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Review Article

THE CURRENT STATUS AND PERSPECTIVES FOR THE EMERGING PANDEMIC: COVID-19

CHANDANA KUMARI V. B.[a], SHASHANK M. PATIL[a], PRITHVI S. SHIRAHATTI[b], SUJAY S.[a], TEJASWINI M.[a], LAKSHMI V. RANGANATHA[c], JAYANTHI M. K.[d], RAMITH RAMU[a*]

[a]Department of Biotechnology and Bioinformatics, School of Life Sciences, JSS Academy of Higher Education and Research, Mysuru 570015, Karnataka, India, [b]Post-Graduation Department of Biotechnology, Teresian College, Siddhartha Nagara, Mysuru 570011, India, [c]Department of Chemistry, The National Institute of Engineering, Manandavadi Road, Mysuru, Karnataka, 570008, India, [d]Department of Pharmacology, JSS Medical College, JSS Academy of Higher Education and Research, Mysuru 570015, Karnataka, India
Email: ramithramu@jssuni.edu.in

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ABSTRACT

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the causative agent of the extremely communicable viral infection coronavirus disease 19 (covid-19). Initially the virus was found at Wuhan, china which spread across the world exponentially and in a very short span. This outbreak has turned out to be a global health crisis and recently WHO regarded it as pandemic. The origin of the virus is predicted as either the natural selection in animal host prior to the transfer of the pathogen from animals to humans or the natural selection in humans and following transfer. Nevertheless, there is an extensive spread of virus by human to human transfer in the form of droplets. A few antiviral drugs are at the stage of clinical trials to eradicate the covid-19. In this review, a comprehensive approach is put forth to scrutinise the etiology, pathogenicity and transmission of SARS CoV-2. The review also deliberates broadly on the diagnosis and status of therapeutic treatment developed. It also focuses on the preventive and controlling measures from different sectors of the society. The review covers the details reported in 70 studies which were chosen after keyword searches carried out leading to over 884 resulting articles.

Keywords: SARS-CoV-2, Coronavirus disease 19 (covid-19), Transmission, Diagnosis, Therapeutics

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INTRODUCTION

The world has witnessed an array of contagious outbreaks since time immemorial. These outbreaks were caused by a series of bacteria, viruses and other pathogens [1]. These outbreaks were either epidemic, where a small population or community gets affected for a limited duration of timeor pandemic, when the whole world might be at risk [2]. Thus, a pandemic is more contagious and dangerous compared to an epidemic and emphasized in this review primarily due to the misinterpretation of the disease in discussion as epidemic at the first mention, which was later declared to be a pandemic [3, 4]. Covid-19 or commonly known as corona virus disease, is caused by a virus, known as Severe Acute Respiratory Syndrome Corona Virus (SARS-COV-2) [5]. Owing to the health and economic crisis it has created around the globe from a past few months, it can be declared that covid-19 is one of the most pernicious outbreaks of all time [6]. The history dates to 2003, when China officially reported the first outbreak of SARS-CoV-1. It was first spotted in humans in the Guangdong province of southern China in 2002 [7]. Another relative virus, Middle East Respiratory Syndrome Corona Virus (MERS-CoV), was first reported in Arabian Peninsula of Saudi Arabia in 2012 [8]. Both virus outbreaks resulted in significant number of deaths around the globe. In December 2019, China had a cluster of unidentified cause of pneumonia patients in Wuhan, with clinical characteristics significantly like viral pneumonia [9, 10]. According to one study, an exotic animal market in Wuhan city became the centre of the outbreak and there was a rapid increase in the rate of transmission [11]. This led to an immediate examination to characterise the cause of the disease and was identified to be due to novel coronavirus (nCoV). Later, it was named as SARS-CoV-2, by International Committee on Taxonomy of Viruses (ICTV) on 11th February 2020 which is also called as covid-19 [12].

The severity of SARS-CoV-2 is attributed to its life cycle which involves potential natural hosts, intermediate hosts and final hosts. SARS-CoV-2 has great transmissibility and infection causing ability [13] compared to its relative viruses, MERS-CoV and SARS-CoV-1. β-coronaviruses are a large family of enveloped, diverse-natured, positive-sense and possess single stranded RNA. It is reported to affect both animals and humans, resulting in neuronal, hepatic, gastrointestinal abnormalities chiefly affecting respiratory system [14-16]. Both MERS-CoV and SARS-CoV-1 are responsible for highest reported mortality rates (10% and 40%) in human beings [5]. Being the centre of the pandemic, initially China reported more than 90% of the cases and deaths. However, eventually an outbreak of the disease was observed in places such as Italy, Spain and USA bringing these countries toll on par with that of China. Most of the reported cases were associated with symptoms resembling pneumonia, including cough, fever, myalgia or fatigue [10]. Up to 23rd April, WHO reported 30,90,445 confirmed active cases with 2,17,769 deaths with India reporting 35,043 active cases with 1,154 deaths. According to WHO, the pandemic has spread over 208 counties [17].

