Potential Therapeutics against COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is an infectious respiratory disease caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) virus. Within few months of its appearance, it has spread to almost every nook and corner of the world thereby severely affecting almost every sector of life– health, education, economy, business and social, to name a few. Global healthcare and economy are in shambles and everyone is eagerly waiting for effective therapeutics against this virus. The current medication involves the use of repurposed drugs that are already available in the market and clinically tested. At the same time, **t**here are also some novel potential drugs which are being assessed for their efficacy against SARS-CoV-2. Apart from these available therapeutics, there are dozens of potential vaccines that are available and some are currently in clinical trials and in use worldwide. As the cases are increasing each day, hence immunity boosters are gaining importance. Plant- based drugs or alternative approaches play a vital role in immune-boosting capability, thereby imparting an important role in virus alleviation. This report summarizes the current therapeutics available or recommended against SARS-CoV-2 and natural products that have been shown to boost the immune system.

Keywords: SARS-CoV-2, anti-viral drugs, traditional medicines, vaccines

Introduction:

In December 2019, "a mighty small pathogen consisting of positive-sense single-stranded RNA wrapped up in protein", namely Severe Acute Respiratory Syndrome Coronavirus 2

(SARS-CoV-2) caused the pandemic Coronavirus Disease 2019 (COVID-19) (Zhou et al. 2020). Out of seven coronaviruses that are pathogenic to humans (HCoV-OC43, HCoV-229E, HCoV-HKU1, HCoV-NL63, SARS-CoV, MERS-CoV and SARS-CoV-2), only two of them and newly identified SARS-CoV-2 have been reported to be highly pathogenic to humans (Tang et al., 2015; Cui et al., 2019, Song et al., 2019; Wu et al., 2020; Lu et al., 2020; Naqvi et al., 2020). SARS-CoV-2 was originally detected in Wuhan (China), and soon became a global pandemic within a few months. As of 19 November, 2021, **255,324,963 cases** of COVID-19 have been reported globally, including **5,127,696 deaths** (*WHO Coronavirus (COVID-19) Dashboard*, n.d.). Its rapid spread in many countries underlines an urgent requirement for efficient drugs and vaccines. Since the onset of this pandemic, several groups are trying to develop antivirals against SARS-CoV-2 in order to combat this virus and delay the epidemic break, also called "Flattening the curve". The good news is a total of **7,370,902,499** vaccine doses have been administered so far till 19 November 2021. All approved SARS-CoV-2 vaccines have proved to provide a high degree of protection against serious symptoms and death. Taking the vaccine jab is the need of the hour as it would help to slow down the spread of the virus ultimately leading to "Flattening the curve". Achieving herd immunity should be the topmost priority.

Objectives of the paper

The objective of the report is to summarize the current therapeutics available or recommended against SARS-CoV-2. The paper also discusses about natural products that have been shown to boost the immune system.

Potential Synthetic Drugs for treatment of COVID-19

Since the onset of this COVID-19 pandemic, several groups around the world are trying hard to identify drug molecules that could combat this virus. In March 2020, WHO initiated "SOLITARY" trials to assess the treatment effects of four existing antiviral compounds with the most promise of efficacy where more than 100 countries have joined to evaluate high profile treatment. The frontline potential candidates/drugs that are being actively considered as potential therapeutics are described in table 1. While some other novel candidates that may have therapeutic use in COVID 19 are described in table 2.

Drugs approved by Indian Council of Medical Research (ICMR)

A wide range of symptoms can be observed in patients suffering of SARS-CoV-2. Some of the most important measures listed under the AIIMS/ICMR-COVID-19 National Task Force guidelines during treatments include social distancing, use of masks indoors, use of anti-pyretics, multivitamins etc., along with proper monitoring. The drugs currently approved for use across the country are listed in the table 3.

Table- 1 Summary of the potential candidates/drugs as therapeutics against COVID 19

