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A Recent Achievement in the Discovery and Development of Vaccines and Therapeutic Agents in the Race for COVID-19 Protection and Treatment

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Abstract

Currently, the coronavirus disease 2019 (COVID-19) is a big challenge to the healthcare systems in the world. Several researchers in the world have immediately carried out clinical investigations for the discovery of vaccines and drugs. Different studies have shown that antiviral measures including small bioactive compounds targeting multifaceted molecular communications take in COVID-19 infection. The drug development archived in this review emphasizes mainly on drugs that are effective for the Management of MERS-CoV, SARS-CoV, and other RNA viruses. The investigation of therapeutic agents for COVID-19 includes anti-inflammatory agents, antibodies, and nucleic acid-based treatments targeting virus gene expression as well as different sorts of vaccines. Numerous patents revealed techniques of these biologics with the potential for treating and preventing coronavirus infections, which may apply to COVID-19. Phase 3 clinical trials such as Sputnik V, AZD1222, mRNA-1273, BNT162b2, Ad5-nCoV, Anti-COVID antibodies, Kevzara; Actemra, Jakafi; Baricitinib, and some others were undergoing in the race for Covid-19 treatment. However, there's still a lack of a review on vaccines and drugs for COVID-19 management. Therefore, this review summarizes different studies that are ongoing in the race for Covid-19 protection and treatment.

Keywords

coronavirus, antiviral drugs, vaccines

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Background

Coronavirus is a single-stranded RNA virus caused by severe acute respiratory syndrome coronavirus 2.[1] Coronavirus can be classified into four groups such as delta, gamma, beta, and alpha. The coronavirus group comprises SARS-CoV-2, MERS-CoV, and SARS-CoV. Both middle East respiratory syndrome and severe acute respiratory syndrome viruses affects the LRS leading to viral pneumonia and as well it affects the CNS, heart, GIT, liver, and kidney led to multiple organ damage. Similarly, SARS-CoV-2 can attack different body parts such as liver, CNS, kidney, GIT, lung, and heart.[2, 3] Recent findings revealed that severe acute respiratory syndrome 2 is more infectious than severe acute respiratory syndrome.[4] COVID-19 have been reported to cause different sign and symptoms such as respiratory distress, pneumonia, fever, cough, and death.[5, 6] COVID-19, being a pandemic infectious disease, could be a genuine risk to human wellbeing.[7-9] According to the most recent data, up to September 21, 2020, the number of confirmed cases in the world reached 31,240,347, of which 965,071 were dead and 22,835,563 were recovered.

Based on the genome sequence, several types of research have been done on existing agents as well as on new biological molecules in the race for COVID-19 protection and treatment.[10] Supportive care and reducing symptoms are the most commonly used modalities in the management of COVID-19.[11] Agents in the clinical trial can act by numerous possible

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Table 1. Existing Drugs in the Race for Covid-19 Treatment.

Name of drug candidates	Target	Possible mechanism of action for COVID-19 infection	Disease indication	Ref
Baricitinib	JAK-kinase	A JAK inhibitor	Used for the treatment of rheumatoid arthritis	14
Lopinavir	3CLpro/PLpro (Viral proteases)	Protease inhibitors	For HIV infection	15
Darunavir			Used for HIV viral infections	16
Favipiravir	RdRp	A purine nucleoside (alternate substrate)	Used for the treatment of influenza	17, 18
Remdesivir	RNA dependent RNA polymerase, and Nascent viral RNA	Block viral nucleotide synthesis	Used for the management of Ebola virus infection	15, 17
Ribavirin			Hepatitis C, viral hemorrhagic fevers and RSV infection,	17, 19
Galidesivir			Ebola virus, Hepatitis C, and Marburg virus	20
Salt form of galidesivir (BCX-4430)			Ebola virus, Marburg virus, and hepatitis C,	20
Arbidol	S protein/ ACE2d	Interrupt binding of viral envelope protein to the host cells and avert viral entry to the target cell	Influenza	10, 21
Nitazoxanide		Prevent viral protein expression	Various helminthic, Protozoal, and viral infection	17
Ivermectin	IMPα/β1 heterodimer	Dissociate the preformed IMPα/β1 heterodimer	Anti-parasitic use	.22
Toremifene	Disturbs proteins related to HCoV, (EIF3F, HNRNPA1, NPM1, EIF3E, EIF3I, and RPL19,)	Averts fusion b/w the viral and endosomal membrane	For the management of advanced breast cancer	23, 24

mechanisms of actions such as targeting vital enzymes (helicase, proteases, and other viral proteins), targeting host cell proteins (protease, endocytosis proteins, S1 RBD, siRNA, neutralizing antibodies, antiviral peptide targeting, anti-sense RNA, and receptors), and targeting several molecules which are attached to the virus.[10,12,13] **Table 1** summarizes different targets, indications, and possible mechanisms of actions of therapeutic agents for COVID-19 protection and treatment. The current review offers a solid rational base for the continuing discovery of vaccines and drugs in the race for Covid-19 treatment.

