Review article

Can human overcome viral hijack-? Comprehensive review on COVID-19 in the view of diagnosis and mitigation across countries

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ABSTRACT

The novel COVID-19, a pandemic disease, is showing an alarming spread and severity throughout the world. Globally, the community transmission of this disease is affecting people in large clusters and so it is necessary to mitigate and control them in order to minimise the social and economic consequences. This review emphasize on the origin of the coronoviral epidemics, discussion on the structural and functional basis of SARS-CoV-2, epidemiology, pathognomonic symptoms, fatality, available rapid diagnostic methods and proposed possible treatment methods for the treatment of COVID-19. The diagnostic markers with respect to genetic material of the virus based on PCR, CRISPR & APTAMER and with respect to proteins based on Antigens were discussed which provides new arena for the development. In control of a pandemic situation the policy adoption and implementation by the governments plays a major role and the policy implementation in different countries are discussed which establishes the effectiveness of the policies framed by the governments. The effectiveness of ethnic traditional medicines of various countries such as India and China in Immunity enhancement, along with their utilisation is also discussed. This review provides an insights towards the COVID-19 which helps in continuous investigation on different dimensions which could help us to understand the mysteries behind the havoc created by this invisible creature.

1. Introduction

A recent viral outbreak, COVID-19 (Coronavirus Disease-2019) is a serious concern in terms of global health as well as global economy. Though there are many drugs which subsides the symptoms of this disease, as of now there is no specific established medicine to treat COVID-19. Generally, viral infections are difficult to treat, as the viruses unlike other pathogens, hijack the host cells and use the host cell machinery to replicate and multiply themselves. Hence, it is difficult to discover a drug that specifically attacks the viruses without harming the host cells. Inspite of the above said risk, many possible methods were also proposed to treat the lethal coronaviral infections. Coronaviruses are a group of viruses that belong to the subfamily Orthocoronavirinae in the family Coronaviridae. They are enveloped viruses with positive sense, RNA genome of size approximately 30 kb. The first human coronaviruses were reported in 1965 by Tyrrell and Bynoe [1]. These viruses are known to cause mild to severe upper and lower tract respiratory diseases in humans and are also known to cause diseases in other mammals and birds. Among the four genera of the Coronaviruses (α, β, γ, δ), β Coronaviruses are known to cause severe respiratory diseases in humans. Two β coronaviruses SARS-CoV and MERS-CoV were already caused epidemics in 2003 and 2012 respectively. The total reported cases in SARS-CoV infection which caused Severe Acute Respiratory Syndrome was about 8096 and 774 associated deaths were reported in

