS, et al. Effectiveness of routine BCG vaccination on buruli ulcer disease: a case-control study in the Democratic Republic of Congo, Ghana and Togo. *PLoS Negl Trop Dis* 2015; 9(1): e3457. https://doi.org/10.1371/journal.pntd.0003457.
18. Moorlag SJCFM, Arts RJW, van Crevel R, Netea MG. Non-specific effects of BCG vaccine on viral infections. *Clin Microbiol Infect* 2019; 25(12): 1473-1478. https://doi.org/10.1016/j.cmi.2019.04.020.
19. Lundgren F, Maranhão B, Martins R, Chatkin JM, Rabahi MF, Corrêa RA, et al. Vaccination in the prevention of infectious respiratory diseases in adults. *Rev Assoc Med Bras (1992)* 2014; 60(1): 4-15. https://doi.org/10.1590/1806-9282.60.02.004.
20. Kim E, Erdos G, Huang S, Kenniston TW, Balmert SC, Carey CD, et al. Microneedle array delivered recombinant coronavirus vaccines: Immunogenicity and rapid translational development. *EBioMedicine* 2020; 55: 102743. https://doi.org/10.1016/j.ebiom.2020.102743.
21. Kallinteris NL, Lu X, Wu S, Hu H, Li Y, Gulfo JV, et al. Ii-Key/MHC class II epitope hybrid peptide vaccines for HIV. *Vaccine* 2003; 21(27-30): 4128-4132. https://doi.org/10.1016/s0264-410x(03)00493-6.
22. Pardi N, Parkhouse K, Kirkpatrick E, McMahon M, Zost SJ, Mui BL, et al. Nucleoside-modified mRNA immunization elicits influenza virus hemagglutinin stalk-specific antibodies. *Nat Commun* 2018; 9(1): 3361. https://doi.org/10.1038/s41467-018-05482-0.
23. Milligan ID, Gibani MM, Sewell R, Clutterbuck EA, Campbell D, Plested E, et al. Safety and Immunogenicity of Novel Adenovirus Type 26- and Modified Vaccinia Ankara-Vectored Ebola Vaccines: A Randomized Clinical Trial. *JAMA* 2016; 315(15): 1610-1623. https://doi.org/10.1001/jama.2016.4218.
24. Winslow RL, Milligan ID, Voysey M, Luhn K, Shukarev G, Douoguih M, et al. Immune Responses to Novel Adenovirus Type 26 and Modified Vaccinia Virus Ankara-Vectored Ebola Vaccines at 1 Year. *JAMA* 2017; 317(10): 1075-1077. https://doi.org/10.1001/jama.2016.20644.
25. Takis, a biotech company in Castel Romano, Rome, announces that it is ready to test its Covid-19 vaccine on pre-clinical models. 2020. https://www.takisbiotech.it/index.php/en/news/209-rome-17-march-

2020-takis-a-biotech-company-in-castel-romano-rome-announces-that-it-is-ready-to-test-its-covid-19-vaccine-on-pre-clinical-models.

26. Vaxart Provides Update on its Oral COVID-19 Vaccine Program. 2020. https://investors.vaxart.com/news-releases/news-release-details/vaxart-provides-update-its-oral-covid-19-vaccine-program.
27. Ibrahim A, Odon V, Kormelink R. Plant Viruses in Plant Molecular Pharming: Toward the Use of Enveloped Viruses. *Front Plant Sci* 2019; 10: 803. https://doi.org/10.3389/fpls.2019.00803.
28. Pushko P, Pumpens P, Grens E. Development of virus-like particle technology from small highly symmetric to large complex virus-like particle structures. *Intervirology* 2013; 56(3): 141-165. https://doi.org/10.1159/000346773.
29. Hodgson J. The pandemic pipeline. *Nat Biotechnol* 2020; 38(5): 523-532. https://doi.org/10.1038/d41587-020-00005-z.
30. Strbo N, Vaccari M, Pahwa S, Kolber MA, Doster MN, Fisher E, et al. Cutting edge: novel vaccination modality provides significant protection against mucosal infection by highly pathogenic simian immunodeficiency virus. *J Immunol* 2013; 190(6): 2495-2499. https://doi.org/10.4049/jimmunol.1202655.