Remdesivir

Remdesivir is a prodrug with a broad-spectrum antiviral effect against RNA viruses and its structure is similar to adenosine. A recent study has revealed that remdesivir is a potential agent for the treatment of COVID-19.[25] Remdesivir produces its effect by inhibiting the RNA polymerase and integrating it into nascent viral RNA. This leads to two important outcomes such as termination of the viral RNA chain and subsequently inhibits the viral genome replication. The previous finding revealed that remdesivir was not effective for the treatment of Ebola. However, it provides the safety of remdesivir in humans, which permitted the remdesivir clinical trial in the treatment and protection of COVID-19 without delay.[26] According to *in vivo* study in mice, treatment of MERS-CoV infected mice with remdesivir revealed a reduction in lung viral load, recover lung function, and reduce lung tissue damage.[15] Likewise, both *in vitro* and *in vivo* studies showed a promising effect of remdesivir in the management of MERS-CoV and SARS-CoV.[27] Currently, remdesivir showed significant antiviral activity against SARS-CoV-2 in the *in-vitro* model.[16]

Favipiravir

Favipiravir is antiviral that inhibits the RNA polymerase (RNA-dependent) through bear a resemblance in structure to the guanine which is an endogenous compound.[28] Thus, favipiravir is capable of reducing viral replication through competitive inhibition. Favipiravir is an approved drug for the treatment of influenza. However, there are no enough clinical studies that support the use of favipiravir for the management of severe acute respiratory syndrome virus 2. Though, patients have been conscripted to assess the effectiveness of interferon-α and favipiravir combination based on the predictable synergistic activities in immune augmentation and viral inhibition. Certainly, favipiravir was the first accepted medication for the treatment of COVID-19 in china, since favipiravir showed promising effects against COVID-19 with minimal side effects.[29]

Ivermectin

Ivermectin is anthelmintic which was approved by the FDA, which also has an antiviral activity for both dengue virus and human immunodeficiency virus. Its antiviral activity is through blockage of IMPα/β1 heterodimer, which is accountable for the nuclear transport of viral protein cargos.[22] Targeting the viral nuclear transport process might be a possible treatment modality for RNA viruses including COVID-19, since the viral nuclear transport process plays a significant role in the embarrassment of the host's antiviral response and enhancing the viral replication cycle.[22] *In vivo* investigation (infection with SARS-CoV-2) has confirmed the antiviral effect of Ivermectin by reducing the viral RNA up to 5,000-fold.[29,30]

Lopinavir/Ritonavir, Ribavirin, Oseltamivir

Medications that are effective against different RNA viruses are being candidates for the management of SARS-CoV-2. As far as this, the most familiar medications tried in patients infected with SARS-CoV-2 are IFN, lopinavir/ritonavir, ribavirin, and some others.[31] These antivirals, irrespective of their antiviral effect reported *in vitro* model, the clinical activity wasn't unswerving,[27] similar finding showed that ribavirin didn't prolong the survival of patients infected with COVID-19 infection.[32] However, the coformulation of lopinavir, ritonavir, and ribavirin showed a promising effect in patients infected with COVID-19 infection.[33] Previous studies revealed that lopinavir and ritonavir are capable of inhibiting the 3CL1pro protease of COVID-19 viral infection.[33,34] Moreover, numerous in vivo and invitro studies revealed the effectiveness of these antivirals for the treatment of MERS and SARS viruses.[16,35] Recently, the coformulation of Lopinavir/ritonavir was tested in patients infected with COVID-19 infection, though, it exhibited a slight advantage for improving the clinical outcome of patients infected with COVID-19.[35,36]

Research conducted in China revealed that following administration of oseltamivir did not show improvement in the viral disease (SARS-CoV-2).[5] Recently, oseltamivir alone and in together with other antiviral medications have been investigated in treating SARS-CoV-2.[37]

Selective Estrogen Receptor Modulators

Gene expression of estrogen receptor exhibited a significant effect in hindering the viral replication.[38] Among the possible mechanism for inhibition of viral replication, the non-classical pathways linked with estrogen receptors take the key role.[38] Selective estrogen receptor modulators hinder viral replication at various steps including post-viral entry and fusion. The antiviral action of selective estrogen receptor modulators is possible in the time off detectable estrogen receptor gene expression.[39]

Toremifene is NSERM, *in vitro* findings revealed it's antiviral effect against Ebola, SARS-CoV, and MERS-CoV viruses.[39,40] Toremifene can hinder the viral replications through averts the fusion between the endosomal membrane and the viral (disrupting the virus membrane glycoprotein).[41] Toremifene highly affects numerous main host proteins linked with HCoV, for instance, EIF3I, RPL19, EIF3F, NPM1, EIF3E, and HNRNPA1,[23,24] Equilin is an estrogenic steroid that can avert the entry of HIV and the Ebola virus.[39] Currently, both equilin and toremifene are on investigation for the management of SARS-CoV-2.[42]

Emodin is an anthraquinone derivative obtained from the root extract of *R. tanguticum*. Emodin has shown antiviral activity through inhibition of SARSCoV-associated 3a protein,[43] and blocked the communication between ACE2 and SARS-CoV spike protein.[44] Thus, a combination of emodin and toremifene could be a potential therapeutic approach for the management of SARS-CoV-2.[42]

Angiotensin Receptor Blockers

Angiotensin receptor blockers play a significant role in the management of viral infection, including SARS-CoV.[45,46] Irbesartan is an angiotensin receptor blocker, which was approved by the FDA for the management of diabetic nephropathy, and hypertension. SLC10A1 is a target for irbesartan, this encodes the NTCP (sodium/bile acid cotransporter) protein which is the preS1-specific receptor for the hepatitis delta virus and hepatitis B virus. Thus, Angiotensin receptor blocker (Irbesartan) is capable of obstructing sodium/bile acid cotransporter, leading to viral entry blockage.[47,48] Angiotensin receptor blockers such as frovatriptan, zolmitriptan, and eletriptan, their targets are mainly linked with HCoV-associated host proteins.[42]