S. No	Name of the drug	Chemical nature	Nature of the drug	Mode of action	Reference
1	Ribavirin/Tribavirin	Synthetic guanosine analogue	Antiviral	Inhibits viral replication and interferes with RNA capping.	(Khalili et al., 2020)
2	Sofosbuvir/Sovaldi	Derivative of uridine 5'-monophosphate	Antiviral	Inhibits RNA-dependent-RNA-polymerase enzyme crucial for viralreplication.	(Nourian &Khalili,2020)
3	Galidesivir/BCX 44 30/Immucillin-A	Adenosine analogue	Antiviral	Prevents the replication and transcription of the viral genome.	(Keni et l., 2020)
4	Umifinovir/Arbidol	Indole derivative	Antiviral	Inhibits membrane fusion of the virus and reduces severe symptoms.	(Nojomi et al., 2020)
5	Nitazoxanide	Synthetic benzamide	Immunomodulators	Interferes with host-regulated pathways involved in viral replication, amplifying cytoplasmicRNA sensing and type I IFN pathways.	(Yavuz & Ünal, n.d.)
6	Type I interferon (IFN-I)	Glycoprotein cytokines	Immunomodulators	Inhibits viral replication, viral proteases, and immunomodulates.	(Lee & Shin, 2020)
7	Kaletra/Lopinavir/ Ritonavir	Dicarboxylic acid diamide (amphetamine)	Anti-retroviral protease inhibitor	Inhibits protease enzyme necessary for viral replication.	(Cao et al. 2020)
8	Nelfinavir/Viracept	Aryl sulfide	Anti-viral protease inhibitor	Inhibits proteases necessary forviral replication and release of mature viral particles from the cell	(Rismanbaf,2020)
9	Darunavir/Prezista	N,N-disubstituted benzenesulfonamide having an unsubstituted amino group at 4^{th} position	Anti-retroviral protease inhibitor	Prevents enzymatic binding, dimerization, and catalytic activity of viral proteases.	(J. Chen etal., 2020)
10	Atazanavir/Revataz	Aza-dipeptide analogue with a bis-aryl substituent on hydrazine group	Anti-retroviral protease inhibitor	Inhibits proteases enzyme and prevents the formation of mature viral particles.	(Fintelman- Rodrigues et al., 2020)
11	Infliximab/ Remicade	Purified rDNA-derived chimeric human-mouse IgG monoclonal antibody	chimeric monoclonal antibody	Tumor necrosis factor inhibitor proposed as a potential treatment for cytokine release syndrome associated with COVID-19.	https://pharmaphorum.com/news/celltrion-trials-infliximab- biosimilar-in- recovering-covid-19-patients/
12	Sarilumab/ Kevzara	Human monoclonal antibody	Monoclonal antibody	Shown promising results in patientsaffected with COVID-19 pneumonia when administered alone or in combination with other Therapeutics.	(Benucci etal., 2020)
13	Fedratinib	Anilinopyrimidine derivative	Selective JAK2 inhibitor	Reduces cytokine storm-mediated symptoms in COVID-19 patients.	(Chilamakuri & Agarwal,2021)

Table- 2 Summary of some other candidates/drugs that may have a potential therapeutic use in COVID 19

S.No	Name of drug	Nature of drug	Mode of action	References
1	EIDD-2801	Isopropylester prodrug of [N4-hydroxycytidine] ribonucleoside analog	Inhibits viral replication as it induces inactivating mutations	Sheahan et al, 2020
2	Mavrilimumab	Monoclonal antibody	Blocks GM-CSF (granulocyte macrophage - colony-stimulating factor), thus reduces hyper Inflammation	Luca et al, 2020
3	CD24Fc	Recombinant fusion protein where CD24 is attached to Fc portion of antibody	Shows reduction of multiple inflammatory cytokines.	https://finance.yahoo.com/news/oncoimmune- receives-fda-approval-covid-184000653.html
4	Lenzilumab	Monoclonal antibody	Blocks GM-CSF (granulocyte macrophage - colony-stimulating factor), and CSF-2 (Colony-stimulating factor-2), therefore prevents hyperinflammation in patients with pneumonia associated with COVID-19.	https://clinicaltrials.gov/ct2/show/NCT04351152
5	Leronlimab(PRO 140)	Humanized IgG4 monoclonal antibody	Enhances the immune response in patients experiencing cytokine release syndrome from respiratory distress caused by COVID-19.	https://www.drugs.com/clinical_trials/leronlimab-seven-patients-severe-covid-19-demonstrated-promise-two-intubated-patients-icu-removed-18486.html
6	Gimsilumab	Human monoclonal antibody	Targets the pro-inflammatory cytokine granulocyte-macrophage colony stimulating factor (GM-CSF),	https://clinicaltrials.gov/ct2/show/NCT04351243
7	Otilimab	Mooclonal antibody	Acts by blocking the interaction of GM-CSF with its cell surfacereceptor.	https://clinicaltrials.gov/ct2/show/NCT04376684
8	JS016	Monoclonal antibody	Binds to the spike protein receptorin SARS-CoV-2 and can block viruses from binding to the ACE2host cell surface receptor.	https://www.nasdaq.com/articles/junshi-eli-lilly-agree-to-co-develop-js016-antibodies-against-covid-19-2020-05-04
9	LY-CoV555	Monoclonal antibody	Binds to the spike protein receptorin SARS-CoV-2 and can block viruses from binding to the ACE2 host cell surface receptor.	https://clinicaltrials.gov/ct2/show/NCT04411628
10	INOpulse	Inhaled nitric oxide	Improves oxygenation and haltsthe progression of virus.	https://www.clinicaltrials.gov/ct2/show/NCT04398290
11	RLF-100 (Aviptad)	Human vasoactive intestinal peptide(VIP)	Decreases mortality and improve oxygenation in the blood for patients with COVID-19 through its anti-inflammatory activity.	https://clinicaltrials.gov/ct2/show/NCT04453839
12	Losmapimod	Mitogen - activated protein kinase (MAPK) inhibitor	Reduces the inflammatory response associated with disease progression in COVID-19 by reducing inflammatory biomarkers such as C-reactive protein and IL-6.	https://www.biospace.com/article/fulcrum-therapeutics-initiates-phase-iii-losmapimod-study-in-covid-19
13	Telbivudine	Antiviral thymine nucleoside analog	Inhibits DNA polymerase activity and causes chain termination.	(Tu et al., 2020)
14	Azithromycin	Antibiotic	Inhibits bacterial protein synthesis and mRNA translation.	(Echeverría-Esnal et al., 2021)