The review was planned to report the status of covid-19 pandemic, including its origin and transmission. As it was designed to highlight the available therapeutics, preventive and control measures, a systematic search was conducted using two major databases. Both Google Scholar and PubMed were used to identify published studies related with details about Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome-1 (SARS-CoV-1), and Severe Acute Respiratory Syndrome-2 (SARS-CoV-2). It was completed in accordance with the guidelines given by Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

The objectives of the review were planned and independently written by all the 8 authors. The corresponding author was engaged to resolve the conflicting interest in the article. For the collection of published studies, we used the key-words like “SARS-CoV-1”, “Covid-19”, “SARS-CoV-2”, “Detection”, “Diagnosis”, “Clinical Symptoms”, “Infection”, “Transmission”, “Pharmacotherapy”, “Immunotherapy”, “Vaccines”, “Prevention” and “Controlling measures”. In this manner, individual studies were collected and further screened according to relevance to suit the requirement. A total of 884 of studies resulted

from our search criteria and were analysed for duplicates and relevant content. In the first screening, 23 of the studies were removed out of which 19 duplicates and 3 belonged to herbal medications. As the study was strictly designed to report current pharmacotherapeutic agents, ongoing clinical trials and immunotherapeutic agents, herbal medications with no clinical proof were discarded. The remaining 861 studies were grouped under the planned objectives, in which major selection was carried out. Furthermore, individual authors reported the number eligible studies as 246. A second and last phase of selection was carried out with respect the perspective of the review. Finally, we found only 70 studies that were able to perfectly fit into the perspective of the review article. The scenario of the search identification and selection has been depicted in the fig. 1.

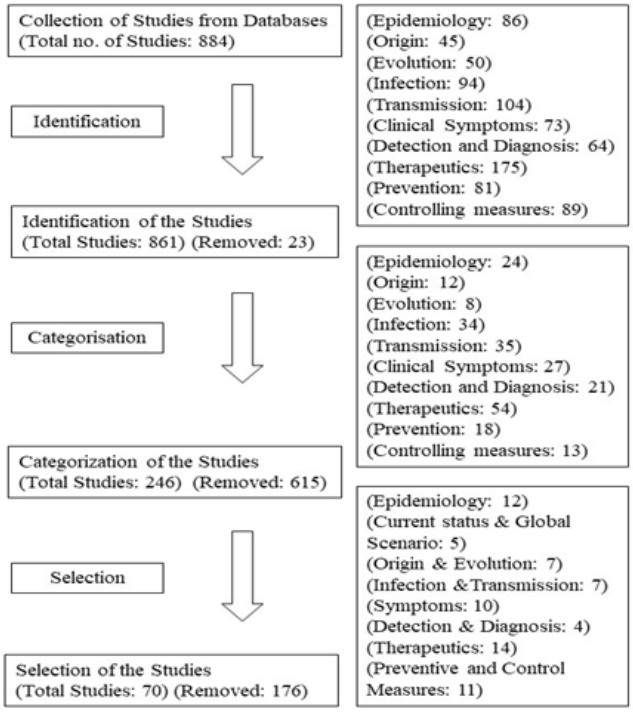

Fig. 1: Flow diagram of the search strategy Created with "BioRender.com"

Current issues and global scenario

It was reported that a total of 44 cases of pneumonia patients of unknown causal agent, from 31 December 2019 through 3 January 2020 in Wuhan city. As the cause was known to be a viral infection there was confirmed cases of SARS-CoV-2, 278 cases in China, 2 cases in Thailand and 1 each case in Japan and Republic of Korea by 20 January 2020 [18]. First case in India was reported on 30 January 2020, almost 649 cases and 13 deaths were reported by 26 March 2020 [19]. Covid-19 is extremely infectious disease with an estimated R0 values of about 2.28 (2.06-2.52), which indicates SARS-CoV-2 is in the epidemic phase and has very strong transmission capacity [20]. Presently, there are about 3 million cases confirmed globally; 1,406,899 infected with 129,311 deaths in European region, 1,213,088 confirmed and 62,404 deaths in America, 176,928 confirmed and 7304 deaths in the Eastern Mediterranean region, 146,449 confirmed and 6037 deaths in Western Pacific region, 51,351 confirmed and 2001 deaths in South-East Asia region and 23,254 confirmed and 903 deaths in Africa as on 29 April 2020 [21]. In India, as on 1 May 2020, there are 25007 active cases with 1147 deaths [22].

Origin and evolution of SARS CoV-2

COVID-19 is also well known as 2019 novel coronavirus, otherwise it is also referred as 2019-nCoV. It was first recognised in Wuhan China and the World Health Organization declared the coronavirus outbreak with an official name covid-19 on 11 February 2020. This virus causes the upper-respiratory tract illness, which was not found to be infecting humans when first identified [23]. In 1937, corona type of virus was first isolated from chickens. Later in the mid-1960s, human coronaviruses were identified for the first time. Coronavirus is a sense-strand RNA virus; single-stranded enveloped consisting genome of 30Kb [16]. Based on the Coronaviridae family, genera can be divided into four: α, β, γ, and δ. The birds get infected usually by γ and δ genera of coronavirus, whereas the humans and mammals are infected by α and β genera. The novel Severe Acute Respiratory Syndrome coronavirus-2 (SARS-CoV-2) infecting the humans are the β-coronavirus that appears as oval or round and crown shape when observed under electron microscope [24]. Further studies on the genera of coronavirus elucidated that the bats usually are the reservoirs of α and β genera while birds carry γ and δ genera of coronavirus. The studies also reported the progenies of the lineage of β-coronavirus within rhodents [25, 26].