Angiotensin-Converting Enzyme 2 Receptor

Angiotensin-converting enzyme2 receptor is considered as an essential target for the treatment of COVID-19. Angiotensin receptor blockers and angiotensin-converting enzyme inhibitors have shown a negative effect on people infected with SARS-CoV-2.[49,50] It is considered that SARS-CoV and SARSCoV-2 bind to human cells by communicating with angiotensin-converting enzyme-2 receptors.[51] *In vivo* studies have shown that long-lasting management with ACE-2 type 1 receptor antagonists such as olmesartan, lisinopril, and losartan enables renal and cardiac ACE-2 receptors gene expression.[52] However, following the entry of SARS-CoV into respiratory epithelial cells inhibits the effect of ACE-2 receptors thereby increases the levels of angiotensin 2. This leading to severe lung impairment.[53] Though, Treatment with Angiotensin receptor blocker and angiotensin-converting enzyme inhibitors may be crucial for the survival of a patient infected with COVID-19 through attenuating the cardiac stress and reduce profibrotic and vasoconstriction activity of angiotensin 2 in alveolar capillaries.[54]

Immunosuppressant or Antineoplastic Agents

According to previous findings, rapamycin complex 1 plays a significant role in regulating the replications of different

viruses such as coronavirus, Andes orthohantavirus, and some others.[55,56] The recent finding revealed that sirolimus decreases the MERS-CoV infection by more than sixty percent.[57] Furthermore, the use of sirolimus significantly improves the disease progressions in patients with acute respiratory failure and H1N1 pneumonia.[58]

Mercaptopurine, an antimetabolite, antineoplastic agent that impedes DNA and RNA synthesis; acts as a false metabolite and is incorporated into DNA and RNA, ultimately constraining their synthesis; specifically for the S phase of the cell cycle.[59] In the previous study, mercaptopurine plays a significant role in interferon stimulation and viral maturation by targeting papain-like protease. Hence, mercaptopurine exhibited a selective inhibitor of SARS-CoV and MERS-CoV.[60] In addition, mercaptopurine can target numerous host proteins such as NCL, PABPC1, NPM1, and JUN.[61]

Anti-Inflammatory Agents

A previous study has been revealed the significant role of inflammatory pathways in viral infections.[62] Recently, melatonin is being a potential agent in the treatment of viral infections.[63,64] Oxidative stress is usually increased secondary to viral infections through immune-inflammatory damage, and lead to impairments in multiple organs.[65] As melatonin exhibited a significant antioxidant activity, it can recover the immune system, eradicate the viral infection and finally, lengthen the survival time of the patients.[66] Eplerenone is a selective aldosterone blocker (potassium-sparing diuretic) that possess comparable anti-inflammatory activity with melatonin through suppressing fibrosis and hindering mast-cell-derived proteinases. In vivo study has revealed the antiviral activity of eplerenone in encephalomyocarditis virus-infected mice.[67]

Sirolimus plus Dactinomycin

Sirolimus is an immunosuppressive agent that constrains the T-lymphocytes proliferation and activation secondary to cytokine and antigenic stimulation and hinders antibody production. Agents that can inhibit rapamycin complex 1 are capable of inhibiting virion release and gene expressions.[58,68] Dactinomycin is an antineoplastic that binds to the guanine portion of DNA intercalating between guanine and cytosine base pairs inhibiting DNA and RNA synthesis and protein synthesis. According to a recent finding, the growth of feline enteric CoV is significantly inhibited by dactinomycin.[69] Studies revealed that both dactinomycin and sirolimus synergistically target HCoV-associated host protein subnetwork through a different mechanism such as by inhibiting the mammalian target of rapamycin, DNA topoisomerase 2-alpha, and DNA topoisomerase 2-beta.[42]

Teicoplanin

Recently, Teicoplanin showed significant activity against SARS-CoV in the *in vitro* model.[70] Teicoplanin has been effective against numerous virus types including SARS-CoV, MERS-CoV, flavivirus, HIV, Ebola, Ebola, and influenza virus.[71,72] Teicoplanin inhibits the virus replication cycle and the release of viral RNA by acting on the early step of the viral life cycle (constraining the low pH cleavage of the viral spike protein). This activity indicates the target sequence that serves as a cleavage site for cathepsin L is conserved among SARS-CoV spike protein.[70] 1.66 μM was the IC_{50} value of teicoplanin that was required to inhibit fifty percent of the virus in the *in vitro* model, which was lesser than the concentration reached in human serum (8.78 μM).[70] Thus, teicoplanin could be used as a potential therapeutic agent for the management of COVID-19

Azithromycin

Azithromycin is a macrolide that disrupts RNA-dependent protein synthesis and blocks transpeptidation by binding to 50 s ribosomal subunit and used to treat different bacterial infections such as bacterial conjunctivitis, community-acquired pneumonia, infective endocarditis, mild to moderate respiratory infection, skin and soft tissue infections, bacterial exacerbation of COPD, urethritis, trachomatis, and some others.[73,74] Furthermore, azithromycin also effective against different viruses such as Ebola and Zika viruses in the *in vitro* model.[75] Recently, several clinical trials are ongoing to show the effect of azithromycin against COVID-19.[76,77]