15	Colchicine	Anti-inflammatory ; antiviral	Interferes with inflammatory pathways alon with superoxide production, inflammasome activation, TNF-α release and inhibits microtubule formation.	(Schlesinger et al., 2020)
16	Cyclosporin	Immunosuppresive drug	Inhibits calcineurin.	(Tu et al., 2020)
17	IDX-184	Antiviral drug	Binds to RNA dependent RNA polymerase and contradict the function of the protein leading to viral eradication.	(Elfiky, 2020)
18	Naproxen	Anti-inflammatory ;antiviral	Decreases inflammatory mediators in SARS-CoV-2.	(Chilamakuri & Agarwal, 2021)
19	Cobicistat/Tybost	Antiviral	Inhibits the CYP3A-mediated metabolism.	(Tu et al., 2020)
20	Ronapreve (casirivimab and imdevimab)	Combination of two monoclonal antibodies	Significantly reduces viral load in seronegative patients who are hospitalised with COVID-19 and did not require high-flow oxygen or mechanical ventilation at baseline.	(Phase II/III Trial Shows RonapreveTM (Casirivimab and Imdevimab) Significantly Reduces Viral Load within Seven Days of Treatment in Patients Hospitalised with COVID-19, n.d.)
21	EvuSheld (tixagevimab and cilgavimab)	Combination of two antibodies	Stops the virus from entering the body's cells and causing infection by attaching it to the spike protein.	(EvuSheld (AZD7442) Long-Acting Antibody Cocktail, n.d.)

Table 3: List of drugs approved for use in our country

S. No	Name of the drug	Chemical nature	Nature of the drug	Mode of action	Reference
1	Dexamethasone	Fluorinated steroid	Anti-imflammatory	Acts by reducing inflammation associated with cytokine release syndrome in patients with COVID-19	(Ledford H. Nature 2020)
2	Methylprednisolone	Synthetic pregnane steroid	Anti-inflammatory and immno-modulator	Reduces severe lung damage.	(Peking Union Medical College3Hospital, 2020)
3	Enoxaparin (low molecular heparin)	Low molecular weight, synthetic heparin	Anticoagulant/ antithrombotic agent	Prevents and treats thromboembolic complications of COVID-19.	(Drago et al., 2020)
4	Apixaban	Pyrozolopyridine	Anticoagulant	Decreases mortality with its prophylactic use	(Billett et al., 2020)
5	Amphotericin b	Isolated from *Streptomyces nodosus*	Antimicrobial, antifungal	Alters the structure of the viral envelope, cell membrane integrity and internal cell organelles besides its immunomodulatory reponse	(AL-Khikani, 2020)
6	Tocilizumab Actemra/	Humanized monoclonal antibody	Monoclonal antibody	Shown promising results in severely affected patients.	(Chilamakuri& Agarwal, 2021)
7	Remdesivir /Veklury	Adenosone triphosphate (ATP) analogue	Antiviral	Inhibits viral replication and has shown in vitro and in vivo activity against SARS-CoV-2.	Wang et al. 2020

Potential Alternative / Traditional Medicines for the treatment of COVID 19

Although many novel/repurposed drugs and vaccines have been identified as promising candidates, these candidates lack experimental pieces of evidence thereby restricting their use in humans. Though repurposed drugs are

being tried on COVID-19 patients, many new molecules and vaccines are under the clinical trial. As the world is grippling with the virus, natural compound-based products have tried to fill the void. Hence, natural product-based alternative traditional medical therapies are being explored to boost the immunity thereby helping in the alleviation of outcomes of COVID 19.