SARS-CoV, MERS-CoV, NL63, HKU1, OC43 and 229E are human coronavirus, among this SARS CoV-2 is the 7th coronavirus infecting humans. Infections by HKU1, OC43, NL63 and 229E cause mild symptoms but the SARS-CoV, MERS-CoV and SARS CoV-2 are associated with severe symptoms and causes disease [27]. Origin of the SARS CoV-2 can have two prospects, firstly its can be predicted that natural selection in animal host prior to the transfer of pathogen from animals to humans. Secondly, we can predict as the natural selection in humans and resulting animal to human transfer. Covid-19 cases were reported initially in Huanan market located in Wuhan. T, which most likely emerged from the animal source owing to its resemblance of SARS CoV-2 to several other coronaviruses. The bat seems to be reservoirs of SARS CoV-like coronaviruses, which were unable to efficiently invade the humans. The mutations in structural covering of spike protein of the virus enabled the access to bind the humans with the aid of ACE2 receptors. As per the first perspective, the animal host would have allowed the natural selection process to effectively cause the necessary changes in order

to escape its host and dwell within the human hosts. There is also a possibility as per the second perspective, that the progenies of SARS CoV-2 hurdled into humans and adapted inits genomic characteristics and then spread the infection rapidly through human to human transfer [28].

Infection and transmission

Mode of transmission

The phylogenetic analysis and the protein sequencing from COVID-19 virus exhibited similarity with ACE2 receptors in turtles and pangolins which are genetically closer to humans and bat. It is suspected that these species can be an alternate intervening hosts transmitting SARS CoV-2 to human [29]. The virus can be transmitted through droplets of saliva, nose discharge and aerosols either from short or long distance by talking, breathing, sneezing and coughing respectively [30]. The person infected can cause transmission through droplets within 1m proximity either by cough or sneeze and the pathogen can enter the healthy person through mouth, nose and eyes. The objects or materials which encountered the infected person or the environment surrounding can also transmit the infection of virus [31]. The virus is present within the droplet mostly reflected as a particle and it cannot be an airborne transmission [32]. Consumption of milk from an infected animal and urine of the animal may also contain virus. The undercooked or uncooked meat consumed directly were also theorised to be main course of transmission [33]. The mode of transmission from primary host to humans has been depicted in fig. 2. [13].

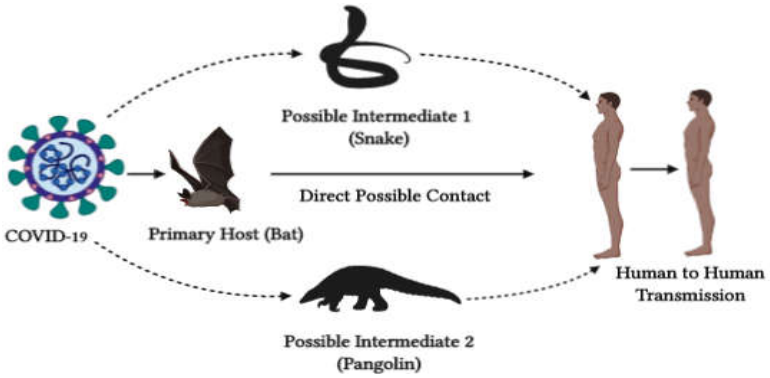

Fig. 2: Mode of transmission of Covid-19 [13] Created with "BioRender.com"

Mode of infection

Structurally, the outermost layer SARS CoV-2 consists of spikes made up of glycoprotein on the surface that helps the virus to invade host cells [34]. The S protein which is recognised by the host ACE2 receptor initiates the virus life cycle in host cell through endocytosis. The endosomal pathway fusion takes place between the viral envelope and the host cell membrane with the release of viral nucleocapsid into the cytoplasm. The RNA of SARS-CoV-2 is released, which gets translated to polyproteins pp1a and 1ab (viral replicase). Later, the viral proteinase cleaves the RNA replicase to smaller fragments which persuade the structural rearrangements in the cell membrane to form double-membrane vesicles (DMVs). A chain of sub genomic mRNAs is produced by polymerases during the process of discontinuous transcription and the viral proteins are translated pertinently. The combination of viral proteins and RNA genome successively accumulate to form a virion in ER-Golgi intermediate complex (ERGIC). Finally, through secretory pathway, the mature virions are transported and released out of the cell in smooth-walled vesicles as shown in the fig. 3 [13, 35].