31. Heat Biologics Announces Research Collaboration with University of Miami to Develop Vaccine Designed to Protect Against COVID-19 Coronavirus. 2020. https://www.accesswire.com/579232/Heat-Biologics-Announces-Research-Collaboration-with-University-of-Miami-to-Develop-Vaccine-Designed-to-Protect-Against-COVID-19-Coronavirus.
32. Schweneker M, Laimbacher AS, Zimmer G, Wagner S, Schraner EM, Wolferstatter M, et al. Recombinant Modified Vaccinia Virus Ankara Generating Ebola Virus-Like Particles. *J Virol* 2017; 91(11): e00343-17. https://doi.org/10.1128/jvi.00343-17.
33. Robinson HL, Marzi A. Ebola virus – prospects for a novel virus-like-particle-expressing modified vaccinia Ankara-based vaccine. *Expert Rev Vaccines* 2018; 17(9): 769-771. https://doi.org/10.1080/14760584.2018.1510775.
34. Sultan HA, Ali A, El Feil WK, Bazid AHI, Zain El-Abideen MA, Kilany WH. Protective Efficacy of Different Live Attenuated Infectious Bronchitis Virus Vaccination Regimes Against Challenge With IBV Variant-2 Circulating in the Middle East. *Front Vet Sci* 2019; 6: 341. https://doi.org/10.3389/fvets.2019.00341.
35. Jordan B. Vaccination against infectious bronchitis virus: A continuous challenge. *Vet Microbiol* 2017; 206: 137-143. https://doi.org/10.1016/j.vetmic.2017.01.002.
36. Noyce RS, Lederman S, Evans DH. Construction of an infectious horsepox virus vaccine from chemically synthesized DNA fragments. *PLoS One* 2018; 13(1): e0188453. https://doi.org/10.1371/journal.pone.0188453.
37. Tulman ER, Delhon G, Afonso CL, Lu Z, Zsak L, Sandybaev NT, et al. Genome of horsepox virus. *J Virol* 2006; 80(18): 9244-9258. https://doi.org/10.1128/jvi.00945-06.
38. Sorrento and smartpharm to collaborate to develop novel gene-encoded antibody vaccine intended to protect against COVID-19. 2020. https://investors.sorrentotherapeutics.com/news-releases/news-release-details/sorrento-and-smartpharm-collaborate-develop-novel-gene-encoded.
39. Dai L, Gao GF. Viral targets for vaccines against COVID-19. *Nat Rev Immunol* 2021; 21(2): 73-82. https://doi.org/10.1038/s41577-020-00480-0.
40. Silveira MM, Moreira GMSG, Mendonça M. DNA vaccines against COVID-19: Perspectives and challenges. *Life Sci* 2021; 267: 118919. https://doi.org/10.1016/j.lfs.2020.118919.
41. Locht C. Vaccines against COVID-19. *Anaesth Crit Care Pain Med* 2020; 39(6): 703-705. https://doi.org/10.1016/j.accpm.2020.10.006.
42. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, et al; C4591001 Clinical Trial Group. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; 383(27): 2603-2615. https://doi.org/10.1056/nejmoa2034577.
43. Sahin U, Muik A, Derhovanessian E, Vogler I, Kranz LM, Vormehr M, et al. COVID-19 vaccine BNT162b1 elicits human antibody and TH1 T cell responses. *Nature* 2020; 586(7830): 594-599. Erratum in: *Nature* 2021;590(7844): E17. https://doi.org/10.1038/s41586-020-2814-7.
44. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, et al; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomized controlled trials in Brazil, South Africa, and the UK. *Lancet* 2021; 397(10269): 99-111. Erratum in: *Lancet* 2021; 397(10269): 98. https://doi.org/10.1016/s0140-6736(20)32661-1. Erratum in: *Lancet* 2021; 397(10269): 98.