26 countries (WHO report as of Dec 31, 2003) and the fatality rate was 9.5%. Recently in 2003, researchers also isolated SARS Corona virus from *Paguna larvata* in wet markets in Shenzhen [2]. Another cluster of β Coronaviruses MERS-CoVs caused Middle East Respiratory Syndrome with Saudi Arabia as the epicentre [3], was spread to 27 countries reporting 2494 confirmed cases of infection and 858 associated deaths (By WHO report at the end of November 2019.) and the fatality rate (34.4%) was higher than that of SARS. Recently, another pandemic, COVID-19 is caused by SARS-CoV2. The outbreak of SARS-CoV2 was epidemiologically linked to the Chinese Sea Food market in Wuhan, Hubei province, China [4]. Now, the WHO has declared COVID-19 as a Public Health Emergency of International Concern [5]. In recent viral outbreaks, Bats are considered as "Viral Reservoirs" for diverse variety of viruses. Although Civet cats were identified as animal origin, Bats were identified as reservoir hosts of SARS-CoV [6]. Similarly, Camels were identified as animal origin and Bats were proposed to carry progenitor viruses of MERS-CoV [7]. Also in COVID-19, laboratory results indicated that SARS-CoV2 is similar to β Coronaviruses identified in Bats [8]. The animal origin of SARS-CoV2 is believed to be Pangolin. The above statements suggest that Bats could be a common reservoir for these β Coronaviruses (SARS-CoV, MERS-CoV, SARS-CoV2). The probable reason might be that bats are the only mammals that can fly and also the second-largest order of mammals. It is also hypothesized that the flying ability of the bats provided them the selection pressure for coexistence with viruses and the migrating ability of the bats can be correlated to the context of disease transmission. The probable reason
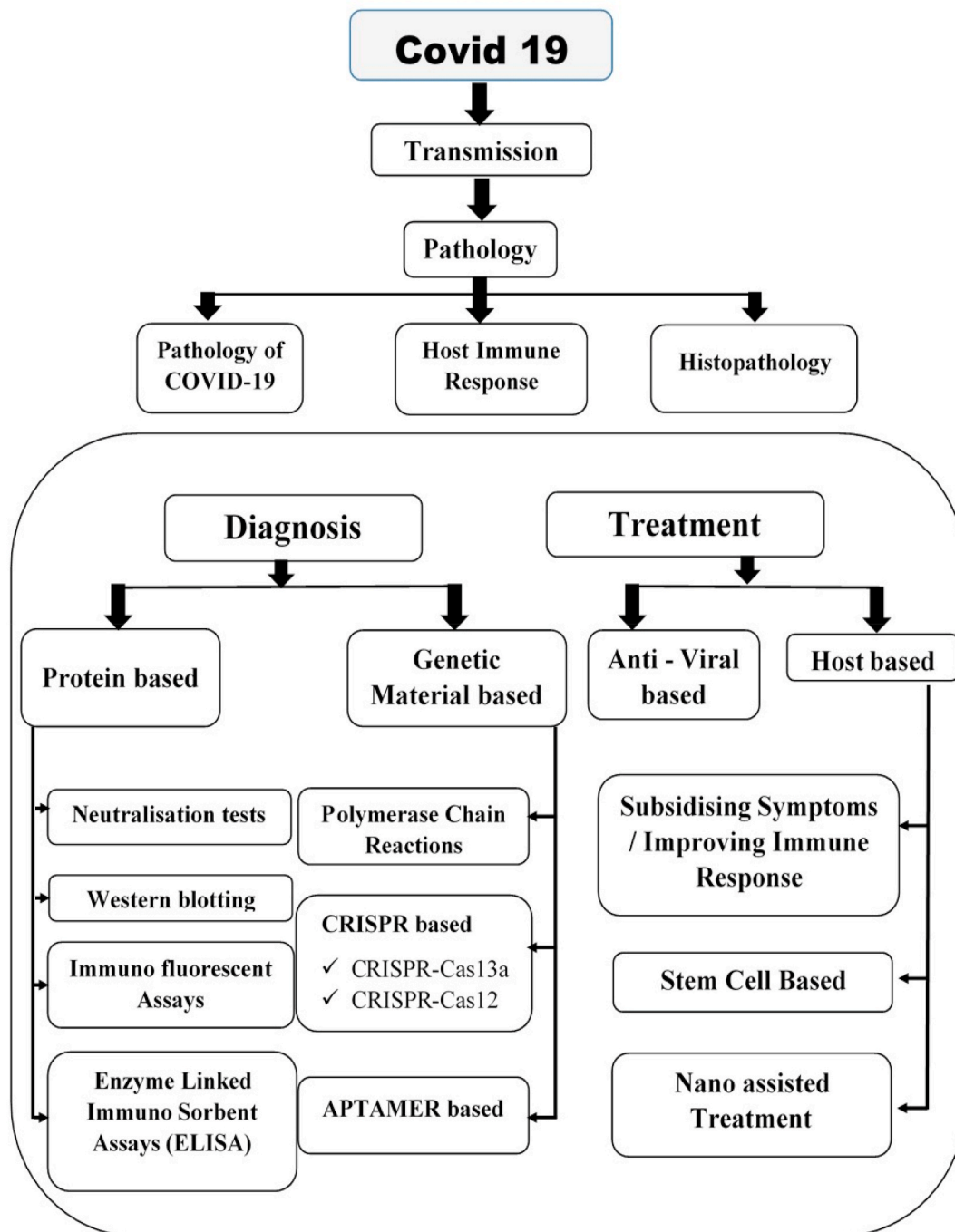