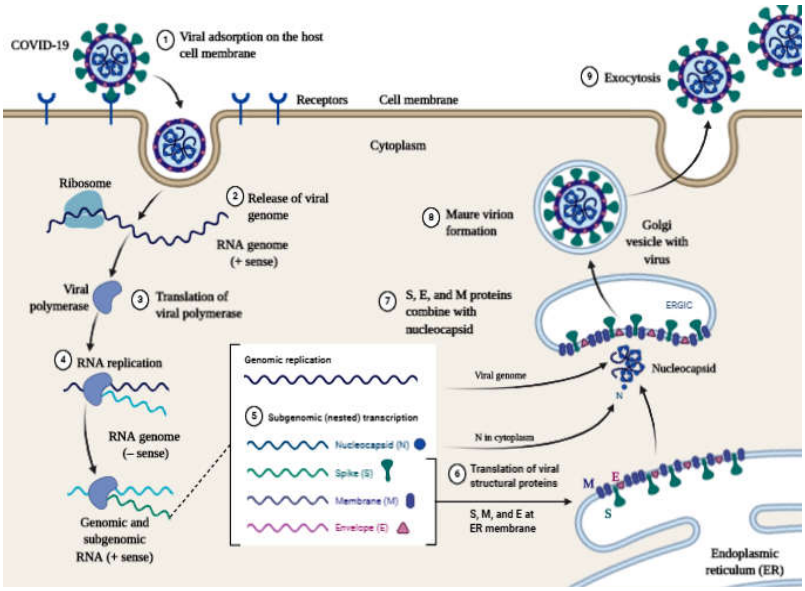

Fig. 3: Mode of infection of Covid-19 [35] Created with "BioRender.com"

Symptoms of infection

Incubation period for covid-19 is 14 d and within 4-5 d one can observe the onset of symptoms. SARS-CoV-2 infection would develop symptoms within 11.5 d in the infected person and although vary between individuals at the onset, most common symptoms are fever, cough, tiredness, eating disorder or also known as anorexia, shortness of breath, excess of sputum production and muscle pain [36]. Least commonly reported symptoms are headache, disorientation, mucus fluid secretions in nasal cavity, sore throat, mucus containing blood stains from the bronchi, larynx, trachea, or lungs, vomiting, and diarrhea [10, 11, 37, 38]. In certain cases, patients also exhibit other common symptoms rarely such as pain in the abdominal region, abdominal distension and recurrent inclination to evacuate the bowels [39]. According to patient's analysis nausea, vomiting and diarrhea appear at variable percentages [40]. The patients admitted initially of heart palpitation and chest tightness were also found to be infected with covid-19. The patients associated with cardiovascular disease will have high secretion of ACE2 compared to a healthy person and therefore more prone to developing symptoms of infection. The patient infected with SARS CoV-2 with comorbidities such hypertension or diabetes mellitus are in extreme danger. It is recommended that greater care should be taken of people suffering from cardiovascular diseases, hypertension and diabetes mellitus to not encounter COVID-19 positive people [41, 42]. Lately, with close observation of patients infected with COVID-19 also exhibited loss of smell that is anosmia, associated with or without parageusia means confusion of the sense of taste [43]. There are also possibility of asymptomatic infections and the transmission of SARS CoV-2, although confirmed yet [44].

Table 1: Available pharmacotherapeutic agents against covid-19

Pharmacotherapeutic agents	Possible covid-19 indication	Mechanism of action	Original indication	Dosage information	References
Hydroxychloroquine/Chloroquine	Off-label use for anti-viral treatment	Increases intracellular pH in host cells, thus inhibiting RNA synthesis. Facilitates the glycosylation impairment of ACE2, by disrupting viral S protein thereby preventing the entry of SARS-COV-2 into the host cell. Also known to possess anti-inflammatory and immunomodulatory effects	Malaria, HIV, Autoimmune Diseases	Hydroxychloroquine: 400 mg on first day followed by 200 mg for four days, twice, orally. Chloroquine: 500 mg twice for 5 d, orally.	Barlow *et al.* 2020; Tu *et al.* 2020; McCreary *et al.* 2020 [53-55].
Remdesivir	Off-label use for anti-viral treatment	Guanosine nucleoside that specifically inhibits viral RNA replication using molecular mimicry mechanism	Ebola virus, MERS-CoV	200 mg on first day, followed by 100 mg for up to 10 d intravenously	Barlow *et al.* 2020; Tu *et al.* 2020; McCreary *et al.* 2020 [53-55]
Lopinavir and Ritonavir	Off-label use for HIV-1 treatment	Acts as an aspartic acid protease inhibitor that inhibits viral replication hence its life cycle	HIV-1	200 mg-100 mg for 14 d through oral consumption	Barlow *et al.* 2020; Tu *et al.* 2020; McCreary *et al.* 2020 [53-55].
Ribavirin	Off-label use for anti-viral treatment	Nucleoside analog that specifically inhibits viral RNA replication using molecular mimicry mechanism	Hepatitis-A, Hepatitis-B, SARS	400 mg for 14 d, twice a day	Barlow *et al.* 2020; Tu *et al.* 2020; McCreary *et al.* 2020 [53-55]
Nitazoxanide	Off-label use for anti-protozoal treatment	Inhibits hemagglutinin formation hence interferes with viral life cycle. It may also act on the electron transfer activity of pyruvate ferredoxinoxidoreductase enzyme, thus interfering in the protozoan energy metabolism.	Diarrhea	Doses recommended for SARS were based on age groups; 1-3-year olds were recommended with 100 mg, 4-11 y with 200 mg, above 12 y with 300 mg for 5 d, orally.	Barlow *et al.* 2020; McCreary *et al.* 2020 [53-55].
Nelfinavir	Off-label use for HIV-1 and anti-viral treatment	Drug binds to the active site of HIV-1 protease enzyme and inhibits the cleavage of precursors of Gag-Pol polyproteinchain, that are essential for the survival of HIV-1 inside the host. The residues left after the molecular process are no longer infectious.	HIV-1	Unknown	Barlow *et al.* 2020; Shetty *et al.* 2020; McCreary *et al.* 2020 [54-56].
Favipiravir	Off-label use for anti-viral treatment	It structurally resembles guanine, and through competitive inhibition, reduces the efficacy of viral replication like remdesivir	Influenza	Unknown	Tu *et al.* 2020; Shetty *et al.* 2020 [53, 56].
Ivermectin	Off-label use for HIV-1 and anti-viral treatment	It can dissociate the preformed IMPα. β1 heterodimer, which aids in the protein displacement. As the protein displacement is essential for the maintenance of viral replication, targeting the protein displacement across the host cell would be a feasible option to inhibit viral life cycle	HIV-1, Dengue	Unknown	Tu *et al.* 2020 [53].
Nafamostat	Off‑label use for anti‑viral treatment	Acts as a serine protease inhibitor, inhibits TMPRSS2 associated fusion process, may prevent the entry of	Pancreatitis	Unknown	Shetty *et al.* 2020 [56].