45. Doria-Rose N, Suthar MS, Makowski M, O'Connell S, McDermott AB, Flach B, et al; mRNA-1273 Study Group. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *N Engl J Med* 2021; 384(23): 2259-2261. https://doi.org/10.1056/nejmc2103916.
46. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US); 2006–. COVID-19 vaccines. 2021. https://pubmed.ncbi.nlm.nih.gov/33355732/.
47. Logunov DY, Dolzhikova IV, Shcheblyakov DV, Tukhvatulin AI, Zubkova OV, Dzharullaeva AS, et al. Safety and efficacy of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine: an interim analysis of a randomized controlled phase 3 trial in Russia. *Lancet* 2021; 397(10275): 671-681. https://doi.org/10.1016/S0140-6736(21)00234-8.
48. Sadoff J, Le Gars M, Shukarev G, Heerwegh D, Truyers C, de Groot AM, et al. Safety and immunogenicity of the Ad26.COV2.S COVID-19 vaccine candidate: interim results of a phase 1/2a, double-blind, randomized, placebo-controlled trial. *MedRxiv. The preprint server for health sciences* 2020: 1-28. https://doi.org/10.1101/2020.09.23.20199604
49. Logunov DY, Dolzhikova IV, Zubkova OV, Tukhvatullin AI, Shcheblyakov DV, Dzharullaeva AS, et al. Safety and immunogenicity of an rAd26 and rAd5 vector-based heterologous prime-boost COVID-19 vaccine in two formulations: two open, non-randomized phase 1/2 studies from Russia. *Lancet* 2020; 396(10255): 887-897. Erratum in: *Lancet* 2021; 397(10269): 98. https://doi.org/10.1016/s0140-6736(20)31866-3.
50. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. *J Clin Invest* 2020; 130(4): 1545-15458. https://doi.org/10.1172/jci138003.
51. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 Critically Ill Patients With COVID-19 With Convalescent Plasma. *JAMA* 2020; 323(16): 1582-1589. https://doi.org/10.1001/jama.2020.4783.
52. Cheng Y, Wong R, Soo YO, Wong WS, Lee CK, Ng MH, et al. Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* 2005; 24(1): 44-46. https://doi.org/10.1007/s10096-004-1271-9.
53. Sahr F, Ansumana R, Massaquoi TA, Idriss BR, Sesay FR, Lamin JM, et al. Evaluation of convalescent whole blood for treating Ebola Virus Disease in Freetown, Sierra Leone. *J Infect* 2017; 74(3): 302-309. https://doi.org/10.1016/j.jinf.2016.11.009.
54. Kilby JM, Eron JJ. Novel Therapies Based on Mechanisms of HIV-1 Cell Entry. *N Engl J Med* 2003; 348(22): 2228-2238. https://doi.org/10.1056/nejmra022812.
55. Hirsch MS, Kaplan JC, D. Aquila RT. Antiviral agents. In: Fields Virology. Vol 1. 3rd ed. Fields BN, Knipe DM, editors. New York: Lippincott-Raven. 1996. 431-436.
56. Zhao S, Tang L, Fan X, Chen L, Zhou R, Dai X. Comparison of the efficacy of lamivudine and telbivudine in the treatment of chronic hepatitis B: a systematic review. *Virol J* 2010; 7: 211. https://doi.org/10.1186/1743-422x-7-211.
57. Patick AK, Potts KE. Protease inhibitors as antiviral agents. *Clin Microbiol Rev* 1998; 11(4): 614-627. https://doi.org/10.1128/cmr.11.4.614.

© 2021, LLC Science and Innovations, Saratov, Russia

58. Katlama C, Murphy R. Emerging role of integrase inhibitors in the management of treatment-experienced patients with HIV infection. *Ther Clin Risk Manag* 2009; 5(2): 331-340. https://doi.org/10.2147/tcrm.s3137.