Traditional Chinese and Indian medicines have been used since a long in order to control viral diseases including SARS and H1N1influenza, common cold, zika, flu illness, and so forth (Chen et al., 2011; Xiaoyan et al., 2018) and they are also useful as immunity boosters. SARS-CoV-2- infected people have been treated with traditional medicines for prevention as well as treatment of COVID-19 in China and Korea (Ang et al., 2020). There are ten plants and their products that have been administered to COVID-19 patients (*Astragalus membranaceus* / Mongolian milkvetch, *Glycyrrhiza uralensis* / *Gan Cao, Saposhnikoviae divaricate* / Fángfēng , *Rhizoma atractylodis macrocephalae* / Bai Zhu, *Lonicerae japonicae flos* / Jinyinhua, *Fructus forsythia* / Forsitia, *Atractylodis rhizoma* /black atractylodes rhizome, *Radix platycodonis* / Platycodon Root, *Agastache rugosa* / wrinkled giant hyssop, *and Cyrtomium fortune* / holly fern (Luo et al., 2019) and they served as source of traditional medicine in China. Similarly, Indian traditional medicines are also practiced for the treatment of infectious viral diseases. Ayurveda, Siddha, and Unani are the three different components of traditional Indian medicine that utilize mainly plant-based extracts/drugs (Thileepan and Prasad, 2018). In India, the Ministry of AYUSH (Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homoeopathy) has recommended the use of effective indigenous drugs which helps in the enhancement of immunity against viral disease. The amalgamation of extracts of 15 different plants (*Zingiber officinale* / Ginger, *Piper longum* / Indian long pepper, *Syzygium aromaticum* / clove, *Tragia involucrate* / Indian stinging nettle, *Anacyclus pyrethrum* / Mount Atlas daisy, *Hygrophilla auriculata* / swampweed, *Terminalia chebula* / chebulic myrobalan, *Adhatoda vasica* / Adusa, *Plectranthus amboinicus* / Indian borage, *Saussurea costus* / costus, *Tinospora cordifolia* / Giloy, *Clerodendrum serratum* / glory bower , *Andrographis paniculate* / creat or green chireta,, *Sida acuta* / wireweed *and Cyperus rotundus* / nutgrass (Prasad et al., 2020) can be used for the prevention and cure of COVID-19. AYUSH has recommended few formulations (aqueous extract / powder of *Withania somnifera* ; aqueous extract / powder of aqueous extract / powder of *Tinospora cordifolia*) for prophylactic care (high risk population, primary contacts) and another formulations (aqueous extracts *Tinospora cordifolia and Piper longum;* AYUSH64) for mild symptoms (https://www.ayush.gov.in/docs/ayush-Protocol-covid-19.pdf). Few plant-based products such as mannose-binding lectins, emodin, aescin, reserpine, phenanthroindolizidines, phenanthroquinolizidines, tetra-O-galloyl-β-d-glucose, luteolin, quercetin derivatives, are also identified that have shown antiviral activity against coronaviruses (Prasad et al., 2020). Plant-based drugs are extracted from common and rare herbs which have a unique immune-boosting property for curing diseases and maintenance of good health. Herbs that are used in traditional medicines have negligible side effects and are hence considered the safest mode for the treatment of diseases. Few plant-based products such as mannose-binding lectins, emodin, aescin, reserpine, phenanthroindolizidines,

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Since no extensive studies have been performed in order to identify the important chemical components of plants and to determine the molecular mechanisms behind their potential role as anti-COVID-19 and as immunity boosters, further investigations in this direction is highly recommended.