		SARS-CoV-2 into host cells.			
Oseltamivir	Off‑label use for anti‑viral treatment	Neuraminidase enzyme inhibitor that may prevent the entry of the virus into host cells. Also reduces shedding and infectivity of the virus	Influenza	75 mg	Shetty *et al.* 2020 [56].
Sofosbuvir	Off‑label use for anti‑viral treatment	Nucleoside analog that specifically inhibits viral RNA replication using molecular mimicry mechanism	Hepatitis-C	Unknown	Shetty *et al.* 2020[56].
Zanamivir	Off‑label use for anti‑viral treatment	Neuraminidase enzyme inhibitor that may prevent the entry of the virus into host cells. Also reduces shedding and infectivity of the virus	Influenza	Unknown	Shetty *et al.* 2020 [56].
Azithromycin	Antibiotic	The drug acts as an anti-bacterial agent and inhibits bacterial infection, may possess anti-viral properties.	Bacterial Infections	500 mg on first day followed by 250 mg for four days	Shetty *et al.* 2020[56].
Emodin	Anti-viral drug under investigation	Disrupting viral S protein thereby preventing the entry of SARS-COV-2 into the host cell	Polycystic Kidney Disease	Unknown	Shetty *et al.* 2020 [56].
Umifenovir (Arbidol Hydrochloride)	Anti-viral drug under investigation	The drug targets hemagglutinin, a glycoprotein present on the surface of the influenza virus. It prevents the fusion of viral membrane with endosome after endocytes.	Influenza and Arbovirus infection	Unknown	Tu *et al.* 2020; McCreary *et al.* 2020 [53, 55].

Table 2: Available immunotherapeutic agents against covid-19

Immunotherapeutic agents	Possible covid-19 indication	Mechanism of action	Original indication	Dosage information	References
Anti-interleukin (IL)-6	Against Acute respiratory distress syndrome	IL-6 can bind to its IL-6 receptor and alternative mRNA splicing. Increased IL-6 content results in reduced lung elasticity and increased bronchoalveolar inflammation. Inhibiting IL-6 may hamper effects of covid-19.	Acute respiratory distress syndrome	Unknown	Tu *et al.* 2020 [53].
TNF-α inhibitors	Anti-inflammatory	Reduces lung inflammation caused by Tumor Necrosis Factor-α. Blocking these factors would resume normal lung functioning.	Psoriasis, Rheumatoid Arthritis, and Inflammatory Bowel Diseases		Tu *et al.* 2020 [53].
Methylprednisolone	Anti-inflammatory	Consumption would suppress the unwanted immune reactions	Arthritis, Blood disorders	Unknown	Tu *et al.* 2020 [53].
Fingolimod	Immunomodulating Drug	Through molecular mimicry, it binds to sphingosine-1-phosphate (S1P1) receptors to reduce the T-lymphocytes in lymph nodes, to attenuate the unwanted immunopathogenesis	Refractory multiple sclerosis	Unknown	Tu *et al.* 2020 [53].
Tocilizumab	Off-label use to hamper unwanted immune response	Monoclonal antibody that binds to IL-6 receptors to block IL-6 pathway	Rheumatoid Arthritis	Unknown	Tu *et al.* 2020 [53].
NK-Cells	Boosting Anti-Viral Response	Increases the number of cytokines and chemokines, without the help of CD8+and antibodies. Migration towards viral site reduces viral activity.	SARS-CoV-2	Unknown	Tu *et al.* 2020 [53].
Anti-C5a Monoclonal Antibody	Anti-inflammatory	Anti-C5a treatment could reduce lung injury by reducing vascular leakage and influx of neutrophils into the damaged site.	SARS-CoV-2	Unknown	Tu *et al.* 2020 [53].
Convalescent Plasma Therapy	Anti-viral response	Antibodies present in the sera from convalescent patients would supress viremia	Reducing infection	Unknown	Shetty *et al.* 2020; McCreary *et al.* 2020 [55, 56].
Thalidomide	Anti-angiogenic, Anti-inflammatory, Anti-fibrotic	Along with the reduction of TNF-α, it reduces multiple inflammatory conditions by supressing inflammatory cells and pro-inflammatory cytokines	Crohns Disease, Bechets Disease	Unknown	Tu *et al.* 2020 [53].
Intravenous Immunoglobulin	Immunomodulatory Activity	Boosts immune system by attenuating the proliferation of inflammatory cells, inhibition of phagocytosis, and interfering antibody mediated cytotoxicity	Neurological, Dermatological, and Rheumatological Disorders	500 mg for 5 d	Tu *et al.* 2020 [53].
SARS-CoV-2-Specific Neutralizing Antibodies	Anti-viral	Recovered from patients of COVID-19, these antibodies would significantly reduce the viral infection	SARS-CoV-2	Unknown	Tu *et al.* 2020 [53].