Dexamethasone

Dexamethasone is a steroid that regulates protein synthesis and depresses the migration of reverses capillary permeability, leukocytes, lysosomal stabilization, and fibroblasts at the cellular level to control and avoid inflammation.[78] A study conducted in UK showed that dexamethasone is effectively decreased deaths by 1/3 in patients infected with COVID-19.[79] Similarly, a study conducted in hospitalized patients revealed that the mortality rate of COVID-19 infected hospitalized patients was significantly ($p<0.001$) varied reliant on respiratory support. Dexamethasone showed a reduction in deaths by 1/3 in patients getting invasive mechanical ventilation ($p<0.001$, 29.00% vs. 40.70%), by 1/5 in patients getting oxygen without invasive mechanical ventilation ($p=0.002$, 21.50% vs. 25.00%). However, dexamethasone didn't decrease mortality in patients not getting respiratory support ($p=0.14$, 17.00% vs. 13.20%).[80]

Current Clinical Trials advance in the Race for Covid-19 Protection and Treatment

There is an urgent necessity to develop an effective therapy for severe COVID-19 treatment that improves mortality.[76] Mostly, vaccines and drugs are required years of testing and investigation before attainment in the health facilities, nevertheless, researchers are trying to develop effective and safe therapeutic agents for coronavirus protection and treatment. Several companies are testing about 89 preclinical vaccines in animals and 36 clinical trials vaccines on humans.[81] Development and

Table 2. Current Clinical Trials Advance in the Race for Covid-19 Protection and Treatment.

Company	Name of vaccine and drug	Type	Descriptions	Progress
Moscow's Gamaleya institute,	Gam-COVID-Vac (Sputnik V)	Vaccine	Gam-COVID-Vac is an adenoviral-based vaccine that displays the SARS-CoV-2 glycoprotein S molecule on its surface. Upon vaccination, the individual will generate an immune response against the glycoprotein S molecule and thus will have endogenous antibodies that will protect them from infection with SARS-CoV-2.	Phase 3
University of Oxford, AstraZeneca, Bill and Melinda Gates Foundation, Iqvia Pty Ltd	AZD1222 (ChAdOx1 nCoV-19)	vaccine	AZD1222 (formerly ChAdOx1 nCoV-19) is an attenuated adenovirus that displays the SARS-CoV-2 spike protein on its surface. Since the virus is attenuated, it is safe to inject it into humans. Upon vaccination, the individual will generate an immune response against the spike protein and thus will have endogenous antibodies that will protect them from infection with SARS-CoV-2.	Phase 3
Moderna Inc.	mRNA-1273	Vaccine	Moderna's mRNA-1273 uses messenger RNA to prompt the body to make a key protein.	Phase 3
Bio N Tech SE, Pfizer Inc., Shanghai Fosun Pharmaceutical Group Co.	BNT162b2	Vaccine	BioNTech's BNT162 program is a messenger RNA vaccine platform that the German company is developing with Pfizer.	Phase 3
Can Sino Biologics Inc.	Ad5-nCoV	Vaccine	The Ad5-nCov vaccine is generated by incorporating a full-length SARS-CoV-2 spike protein into a replication-defective Adenovirus Type 5 vector. It is then injected intramuscularly into patients and antibodies will be generated against the SARS-CoV-2 spike protein.	Phase 3
Sinovac Biotech Ltd	CoronaVac	Vaccine	The vaccine uses an inactivated virus, which can help the body develop antibodies to the pathogen without risking infection.	Phase 3
Wuhan Institute of Biological Products, Sinopharm, China National Biotec Group Company Limited, G42 Healthcare company, Abu Dhabi Health Services Company	Unnamed Inactive Vaccine	vaccine	Inactive viral vaccines are created by propagating viruses in cell culture (such as in Vero cells) followed by inactivation using a chemical reagent (such as beta-propiolactone). Upon vaccination, this allows the body to generate a diverse immune response against numerous viral antigens while having no threat of actually being infected because the virus is inactive.	Phase 3
Gilead Sciences Inc.	Remdesivir	Antiviral	Remdesivir targets genetic material named RNA and is intended to stop SARS-CoV-2 from replicating.	Authorized
AstraZeneca Plc, Eli Lilly & Co., Regeneron Pharmaceuticals Inc., GlaxoSmithKline Plc, Vir Biotechnology Inc., and others	Anti-Covid Antibodies	Antiviral	Antibodies revealed by drug makers can copycat an immune-system response to the virus.	Phase 3
hejiang Hisun Pharmaceutical Co.	Favipiravir	Antiviral	Favipiravir is a flu drug that targets viral RNA to halt the spread of the virus.	Authorized

(continued)

Table 2. (continued)