59. Jefferson TO, Demicheli V, Di Pietrantonj C, Jones M, Rivetti D. Neuraminidase inhibitors for preventing and treating influenza in healthy adults. *Cochrane Database Syst Rev* 2006; (3): CD001265. https://doi.org/10.1002/14651858.cd001265.pub2.
60. Kupferschmidt K. New drug forces flu virus into 'error catastrophe,' overwhelming it with mutations. *Science* 2019. https://www.science.org/content/article/new-drug-forces-flu-virus-error-catastrophe-overwhelming-it-mutations#2019.
61. Caly L, Druce JD, Catton MG, Jans DA, Wagstaff KM. The FDA-approved Drug Ivermectin inhibits the replication of SARS-CoV-2 in vitro. *Antiviral Res* 2020; 178: 104787. https://doi.org/10.1016/j.antiviral.2020.104787.
62. Tay MY, Fraser JE, Chan WK, Moreland NJ, Rathore AP, Wang C, et al. Nuclear localization of dengue virus (DENV) 1–4 non-structural protein 5; protection against all 4 DENV serotypes by the inhibitor Ivermectin. *Antiviral Res* 2013; 99(3): 301-306. https://doi.org/10.1016/j.antiviral.2013.06.002.
63. Wagstaff KM, Sivakumaran H, Heaton SM, Harrich D, Jans DA. Ivermectin is a specific inhibitor of importin α/β-mediated nuclear import able to inhibit replication of HIV-1 and dengue virus. *Biochem J* 2012; 443(3): 851-856. https://doi.org/10.1042/bj20120150.
64. Yang SNY, Atkinson SC, Wang C, Lee A, Bogoyevitch MA, Borg NA, et al. The broad spectrum antiviral ivermectin targets the host nuclear transport importin α/β1 heterodimer. *Antiviral Res* 2020; 177: 104760. https://doi.org/10.1016/j.antiviral.2020.104760.
65. Lundberg L, Pinkham C, Baer A, Amaya M, Narayanan A, Wagstaff KM, et al. Nuclear import and export inhibitors alter capsid protein distribution in mammalian cells and reduce Venezuelan Equine Encephalitis Virus replication. *Antiviral Res* 2013; 100(3): 662-672. https://doi.org/10.1016/j.antiviral.2013.10.004.
66. Götz V, Magar L, Dornfeld D, Giese S, Pohlmann A, Höper D, et al. Influenza A viruses escape from MxA restriction at the expense of efficient nuclear vRNP import. *Sci Rep* 2016; 6: 23138. https://doi.org/10.1038/srep23138.
67. Taylor P. Apeiron starts mid-stage trial of drug that blocks coronavirus. *Pharmaphorum* 2020. https://pharmaphorum.com/news/apeiron-starts-mid-stage-trial-of-drug-that-blocks-coronavirus.
68. Monteil V, Kwon H, Prado P, Hagelkrüys A, Wimmer RA, Stahl M, et al. Inhibition of SARS-CoV-2 infections in engineered human tissues using clinical-grade soluble human ACE2. *Cell* 2020; 181(4), 905-913.e7. https://doi.org/10.1016/j.cell.2020.04.004.
69. Lim J, Jeon S, Shin HY, Kim MJ, Seong YM, Lee WJ, et al. Case of the Index Patient Who Caused Tertiary Transmission of COVID-19 Infection in Korea: the Application of Lopinavir/Ritonavir for the Treatment of COVID-19 Infected Pneumonia Monitored by Quantitative RT-PCR. *J Korean Med Sci* 2020; 35(6): e79. https://doi.org/10.3346/jkms.2020.35.e79.
70. Liu X, Wang X-J. Potential inhibitors for 2019-nCoV coronavirus M protease from clinically approved medicines. *J Genet Genomics* 2020: 47(2): 119-121. https://doi.org/10.1016/j.jgg.2020.02.001.
71. Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al; Washington State 2019-nCoV Case Investigation Team. First Case of 2019 Novel Coronavirus in the United States. *N Engl J Med* 2020; 382(10): 929-936. https://doi.org/10.1056/nejmoa2001191.