Fig. 1. Overall Scheme of Covid 19 Outbreak – In the view of pathology, diagnosis and treatment.

for the frequent viral outbreaks in the world could be due to diverse climates, alarming environmental pollution which attributes to the natural selection of different biodiversity across the world. There is also a belief in food culture that slaughtered raw animals are more nutritious than the cooked ones, this can be attributed to the disease transmission from animals to humans [6]. The overall scheme of the review is given in terms of pathology, diagnosis and treatment (Fig. 1).

2. Human to human transmission

Transmission is one of the major reason in the chain of viral infection. The rate of infection can be well explained by the four stages of transmission (Fig. 2). It is evident that the transmission may occur due to direct exposure to the respiratory droplets or might be due to the fomites in the immediate environment around the infected person and some cases airborne transmission is also possible at situations where aerosol-generating medical treatments are carried out [9].

Health care workers are in the front line in the risk of infection during the viral outbreak due to long exposure of pathogen, occupational stress, fatigue and violence that occurs between physical and psychological health [10]. To identify and assess the transmission potential of an emerging pathogen a basic useful metric called reproduction number (R_o) which measures the average number of secondary cases from each infected person is used, higher the R_o higher is the rate of infection and the spread of the epidemic becomes rapid and when the R_o falls below 1 it indicates that the epidemic is likely to fall out and it decreases the rate of infection. The R_o value of SARS-CoV, MERS-CoV, SARS CoV-2 lies in the range of 2.57, 0.42–0.92 and 2–3 respectively [11–13]. It is very well clear that SARS CoV 2 has an increased risk of transmission in comparison with MERS CoV and SARS CoV based on its R_o value and hence there emerges an alarming threat to take immediate control measures to bring the rate of infection in control. The situation report by the World Health Organisation dated August 31, 2020 reported 24,854,140 confirmed cases and 838924 deaths globally, shown in Table 1.

The risks of COVID-19 can be measured by a term Case Fatality Rate (CFR) Eq. (1),

$$CFR = \frac{Number\ of\ deaths\ of\ COVID-19}{Number\ of\ diagnosed\ cases\ of\ COVID-19} \tag{1}$$

The factors which influence CFR are the age of an individual, gender of an individual and comorbidity that is the pre-existing health condition of the individual. Elderly people above 65 years and people with a weaker immune response or with pre-existing health conditions such as cardiovascular, diabetes, hypertension, cancer and Chronic Respiratory Disease have shown increases in mortality rate by COVID-19 infection. It is also proved that males are more suspicious towards COVID-19 than females. The probable reasons could be increased rate of smoking and alcohol consumption by male than female [14]. Consumption of alcohol severely affects the immune cells count, proliferation and also its response against pathogen. Ethanol can modulate the function of dendritic cells by affecting the antigen presentation to T-cells. An early study with female mice revealed that alveolar macrophages get affected upon alcohol consumption. It also decreases the T-cell count in heavy drinkers. Alcohol abuse can lead the host prone to viral and bacterial infections [15]. Smoking is also another reason for weakening of immune system. It can decrease IgA concentration, basophil count and NK cells count in active smokers [16].

3. Diagnosis of COVID-19 through different strategies

The World Health Organisation (WHO) along with other health agencies and researchers are paying much attention towards developing diagnostic kits for detection of this novel corona virus. Rapid diagnostic methods can help in quick isolation of infected individuals, by which transmission can be reduced to a greater extent. Currently, diagnostics are carried out with the samples collected from upper and lower respiratory tract and also with blood and stool samples.