Company	Name of vaccine and drug	Type	Descriptions	Progress
Regeneron Pharmaceuticals Inc. and Sanofi	Kevzara; Actemra	DMARD	These drugs are used for the treatment of rheumatoid arthritis by targeting a pathway known as interleukin-6 or IL-6. These drugs could support patients with Covid-19 from respiratory distress.	Phase 3
Incyte Corp., Novartis AG; Eli Lilly & Co. Drug	Jakafi; Baricitinib	JAK inhibitors	JAK inhibitors that target inflammation and block cellular proliferation. Baricitinib, advertised by the brand-name Olumiant.	Phase 3
Inovio Pharmaceuticals Inc.	NO-4800	Vaccine	Novio's experimental vaccine used DNA to trigger the immune system of the patients.	Phase 2
Novavax Inc.	NVX-CoV2373	Vaccine	Novavax's vaccine comprises copied spike proteins.	Phase 2
Johnson & Johnson	Multiple unnamed candidates	Vaccine	J&J is employed on an unnamed adenovirus-based vaccine along with 2 backups.	Phase 2
Arcturus Therapeutics Holdings Inc., Duke-NUS	LUNAR-COV19	Vaccine	Duke-NUS and Arcturus are emerging a single-dose messenger RNA vaccine.	Phase 2
Merck & Co.	V591, V590	Vaccine	Merck's 2 vaccine candidates employ prevailing technology behind a measles virus vector platform.	Phase 1
Sichuan Clover Biopharmaceuticals Inc.,	CB-2019	Vaccine	Produces proteins similar to the virus's spike protein in mammalian cell culture and vaccinates them into muscles to activate an immune response.	Phase 1
AstraZeneca Plc	AZD7442	Antiviral	AstraZeneca's antibody cocktail comprises of 2 antibodies.	Phase 1

discovery of safe and effective therapy for severe COVID-19 treatment and protection require investment and commitment.[82] Table 2 provides a summary of current clinical trials advance in the race for COVID-19.

Traditional Herbal Medicines

The use of traditional medicines for the management of infectious disease has increased because of several reasons including the participation of different concerning bodies in the production and investigations of herbal-based medicines.[83,84] Recently, several studies were conducted in elucidating the medicinal values of herbal medicines for the management of COVID-19.[85] Previously, plant-derived herbal medicines have been employed for the management of different outbreaks including H1N1 influenza and SARS.[86,87] Currently, several countries such as South Korea and China have agreed on guidelines on the use of traditional medicine for the management of COVID-19.[88] In China, eighty-five percent of COVID-19 infected patients were received traditional medicine.[85] A recent study showed that traditional medicines are supposed to competitively targets angiotensin-converting enzyme2 receptor similar to SARS-CoV- 2 and SARS-CoV. This revealed the possibilities of traditional medicine for the management of SARS-CoV-2.[89] Among the commonly used plant-based traditional medicine in China: *Atractylodis Rhizoma, Saposhnikoviae divaricata, Astragalus membranaceus, Cyrtomium fortunei J. Sm, Glycyrrhiza uralensis, Lonicerae Japonicae Flos, Radix platycodonis, Fructus forsythia, Agastache rugosa, and Rhizoma Atractylodis Macrocephalae* are used for the management of COVID-19.[90] Besides, Re Du Ning and Shen Fu Injection are herbal-based traditional medicine that possessed significant immunosuppressive activity and thus they can reduce the level of different type of cytokines such as IL-6, IL-1β, IL-8, TNF-α, IL-10, and some other cytokines, leading to the prevention of acute lung injury and lung inflammation.[91,92]

Conclusion and Recommendation

Investigators are searching for a safe and effective vaccine and therapeutics agents for the management of the fatal COVID-19 infection. As is evident from this review, different drugs are an efficient therapeutic option intervention against COVID-19. The drug-repurposing trial summarized in the present review mainly concentrated on agents presently identified to be effective against RNA viruses such as influenza, SARS-CoV, Ebola, MERS-CoV, and HCV as well as Ivermectin, Anti-inflammatory, and Anticancer medications. The possible effect of biologics for management of COVID-19 is auspicious and comprises numerous options including vectored antibodies, nucleic acid-based therapies targeting virus gene expression, bioengineered, cytokines, and several kinds of vaccines and existing drugs.

In the present review, studies on the discovery of vaccines and drugs in the race for COVID-19 treatment were summarized. Most of these agents were previously approved and used for the prevention and treatment of various diseases other than COVID-19 infection. These agents could be classified into wide groups, those based on immunotherapy approaches and those that target the virus replication cycle. On the other hand, therapeutic agents and vaccines that may explicitly target SARS-CoV-2 are also being investigated. The information provided in the present review offers a strong intellectual base for the ongoing discovery of vaccines and drugs in the race for Covid-19 treatment. Further researches are needed to investigate the transmission dynamics, replication, and pathogenesis in humans. This could support the researchers to develop and assess potential therapeutic strategies against Covid-19 infection.