Table 3: Available cellular therapeutic agents against covid-19

Cellular therapeutic agents	Possible covid-19 indication	Mechanism of action	Original indication	Dosage information	References
Mesenchymal Stem Cells (MSC's)	Anti-inflammatory	Boost immune system by supressing inflammatory cells and pro-inflammatory cytokines. Produce paracrine factors to aid tissue repairs.	SARS-CoV-2	Unknown	Golchin *et al.* 2020 [57].
CAR T Cells	Anti-viral activity	Specifically binds to the surface antigen present on the virus and inhibits the viral replication inside the host	Cancer, Hepatitis-B, HIV-1	Unknown	Bachanova *et al.* 2020 [58].

Table 4: Ongoing vaccine developments against COVID-19

Company/Institution	Estimated timeline	Technology	Stage/Funding	References
Moderna Therapeutics—US National Institute of Allergy and Infectious Diseases	3 mo to early stage (phase 1) clinical trial in US (earliest); much longer for full testing and regulatory approval	Messenger RNA vaccine	Preclinical Awaiting preclinical tests and phase 1 study by NIAID, Funding by CEPI.	Pang *et al.* 2020 [52].
Inovio Pharmaceuticals	Human testing in the next few months	INO-4800-DNA based vaccine (DNA synthesized in lab, does not require actual virus sample)	Preclinical Funding by Coalition for Epidemic Preparedness Innovations (CEPI), up to $9 million	Pang *et al.* 2020 [52].
Novavax	3 mo	Nanoparticle vaccine	Preclinical	Pang *et al.* 2020 [52].
University of Queensland	6 mo	Rapid Response Technology, 'Molecular clamp' vaccine platform (gene added to viral proteins, misleads body to generate antibodies)	Preclinical Funding by Coalition for Epidemic Preparedness Innovations (CEPI)	Pang *et al.* 2020 [52].
Vir Biotechnology	Not available	Anti-coronavirus monoclonal antibodies. Additionally, using "whole-genome CRISPR based screening capabilities to identify the host receptor for Wuhan coronavirus"	Preclinical	Pang *et al.* 2020 [52].
Chinese Centre for Disease Control and Prevention (CDC)	At least 1 mo for development, 2–3 y before availability for use	Not available Inactivated virus vaccine (postulated, not verified)	Preclinical; virus successfully isolated, currently selecting strain	Pang *et al.* 2020 [52].
Shanghai East Hospital (Tongji University)-Stermirna Therapeutics	<40 d for manufacture of vaccine samples	mRNA technology	Preclinical	Pang *et al.* 2020 [52].
Johnson and Johnson	1 y to market	Adenovirus—vectored technology used for Ebola vaccine (and Zika and HIV vaccine candidates)	Preclinical	Pang *et al.* 2020 [52].
University of Hong Kong	Months for animal testing, At least 1 y for clinical trials on humans	Modified nasal spray influenza vaccine (with surface antigen of coronavirus) prevents both influenza and corona virus	Preclinical; vaccine developed	Pang *et al.* 2020 [52].
University of Saskatchewan (VIDO-InterVac)	Target for animal testing in 6–8 w, human trials in at least a year	Not available	Preclinical	Pang *et al.* 2020 [52].
GeoVax—BravoVax	Not available	Modified Vaccina Ankara—Virus Like Particles (MVA-VLP) vaccine platform	Preclinical	Pang *et al.* 2020 [52].
Clover Biopharmaceuticals	Not available	Highly purified recombinant 2019-nCoV S protein subunit-trimer vaccine (S-Trimer), produced using Trimer-Tag© technology	Preclinical	Pang *et al.* 2020 [52].
CureVac	Not available	mRNA technology	Preclinical	Pang *et al.* 2020 [52].
Texas Children's Hospital Center for Vaccine Development at Baylor College of Medicine	Not available	Not available	Not available	Pang *et al.* 2020 [52].
Codagenix	Not available	Not available	Not available	Pang *et al.* 2020 [52].