Table 4: List of authorized or approved vaccines worldwide

S.No	Name of vaccine	Number of doses	Vaccine type	Route of administration	Developer
1	Comirnaty (BNT162b2)	2	mRNA-based vaccine	Intramuscular	Pfizer/BioNTech, Fosun Pharma
2	Moderna COVID-19 Vaccine (Mrna-1273)/Spikevax	3	mRNA-based vaccine	Intramuscular	Moderna,BARDA,NIAID
3	COVID-19 Vaccine AstraZeneca (AZD1222/Vaxzevria / Covishield	1-2	Adenovirusvaccine	Intramuscular	AstraZeneca, University of Oxford
4	Sputnik V (Gam-COVID-Vac)	2	Recombinant adenovirus vaccine (rAd26 and rAd5); non-replicating viral vector	Intramuscular	Gamaleya Research Institute, Acellena Contract Drug Research and Development
5	Sputnik Light	1	Recombinant adenovirus vaccine (rAd26); non-replicating viral vector	Intramuscular	Gamaleya Research Institute, Acellena Contract Drug Research and Development
6	COVID-19 Vaccine Janssen (JNJ-78436735; Ad26.COV2.S)	1-2	Non-replicating viral vector	Intramuscular	Janssen Pharmaceutical (Johnson & Johnson)
7	CoronaVac	2	Inactivated vaccine (formalin with alum adjuvant)	Intramuscular	Sinovac Research and Development Co.,Ltd
8	BBIBP-CorV	2	Inactivated vaccine	Intramuscular	Beijing Institute of Biological Products; China National Biotec Group; Sinopharm
9	EpiVacCorona	2	Peptide vaccine	Intramuscular	Federal Budgetary Research Institution State Research Center of Virology and Biotechnology
10	Convidicea (PakVac, Ad5-nCoV)	1	Recombinant vaccine (adenovirus type 5 vector)	Intramuscular	CanSino Biological Inc.
11	Covaxin (BBV152)	2	Inactivated vaccine	Intramuscular	Bharat Biotech, ICMR; Ocugen; ViroVax
12	WIBP-CorV		Inactivated vaccine	Intramuscular	Wuhan Institute of Biological Products; China National Pharmaceutical Group (Sinopharm)
13	CoviVac	2	Inactivatedvaccine	Intramuscular	Chumakov Federal ScientificCenter for Research and Development of Immune and Biological Products

14	ZF2001	2-3	Recombinantvaccine	Intramuscular	Anhui Zhifei Longcom Biopharmaceutical, Institute of Microbiology of the Chinese Academy of Sciences
15	QazVac (QazCovid-in)	2	Inactivatedvaccine	Intramuscular	Research Institute for Biological Safety Problems, Rep. of Kazakhstan
16	KCONVAC	2	Inactivatedvaccine	Intramuscular	Beijing Minhai Biotechnology Co.; Kangtai Biological Products Co. Ltd.
17	COVIran Barekat	2	Inactivated vaccine	Intramuscular	Shifa Pharmed Industrial Group
18	IMBCAMS Covid-19 Vaccine (Covidful)	2	Inactivatedvaccine	Intramuscular	Chinese Academy of MedicalSciences, Institute of MedicalBiology
19	Abdala (CIGB66)	3	Protein bunit vaccine	Intramuscular	Center for Genetic Engineeringand Biotechnology
20	Soberana 02 (FINLAY-FR-2)	2	Conjugate vaccine	Intramuscular	Finlay Institute of Vaccines; Pasteur Institute
21	MVC-COV1901/ Medigen COVID-19 vaccine	2	Protein subunit vaccine	Intramuscular	Medigen Vaccine Biologics Corp.; Dynavax
22	ZyCoV-D	3	DNA plasmid-based vaccine	Intradermal	Zydus Cadila
23	Spikogen (COVAX-19)	2	Monovalent recombinant protein vaccine	Intramuscular	Vaxine Pty Ltd.; CinnaGen
24	FAKHRAVAC/MIVAC/Fakhra	2	Inactivated vaccine	Intramuscular	The Stem Cell Technology Research Center; Organization of Defensive Innovation and Research
25	NVX-CoV2373/Covovax	2	Recombinant nanoparticle vaccine	Intramuscular	Novovax; CEPI

Vaccines against SARS-CoV-2 under use

According to the WHO vaccine tracker, 108 vaccines are in clinical development while 184 are in pre-clinical development (*COVID-19 Vaccine Tracker and Landscape*, n.d.). Out of these 108 candidates under clinical development, 20 vaccines (described in table 4) are currently in use worldwide (*COVID-19 Vaccine Tracker*, n.d.) and 8 are being approved by WHO.

As the COVID-19 infection continues to surge worldwide, experts caution against rushing the process of developing a potential vaccine. The use of novel technologies for vaccine development needs extensive testing for the safety and efficacy of a vaccine. In India itself, more than six biotech establishments are working in collaboration with various vaccine developers worldwide for vaccines (Kaur & Gupta, 2020).

Conclusion and Future Perspective

The emergence of this virus in late 2019 caused a large global outbreak that severely demobilized the global economy. As the COVID-19 infection continues to surge worldwide, experts caution against rushing the process of developing a potential vaccine. It cannot be stressed more than a fast tract vaccine development in accordance with the globally accepted norms is the need of the hour. Although the virus is affecting our health – both physical and mental, and scientists all over the world are trying their best to find a solution, we also need to think of some immediate measures about people's well-being and their recovery during and after a major global health crisis.

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