72. Agostini ML, Andres EL, Sims AC, Graham RL, Sheahan TP, Lu X, et al. Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio* 2018; 9(2): e00221-18. https://doi.org/10.1128/mbio.00221-18.
73. Wang M, Cao R, Zhang L, Yang X, Liu J, Xu M, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res* 2020; 30(3): 269-271. https://doi.org/10.1038/s41422-020-0282-0.
74. Brown AJ, Won JJ, Graham RL, Dinnon KH 3rd, Sims AC, Feng JY, et al. Broad spectrum antiviral remdesivir inhibits human endemic and zoonotic deltacoronaviruses with a highly divergent RNA dependent RNA polymerase. *Antiviral Res* 2019; 169: 104541. https://doi.org/10.1016/j.antiviral.2019.104541.
75. Scavone C, Brusco S, Bertini M, Sportiello L, Rafaniello C, Zoccoli A, et al. Current pharmacological treatments for COVID-19: what's next? *Br J Pharmacol* 2020; 177(21): 4813-4824. https://doi.org/10.1111/bph.15072.
76. Niyomrattanakit P, Chen YL, Dong H, Yin Z, Qing M, Glickman JF, et al. Inhibition of Dengue Virus Polymerase by Blocking of the RNA Tunnel. *J Virol* 2010; 84(11): 5678-5686. https://doi.org/10.1128/jvi.02451-09.
77. Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): A Review and Perspective. *Int J Biol Sci* 2020; 16(10): 1708-1717. https://doi.org/10.7150/ijbs.45538.
78. Niyomrattanakit P, Chen YL, Dong H, Yin Z, Qing M, Glickman JF, et al. Inhibition of dengue virus polymerase by blocking of the RNA tunnel. *J Virol* 2010; 84(11): 5678-5686. https://doi.org/10.1128/JVI.02451-09.
79. Kaul TN, Middleton E Jr, Ogra PL. Antiviral effect of flavonoids on human viruses. *J Med Virol* 1985; 15(1): 71-79. https://doi.org/10.1002/jmv.1890150110.
80. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. *J Nutr Sci* 2016; 5: e47. https:// doi.org/10.1017/jns.2016.41.
81. Jo S, Kim S, Shin DH, Kim MS. Inhibition of SARS-CoV 3CL protease by flavonoids. *J Enzyme Inhib Med Chem* 2020; 35(1): 145-151. https://doi.org/10.1080/14756366.2019.1690480.
82. Khalifa I, Zhu W, Nafie MS, Dutta K, Li C. Anti-COVID-19 effects of ten structurally different hydrolysable tannins through binding 1 with the catalytic-closed sites of COVID-19 main protease: An in-silico approach. *Preprints* 2020: 2020030277 https://doi.org/10.20944/preprints202003.0277.v1.
83. Khaerunnisa S, Kurniawan H, Awaluddin R, Suhartati S, Soetjipto S. Potential Inhibitor of COVID-19 Main Protease (M^{pro}) From Several Medicinal Plant Compounds by Molecular Docking Study. *Preprints* 2020: 2020030226. https://doi.org/10.20944/preprints202003.0226.v1.
84. Nettleton JA, Harnack LJ, Scrafford CG, Mink PJ, Barraj LM, Jacobs DR Jr. Dietary flavonoids and flavonoid-rich foods are not associated with risk of type 2 diabetes in postmenopausal women. *J Nutr* 2006; 136(12): 3039-3045. https://doi.org/10.1093/jn/136.12.3039.
85. Kozłowska A, Szostak-Wegierek D. Flavonoids--food sources and health benefits. *Rocz Panstw Zakl Hig* 2014; 65(2): 79-85. https://pubmed.ncbi.nlm.nih.gov/25272572.
86. Smeriglio A, Barreca D, Bellocco E, Trombetta D. Proanthocyanidins and hydrolysable tannins: occurrence, dietary intake and pharmacological effects. *Br J Pharmacol* 2017; 174(11): 1244-1262. https://doi.org/10.1111/bph.13630.