Detection and diagnosis

After the outbreak of COVID-19 in Wuhan(China), WHO has recommended that samples should be taken from suspects of SARS-CoV-2 of respiratory tract specimens like bronchoalveolar lavage fluid, pharyngeal and nasal swabs which are subjected to nucleic acid amplification diagnostic test, RT-PCR assay and specific method to identify patients with respiratory pathogens/infection [45]. To detect the infected cases of covid-19, molecular-based approaches (Nucleic acid test) are important. Other techniques like serological

antibody test are also used, which takes shorter time to detect the infection [46, 47]. RT-PCR and next-generation sequencing techniques are used to check for the presence of SARS-CoV-2 in the specimens of respiratory tract, which are time consuming but far more sensitive and efficient. Sequencing of genome is performed to design primers and probes that are specific to detect SARS-CoV-2. Viral RNA extract of COVID-19 is used as positive control in all assays. In real time RT-PCR assay primers and probes that specifically target gene of SARS-CoV-2 is used. For SARS-CoV-2 identification, open reading frames (ORF 1a and 1b), RNA-dependent RNA polymerase gene (RdRp), envelope (E), and nucleocapsid(N) are key sequences for diagnose [17].

Advancements in therapeutics treating Covid-19

One must accept with anguish that there is no specific treatment option found to treat COVID-19 till date [5, 48]. All the therapeutics now used to treat COVID-19 were once used to treat similar viruses named SARS-CoV or MERS-CoV, the outbreaks reported in 2003 and 2012, respectively [49]. Although they possess an array of working mechanisms, these drugs are not 'specifically' designed for the said infection [48]. Medical professionals are using these drugs either separately or in combination for specific duration. In the following sections, we have briefly discussed about the ongoing therapeutics for covid-19.

The first and important step that comes into light in case of viral or any infectious disease is to be away from the infected person or patients termed as social distancing. covid-19 is highly infectious and can enter the host through aerosols, just like tuberculosis [50, 51]. Therefore, it becomes essential to maintain adequate isolation to control the viral transmission. Care should be taken that even mild symptoms should be reported to medical professionals, so that further transmission can be prevented from confirmed patients. The medical treatment involves usage of pharmacotherapy, immunotherapy, cell therapy and vaccines [52-54]. Tables 1-4 briefly depict the details of all the therapeutics currently being used.

Apart from pharmacotherapy and other modes of treating covid-19, there is no available vaccine against the pandemic. Though it takes significant time to develop vaccines many of the firms and institutions have joined hands for the development of vaccines against COVID-19 [52, 53]. They are working around the globe to ensure that they explore every part of the virus characteristics. It should be taken care that cross-contaminations of other vaccines can occur, and the effect may be even worse than covid-19 [59].

Preventive and control measures

Every health malady outbreak results in the initiation of preventive measures at different levels inside a region, apart from the medications. Following these preventive measures would help in saving lives, hence would maintain the population levels at constant rate [50]. In case of COVID-19, as no specific medications are available, prevention would be the best opportunity to survive against this global pandemic [50]. The preventive measures can be followed in 3 levels including personal level, community level and population level. Laws should be made to facilitate the strict implementation of preventive measures at every level.

Role of individuals in the prevention of covid-19

The transmission of COVID-19 occurs through the exchange of aerosols when a healthy individual receives them from a sick person [60]. As it belongs to the category of severe acute respiratory syndrome (SARS), the highest viral content is possessed by the sputum and upper airway secretions [60]. The virus can even remain for days on the surface and can result in further complications [10]. Thus, it becomes important to wear a fluid resistant (Type-IIR) personal protective equipment (PPE) masks to avoid the entry of the aerosols and to maintain at-least a two-metre limit on contact. These masks should be used by both patients and healthcare professionals to avoid further spreading of the virus [61]. FFP2, FF3 and N95 are the types of high filtering masks that are usually referred to use against droplets. The WHO recommends the use of undamaged FFP2/3 and N95 masks for up to 4 h, as it is a median healthcare tolerance time for healthcare workers [51]. It is also recommended that regular washing of hands should be done with soap, disinfectant or sanitizer with minimum 60% alcohol in it. Touching of nose, mouth and eyes should be avoided with unwashed hands [48].

Apart from protecting the body from the external aspects, it also becomes vital to maintain the health from internal side. It is reported that the western diet mainly comprises of saturated fatty acids, refined carbohydrates and fats, leads to the chronic activation of innate immune system and attenuation of the adaptive immune system [62]. It activates macrophages, neutrophils and dendritic cells, thus triggering activation of pro-inflammatory mediators. Also, consumption of high fat diet leads to B and T lymphocyte inactivation, macrophage infiltration to lungs which in turn leads to lung or possible neuro-inflammatory conditions [62]. On the other hand, obese people with a habit of high consumption of fats showed less response to COVID-19 vaccines [62]. In sum, it is important to consider the effects of our daily food and lifestyle on the susceptibility to COVID-19 infection. Therefore, it is recommended that individuals must shift their diet plans to high amounts of fiber, unsaturated fats, antioxidants and whole grains from eating unhealthy refined carbohydrates and saturated fatty acids [62].

In addition to this, one must look after the safety protocols in clinics and hospitals. Room ventilation is believed to clear most of the viral aerosols (63%). After 2 exchanges, the viral load reduces in to 14% and after 5th exchange, <1%, which becomes an optimum environment for the patients [51]. Thus, it also becomes important to maintain regular room ventilation protocols. Apart from ventilation, it also becomes essential to maintain protocols to avoid cross-infection, through the only available way, that is PPE. Avoidance of patients, staff or visitors exposed to the virus, repeated handwashing, isolation of patients, cleaning the equipment regularly and proper disposal of PPE can help in the effective prevention of covid-19 transmission [48, 51].