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References

1. Anthony SJ, Johnson CK, Greig DJ, et al. Global patterns in coronavirus diversity. *Virus Evol*. 2017;3(1):vex012.
2. Su S, Wong G, Shi W, et al. Epidemiology, genetic recombination, and pathogenesis of coronaviruses. *Trends Microbiol*. 2016; 24(6):490–502.
3. Zhu N, Zhang D, Wang W, et al. A novel coronavirus from patients with pneumonia in China, 2019. *N E J Med*. 2020;382 (8):727–733.
4. Tang B, Bragazzi NL, Li Q, Tang S, Xiao Y, Wu J. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov). *Infect Dis Model*. 2020;5:248–255.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama*. 2020;323(11):1061–1069.
6. Waters E, Doyle J. Systematic reviews of public health in developing countries are in train. *Bmj*. 2004;328(7439):585.
7. The LID. Challenges of coronavirus disease 2019. *Lancet Infect Dis*. 2020;20(3):261.
8. Burki T. Outbreak of coronavirus disease 2019. *Lancet Infect Dis*. 2020;20(3):292–293.
9. Vickers NJ. Animal communication: when I'm calling you, will you answer too? *Curr Biol*. 2017;27(14): R713–R5.
10. Liu C, Zhou Q, Li Y, et al. *Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases*. ACS Publications; 2020.
11. Van Kampen KR, Shi Z, Gao P, et al. Safety and immunogenicity of adenovirus-vectored nasal and epicutaneous influenza vaccines in humans. *Vaccine*. 2005;23(8):1029–1036.
12. Lu H. Drug treatment options for the 2019-new coronavirus (2019-nCoV). *Biosci Trends*. 2020. 2020;14(1):69–71.

13. Kumar V, Jung YS, Liang PH. Anti-SARS coronavirus agents: a patent review (2008–present). *Expert Opin Ther Pat*. 2013;23 (10):1337–1348.
14. Richardson P, Griffin I, Tucker C, et al. Baricitinib as potential treatment for 2019-nCoV acute respiratory disease. *The Lancet*. 2020;395(10223):e30–e1.
15. Sheahan TP, Sims AC, Leist SR, et al. Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun*. 2020;11(1): 1–14.
16. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30(3):269–271.
17. Guo D. Old weapon for new enemy: drug repurposing for treatment of newly emerging viral diseases. *Virol Sin*. 2020;35(3): 253–255.
18. Mifsud EJ, Hayden FG, Hurt AC. Antivirals targeting the polymerase complex of influenza viruses. *Antiviral Res*. 2019;169: 104545.
19. Morse JS, Lalonde T, Xu S, Liu W. Learning from the past: possible urgent prevention and treatment options for severe acute respiratory infections caused by 2019-nCoV. *Chembiochem*. 2020;21(5):730–738.
20. Warren TK, Wells J, Panchal RG, et al. Protection against filovirus diseases by a novel broad-spectrum nucleoside analogue BCX4430. *Nature*. 2014;508(7496):402–405.
21. Qiu R, Wei X, Zhao M, et al. Outcome reporting from protocols of clinical trials of Coronavirus Disease 2019 (COVID-19): a review. *medRxiv*. 2020.
22. 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.
23. Emmott E, Munday D, Bickerton E, et al. The cellular interactome of the coronavirus infectious bronchitis virus nucleocapsid protein and functional implications for virus biology. *J Virol*. 2013;87(17):9486–9500.
24. V'kovski P, Gerber M, Kelly J, et al. Determination of host proteins composing the microenvironment of coronavirus replicase complexes by proximity-labeling. *Elife*. 2019;8:e42037.
25. Siegel D, Hui HC, Doerffler E, et al. *Discovery and Synthesis of a Phosphoramidate Prodrug of a Pyrrolo [2, 1-f][triazin-4-amino] Adenine C-Nucleoside (GS-5734) for the Treatment of Ebola and Emerging Viruses*. ACS Publications; 2017.
26. Mulangu S, Dodd LE, Davey Jr RT, et al. A randomized, controlled trial of Ebola virus disease therapeutics. *N E J Med*. 2019; 381(24):2293–2303.
27. Sheahan TP, Sims AC, Graham RL, et al. Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Sci Transl Med*. 2017;9(396):eaal3653.
28. Furuta Y, Komeno T, Nakamura T. Favipiravir (T-705), a broad spectrum inhibitor of viral RNA polymerase. *Proceed Jpn Acad Ser B*. 2017;93(7):449–463.
29. Tu YF, Chien CS, Yarmishyn AA, et al. A review of SARS-CoV-2 and the ongoing clinical trials. *Int J Mol Sci*. 2020;21(7):2657..
30. 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.
31. Omrani AS, Saad MM, Baig K, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis*. 2014;14 (11):1090–1095.
32. Gross AE, Bryson ML. Oral ribavirin for the treatment of noninfluenza respiratory viral infections: a systematic review. *Ann Pharmacother*. 2015;49(10):1125–1135.
33. Chu C, Cheng V, Hung I, et al. Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax*. 2004;59(3):252–256.
34. Que T, Wong V, Yuen K. Treatment of severe acute respiratory syndrome with lopinavir/ritonavir: a multicentre retrospective matched cohort study. *Hong Kong Med J*. 2003;9(6):399–406.
35. Agostini ML, Andres EL, Sims AC, 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.
36. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe Covid-19. *N E J Med*. 2020;382 (19):1787–1799.
37. Rosa SGV, Santos WC. Clinical trials on drug repositioning for COVID-19 treatment. *Revista Panamericana de Salud Pública*. 2020;44:e40.
38. Lasso G, Mayer SV, Winkelmann ER, et al. A structure-informed atlas of human-virus interactions. *Cell*. 2019;178(6): 1526–1541. e16.
39. Johansen LM, Brannan JM, Delos SE, et al. FDA-approved selective estrogen receptor modulators inhibit Ebola virus infection. *Sci Transl Med*. 2013;5(190):190ra79–ra79.
40. Dyall J, Coleman CM, Hart BJ, et al. Repurposing of clinically developed drugs for treatment of Middle East respiratory syndrome coronavirus infection. *Antimicrobial Agents Chemother*. 2014;58(8):4885–4893.
41. Zhao Y, Ren J, Harlos K, et al. Toremifene interacts with and destabilizes the Ebola virus glycoprotein. *Nature*. 2016;535 (7610):169–172.
42. Zhou Y, Hou Y, Shen J, Huang Y, Martin W, Cheng F. Network-based drug repurposing for novel coronavirus 2019-nCoV/SARS-CoV-2. *Cell Discov*. 2020;6(1):1–18.
43. Schwarz S, Wang K, Yu W, Sun B, Schwarz W. Emodin inhibits current through SARS-associated coronavirus 3a protein. *Antiviral Res*. 2011;90(1):64–69.
44. Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Res*. 2007;74(2):92–101.
45. Moskowitz DW, Johnson FE. The central role of angiotensin I-converting enzyme in vertebrate pathophysiology. *Curr Top Med Chem*. 2004;4(13):1431–1452.
46. Erlandson KM, Kitch D, Wester CW, et al. The impact of statin and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy on cognitive function in adults with human immunodeficiency virus infection. *Clin Infect Dis*. 2017;65(12): 2042–2049.