Obtaining lung tissue using autopsy techniques and paired serum will also be beneficial when serological tests are to be done. Specimens should be stored properly and maintained at 2–8° C for correct handling. The diagnosis of COVID-19, is aimed either by targeting the (a) Genetic material of the virus, (b) Protein component of the virus.

3.1. Diagnostic marker - genetic material of the virus: PCR, CRISPR & APTAMER

Most of the testing tools which are being used nowadays, have also turned their focus towards reverse transcription polymerase chain reaction (RT-PCR), a nucleic acid amplification test for the diagnosis of SARS-CoV 2 genetic material [17]. Diagnostic method using real time RT-PCR includes the following steps: (a)Collection of Nasopharyngeal and Oropharyngeal swabs, (b) RNA extraction from the specimens and Purification, (c) Reverse transcription of RNA to cDNA, (d) Amplification of cDNA, (e) Fluorescent signal detection. Many laboratories have started to customize their PCR kits for analysing this viral genome and have tried to study more about the pathology of infection. Using CRISPR (Clustered Regularly Interspaced Short Palindrome Repeats) related approaches, the rapid progress in the diagnosis of COVID-19 is possible. Recent studies reveals two approaches of CRISPR, using CRISPR-Cas13a (also named as SHERLOCK - Specific High Sensitivity Enzymatic Reporter UnLOCKing technique [18] and CRISPR-Cas12 [19]. Both these methods can diagnose a viral genome in minutes. First step in these approaches is to amplify the extracted nucleic acid isothermally using Recombinase Polymerase Amplification Kit and it takes about 25 min. Second step involves detection of target viral gene either using Cas13a (in SHERLOCK) or Cas12, and this requires a period of 30 min. This step is then followed by visual read out for detection which involves 2 min incubation. In CRISPR based SHERLOCK technique, Cas 13a which is a RNA guided RNase, cleaves the non-targeted RNA including RNA probes after it binds to target gene. This collateral cleavage of RNA probes results in emission of signal which can be detected visually. In CRISPR Cas 12 system, reverse transcription of viral RNA will be performed and
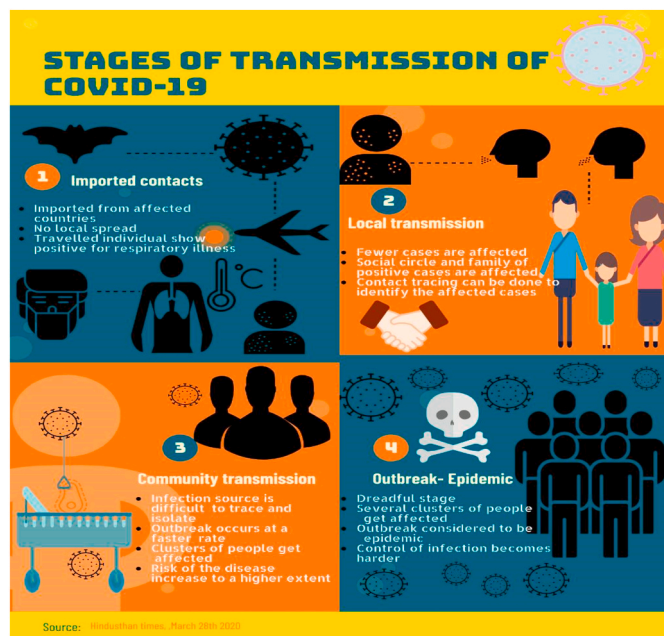

Fig. 2. Stages of transmission of COVID-19 (Source: Hindustan Times, March 28th, 2020).

Table 1
Region wise Covid 19 diagnosed and death cases as on March 29, 2020.