Role of society in the prevention of covid-19

Along with personal efforts to stay away from the pandemic, efforts from other two levels, i.e., community and population are also essential. In the middle of the pandemic without availability of proper and specific therapeutic options, social distancing and quarantine prove efficient options to control the further spreading of the disease [63]. Social distancing refers to the maintenance of safe distance from individuals during interactions in public places like utility stores, hotels, theatres etc [64]. While quarantine can be defined as the restriction on infected persons in an isolated place from the public [63]. It is one of the most misunderstood and feared methods of controlling covid-19, because it may affect both infected and non-infected individuals with psychological, economical, and emotional complications such as post-traumatic stress disorder, depression, insomnia, mood swings etc [65]. From the economical point of view, quarantine reduces the productivity, hence minimalizes the economic growth [66]. According one study, the restrictions on travelling and traffic significantly reduced the transmission of the virus. Another study showed that quarantine strategies are more effective than traffic restrictions. According to them, it is estimated to reduce the number of cases by 89.7% [50]. Similarly, the idea of city lockdown was proved to be effective when a study reported 72% drop in the number of infected people. They also suggested that, postponing lockdown would worsen the situation by 5 times [50]. Owing to these factors, it becomes clear that quarantine can be the best self-preventive method that can be practiced at community and national level.

Contribution of pharmacy and healthline services

Being in the front line against the pandemic, a lot can be expected from the pharmacy and healthline services. Preventive and control measures can be at their best with the combination of quarantine and activity of healthline services [67]. The pharmacists can develop guidance for providing pharmacy services, where researchers across the globe, epidemiologists and clinicians can share their views and studies on the virus' characters and controlling methods [68]. This hub can result in the development of preventive and control methods. Also, on the other hand, pharmacists can put forward their formulary manuals and medicine news. Through this approach,

dosage, uses, ingredients and precautions about covid-19 therapeutics can be made available for the public [68]. Conducting drug-based research and evaluation of the drugs can also help the nation to look forward to developing new ways to fight the pandemic [68]. Establishment of digital platforms to create awareness about the pharmacotherapeutic approaches can help the people to overcome their misbelieves and confusions about the pandemic and its treatment. This system can be the best method in situations like city lockdown and quarantine [68].

With respect to the healthline services, doctors and medical staff should provide their best service to treat the infected as well as to create awareness, among others [69]. Specialists and trained staff are the two most important necessities in battling covid-19. Providing individual care, enough time, facilities to patients can result in quick recovery from the disease [69]. Along with this, opening medical helplines, telecommunication for remote areas to provide information about available treatment information and preventive measures would be helpful [68]. It would be better if mobile health services get into the front, edifying as well as providing medical assistance. This would be considered as a better option in conditions like lock-down. Fig. 5 depicts the role of pharmacy and healthline in the prevention of covid-19.

Essentialities in research and development

Owing to the considerable impact of ongoing covid-19 pandemic on health security and global economy, one of the major problems raised was inadequate diagnostic and medical equipment, including test kits, face masks, sanitizers and therapeutic drugs [69]. It has now become necessary for scientists to standardize and develop the diagnostic test strips and enzyme linked immunosorbent assay (ELISA) kits as additional procurement [70]. Computational biological tools and bio-informatics analysis of covid-19 can be the resourceful keys to develop the molecular imaging of structural proteins and possible mutations [70]. The detection of possible reservoir and carriers of the virus can be done with serological surveys of suspected animals. This would surely help in the controlling the pandemic [70]. On the other hand, it is still essential to consider factors like temperature, UV, humidity, behaviour of aerosols and biophysical evaluation of all these factors for the effective study of covid-19, thus finding a pavement for its permanent cure [70].

CONCLUSION

The covid-19 pandemic has been the most dreadful disease in the history so far, accounting for loss of millions of lives. It has also resulted in the complete halt of importing and exporting essential things across the worlds, thus has impaired the global economy. The similarity of the virus with the already known viruses is considered because of the therapies working on it. Compared to the other viruses from the same family, it appears that covid-19 has been evolved to withstand all those therapeutics once effective against MERS-CoV and SARS-CoV-1. The ongoing therapeutics are used as a combination to reduce the viral load in patients, as no specific drug is available and many of them are yet to clear the clinical trials, including vaccines.

Though it possesses symptoms like pneumonia, it is lethal and highly contagious. Thus, it becomes utmost important to maintain the social distancing through lockdown. As no specific drug available, it is better to avoid the exposure by maintaining social distancing. Every citizen of the country must play his/her role in the prevention and control of the pandemic. It is recommended that both lock-down would result in significant decrease of mortality rate. The pharmacy and healthcare services are already doing their best to fight the pandemic. To boost up the efforts, one health approach is recommended. Along with the good practices, effective treatment, development of quick and precise diagnosing kits, ample production and distribution of PPE can reduce the effect of the pandemic significantly.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

Declared none

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