47. Wang XJ, Hu W, Zhang TY, Mao YY, Liu NN, Wang SQ. Irbesartan, an FDA approved drug for hypertension and diabetic nephropathy, is a potent inhibitor for hepatitis B virus entry by disturbing Na+-dependent taurocholate cotransporting polypeptide activity. *Antiviral Res*. 2015;120:140–146.
48. Ko C, Park WJ, Park S, Kim S, Windisch MP, Ryu WS. The FDA-approved drug irbesartan inhibits HBV-infection in HepG2 cells stably expressing sodium taurocholate co-transporting polypeptide. *Antivir Ther*. 2015;20(8):835–842.
49. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475–481.
50. Fang L, Karakiulakis G, Roth M. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? *Lancet Respir Med*. 2020;8(4):e21.
51. Wan Y, Shang J, Graham R, Baric RS, Li F. Receptor recognition by the novel coronavirus from Wuhan: an analysis based on decade-long structural studies of SARS coronavirus. *J Virol*. 2020;94(7):e00127–20.
52. Ferrario CM, Jessup J, Chappell MC, et al. Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*. 2005; 111(20):2605–2610.
53. Gurwitz D. Angiotensin receptor blockers as tentative SARS-CoV-2 therapeutics. *Drug Dev Res*. 2020;81(5):537–540.
54. Wu R, Wang L, Kuo HCD, et al. An update on current therapeutic drugs treating COVID-19. *Curr Pharmacol Rep*. 2020;11:1–15.
55. McNulty S, Flint M, Nichol ST, Spiropoulou CF. Host mTORC1 signaling regulates andes virus replication. *J Virol*. 2013;87(2): 912–922.
56. Stöhr S, Costa R, Sandmann L, et al. Host cell mTORC1 is required for HCV RNA replication. *Gut*. 2016;65(12): 2017–2028.
57. Dyall J, Gross R, Kindrachuk J, et al. Middle East respiratory syndrome and severe acute respiratory syndrome: current therapeutic options and potential targets for novel therapies. *Drugs*. 2017;77(18):1935–1966.
58. Wang CH, Chung FT, Lin SM, et al. Adjuvant treatment with a mammalian target of rapamycin inhibitor, sirolimus, and steroids improves outcomes in patients with severe H1N1 pneumonia and acute respiratory failure. *Crit Care Med*. 2014;42(2):313–321.
59. Karran P, Attard N. Thiopurines in current medical practice: molecular mechanisms and contributions to therapy-related cancer. *Nat Rev Cancer*. 2008;8(1):24–36.
60. Cheng KW, Cheng SC, Chen WY, et al. Thiopurine analogs and mycophenolic acid synergistically inhibit the papain-like protease of Middle East respiratory syndrome coronavirus. *Antiviral Res*. 2015;115:9–16.
61. Chen H, Wurm T, Britton P, Brooks G, Hiscox JA. Interaction of the coronavirus nucleoprotein with nucleolar antigens and the host cell. *J Virol*. 2002;76(10):5233–5250.
62. Rainsford K. Influenza ("Bird Flu"), inflammation and anti-inflammatory/analgesic drugs. *Inflammopharmacology*. 2006;14 (1-2):2–9.
63. Silvestri M, Rossi GA. Melatonin: its possible role in the management of viral infections-a brief review. *Ital J Pediatr*. 2013;39 (1):61.
64. Srinivasan V, Mohamed M, Kato H. Melatonin in bacterial and viral infections with focus on sepsis: a review. *Recent Pat Endocr Metab Immune Drug Discov*. 2012;6(1):30–39.
65. Tan DX, Korkmaz A, Reiter RJ, Manchester LC. Ebola virus disease: potential use of melatonin as a treatment. *J Pineal Res*. 2014;57(4):381–384.
66. Galano A, Tan DX, Reiter RJ. On the free radical scavenging activities of melatonin's metabolites, AFMK and AMK. *J Pineal Res*. 2013;54(3):245–257.
67. Xiao J, Shimada M, Liu W, Hu D, Matsumori A. Anti-inflammatory effects of eplerenone on viral myocarditis. *Eur J Heart Fail*. 2009;11(4):349–353.
68. Kindrachuk J, Ork B, Hart BJ, et al. Antiviral potential of ERK/MAPK and PI3K/AKT/mTOR signaling modulation for Middle East respiratory syndrome coronavirus infection as identified by temporal kinome analysis. *Antimicrob Agents Chemother*. 2015; 59(2):1088–1099.
69. Lewis EL, Harbour D, Beringer J, Grinsted J. Differential in vitro inhibition of feline enteric coronavirus and feline infectious peritonitis virus by actinomycin D. *J General Virol*. 1992;73(12): 3285–3288.
70. Zhang J, Ma X, Yu F, et al. Teicoplanin potently blocks the cell entry of 2019-nCoV. *bioRxiv*. 2020.
71. Zhou N, Pan T, Zhang J, et al. Glycopeptide antibiotics potently inhibit cathepsin L in the late endosome/lysosome and block the entry of Ebola virus, Middle East respiratory syndrome coronavirus (MERS-CoV), and severe acute respiratory syndrome coronavirus (SARS-CoV). *J Biol Chem*. 2016;291(17):9218–9232.
72. Colson P, Raoult D. Fighting viruses with antibiotics: an overlooked path. *Int J Antimicrobial Agents*. 2016;48(4):349.
73. Peters DH, Friedel HA, McTavish D. Azithromycin: a review of its antimicrobial activity, pharmacokinetic properties and clinical efficiency. *Drugs*. 1992;44(5):750–799.
74. Akinyotu O, Bello F, Abdus-Salam R, Arowojolu A. A randomized controlled trial of azithromycin and sulphadoxine–pyrimethamine as prophylaxis against malaria in pregnancy among human immunodeficiency virus–positive women. *Trans R Soc Trop Med Hyg*. 2019;113(8):463–470.
75. Madrid PB, Panchal RG, Warren TK, et al. Evaluation of Ebola virus inhibitors for drug repurposing. *ACS Infect Dis*. 2015;1(7): 317–326.
76. Gautret P, Lagier JC, Parola P, et al. Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. *Int J Antimicrobial Agents*. 2020;56:105949.
77. Molina JM, Delaugerre C, Le Goff J, et al. No evidence of rapid antiviral clearance or clinical benefit with the combination of hydroxychloroquine and azithromycin in patients with severe COVID-19 infection. *Med Mal Infect*. 2020;50(4):384.
78. McKay LI, Cidlowski JA. Physiologic and pharmacologic effects of corticosteroids.