87. Liu J, Cao R, Xu M, Wang X, Zhang H, Hu H, et al. Hydroxychloroquine, a less toxic derivative of chloroquine, is effective in inhibiting SARS-CoV-2 infection in vitro. *Cell Discov* 2020; 6: 16. https://doi.org/10.1038/s41421-020-0156-0.
88. Rolain JM, Colson P, Raoult D. Recycling of chloroquine and its hydroxyl analogue to face bacterial, fungal and viral infections in the 21st century. *Int J Antimicrob Agents* 2007; 30(4): 297-308. https://doi.org/10.1016/j.ijantimicag.2007.05.015.
89. Singh AK, Sidhu GS, Friedman RM, Maheshwari RK. Mechanism of Enhancement of the Antiviral Action of Interferon Against Herpes Simplex Virus-1 by Chloroquine. *J Interferon Cytokine Res* 1996; 16(9): 725-731. https://doi.org/10.1089/jir.1996.16.725.
90. Xue J, Moyer A, Peng B, Wu J, Hannafon BN, Ding WQ. Chloroquine is a zinc ionophore. *PLoS One* 2014; 9(10): e109180. https://doi.org/10.1371/journal.pone.0109180.

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91. Kaushik N, Subramani C, Anang S, Muthumohan R, Shalimar, Nayak B, et al. Zinc Salts Block Hepatitis E Virus Replication by Inhibiting the Activity of Viral RNA-Dependent RNA Polymerase. *J Virol* 2017; 91(21): e00754-17. https://doi.org/10.1128/jvi.00754-17.
92. liu W, Li H. COVID-19: Attacks the 1-Beta Chain of Hemoglobin and Captures the Porphyrin to Inhibit Human Heme Metabolism. ChemRxiv. Cambridge: Cambridge Open Engage. 2021. https://chemrxiv.org/engage/chemrxiv/article-details/6142e0d5b817b45fbb1e9b19.
93. Yao X, Ye F, Zhang M, Cui C, Huang B, Niu P, et al. In Vitro Antiviral Activity and Projection of Optimized Dosing Design of Hydroxychloroquine for the Treatment of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). *Clin Infect Dis* 2020; 71(15): 732-739. https://doi.org/10.1093/cid/ciaa237.
94. Weniger H. Review of side effects and toxicity of chloroquine. World Health Organization. 1979; 26 p. https://apps.who.int/iris/handle/10665/65773.
95. Wang G. Favipiravir Combined With Tocilizumab in the Treatment of Corona Virus Disease 2019. https://clinicaltrials.gov/ct2/show/NCT04310228?cond=Coronavirus&intr=Tocilizumab2020.
96. Kowalski RP, Romanowski EG, Yates KA, Mah FS. An Independent Evaluation of a Novel Peptide Mimetic, Brilacidin (PMX30063), for Ocular Anti-infective. *J Ocul Pharmacol Ther* 2016; 32(1): 23-27. https://doi.org/10.1089/jop.2015.0098.
97. Alkanfari I, Freeman KB, Roy S, Jahan T, Scott RW, Ali H. Small-Molecule Host-Defense Peptide Mimetic Antibacterial and Antifungal Agents Activate Human and Mouse Mast Cells via Mas-Related GPCRs. *Cells* 2019; 8(4): 311. https://doi.org/10.3390/cells8040311.
98. Neher RA, Dyrdak R, Druelle V, Hodcroft EB, Albert J. Potential impact of seasonal forcing on a SARS-CoV-2 pandemic. *Swiss Med Wkly* 2020; 150: w20224. https://doi.org/10.4414/smw.2020.20224.
99. Sun Z, Thilakavathy K, Kumar SS, He G, Liu SV. Potential Factors Influencing Repeated SARS Outbreaks in China. *Int J Environ Res Public Health* 2020; 17(5): 1633. https://doi.org/10.3390/ijerph17051633.

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