79. Durand M, Sardesai S, McEvoy C. Effects of early dexamethasone therapy on pulmonary mechanics and chronic lung disease in very low birth weight infants: a randomized, controlled trial. *Pediatrics*. 1995;95(4):584–590.
80. Landray PWHaMJ. *Effect of Dexamethasone in Hospitalized Patients with COVID-19 – Preliminary Repor*. CC-BY 40 International licenseIt; 2020.
81. Santos Rutschman A. The COVID-19 vaccine race: intellectual property, collaboration (s), nationalism and misinformation. *Washington Univ J Law Policy*. 2020;64:22.
82. Organization WH. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected: interim guidance, 25 January 2020. 2020.
83. García-Risco MR, Mouhid L, Salas-Pérez L, et al. Biological activities of Asteraceae (Achillea millefolium and Calendula officinalis) and Lamiaceae (Melissa officinalis and Origanum majorana) plant extracts. *Plant Foods Hum Nutr*. 2017;72(1):96–102.
84. Gupta B, Sharma I, Kohli N, Sharma S, Rathi A, Sharma A. Preliminary clinical assessment and non-toxicity evaluation of an ayurvedic formulation BGR-34 in NIDDM. *J Tradit Complement Med*. 2018;8(4):506–514.
85. 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.
86. Chen W, Lim CED, Kang HJ, Liu J. Chinese herbal medicines for the treatment of type A H1N1 influenza: a systematic review of randomized controlled trials. *PloS one*. 2011;6(12):e28093.
87. Xiaoyan L, Lundborg CS, Banghan D, et al. Clinical outcomes of influenza-like illness treated with Chinese herbal medicine: an observational study. *J Tradit Chin Med*. 2018;38(1):107–116.
88. Ang L, Lee HW, Choi JY, Zhang J, Lee MS. Herbal medicine and pattern identification for treating COVID-19: a rapid review of guidelines. *Integr Med Res*. 2020;9(2):100407.
89. Ding J, Zhang B, Wang PJ, et al. Analysis on mechanisms and medication rules of herbal prescriptions for nonalcoholic fatty liver disease based on methods of data mining and biological information. *Zhongguo Zhong yao za zhi= Zhongguo zhongyao zazhi= China journal of Chinese Materia Medica*. 2019;44(8):1689–1695.
90. Luo H, Tang QL, Shang YX, et al. Can Chinese medicine be used for prevention of corona virus disease 2019 (COVID-19)? A review of historical classics, research evidence and current prevention programs. *Chinese J Integr Med*. 2020:26(4):243–250.
91. Wang J, Qiao LF, Yang GT. Role of Shenfu Injection (参附注射液) in rats with systemic inflammatory response syndrome. *Chinese J Integr Med*. 2008;14(1):51–55.
92. Chang X, Zhang S, Jiang Y, et al. Mechanism of Reduning Injection on anti-acute lung injury in rats based on cytokine storm. *Chin Tradit Herb Drugs*. 2015;46(2):236–239.