Region	January'20-March'20			April'20-June'20			July'20-August'20		
	CC	D	CFR (%)	CC	D	CFR (%)	CC	D	CFR (%)
Western Pacific	104868	3671	3.501	110698	3769	3.405	272005	3122	1.148
European	423946	26694	6.297	2268140	170560	7.520	1513622	21877	1.445
South East Asia	4215	166	3.938	780716	21427	2.745	3288217	53683	1.633
Eastern Mediterranean	50349	2954	5.867	1007706	21469	2.130	845492	26043	3.080
America	163014	2836	1.740	4973691	244293	4.912	8002207	214625	2.682
Africa	3786	77	2.034	293504	5933	2.021	747223	15712	2.103

cDNA will be amplified. After recognition of target gene, the Cas 12 which is a RNA guided DNase will cleave the single stranded DNA. For this, single stranded DNA probes are designed which are also cleaved by Cas12, thus emitting the signal. APTAMER based approaches can help in easy detection of RNA molecules as they are short oligonucleotide or peptide molecules and can bind easily with specific targets such as proteins, small molecules, etc,. As they are extremely specific and selective towards their targets, they have wider application in therapeutic and diagnostic pipelines and can perform target recognition and binding by hydrophobic interactions, base stacking and intercalations. The aptamers of high affinity and selectivity towards the target molecules can be synthesised by using SELEX method (Systemic Evolution of Ligands by Exponential Enrichment), an invitro technology in which non-binding aptamers are discarded and the aptamers which fit into targets are expanded and selected for further processes. Currently, these aptamers are being used to diagnose viral infections by immunological and molecular methods. Some aptamer based sensors, known as aptasensors are also used to diagnose viral infections in which aptamers act as bioreceptors or transducers [20]. Based on the type of transducer, they can be optical aptasensors or electronic aptasensors and their classification is dicussed in the below figure. RNA aptamers for the sensitive detection of SARS CoV was also developed by targeting the nucleocapsid protein [21]. Specific binding of selected RNA with N protein was also studied. It revealed that SARS CoV N protein has RNA binding domain at both N terminal and C terminal. But the selected aptamer bound with C terminal and dimeric form of N protein. Aptamer based chemiluminescene immunosorbent assay was also developed and insights on nanoarray aptamer chip was discussed. This work can help in developing similar kind of aptamer based diagnostic chip for SARS CoV 2.

3.2. Diagnostic marker – protein component of the virus: serological tests

As these RT-PCR systems require sophisticated instruments, more time and do not provide sufficient knowledge about the complete history of infection, many countries such as Singapore have moved towards serological tests, as they look deep into the history of antibodies to know more about the past infections of a community and their associated antibodies. These serological tests are of different types: i) Neutralisation tests: measures the functional and active antibodies present in a patient body against a particular pathogen, ii) Immuno fluorescent assays (IFA): displays a fluorescent signal in response to the interaction between antibodies and the viral proteins [22] iii) Enzyme Linked Immuno Sorbent Assays (ELISA): detects the active antibodies by measuring the antigen-antibody interaction [23]. Iv) Western blotting: emits a fluorescent signal when an antibody interacts with viral protein. Many researchers and organisations are performing continued studies to develop accurate serological tests that can rapidly detect the presence of viral protein within a shorter duration of time. There are four important structural proteins in a corona virus which are the spike proteins, membrane proteins, envelope proteins and nucleocapsid proteins. In particular, the spike protein has been found as one of the primary proteins which interacts with the immune cells of patients affected with COVID-19 [24]. Few companies have started selling these viral antigens

and few are producing antibodies against this to create rapid tests for quick diagnosis of a large number of people. Among these methods, immunoassays and CRISPR technology could diagnose within short period of time and they are highly specific too. During the initial stages of diagnosis of COVID-19, Computer Tomography (CT) imaging is useful in examining the abnormalities associated with lungs such as lesion distribution, morphology, density, staging, etc [25]. This method provides a complete pathological analysis of the lung inflammations and any kind of lung opacities with high density resolutions and high sensitivities within a short period of examination time. It provides a conclusion about the severity of the disease and helps in facilitating further treatment processes [26]. As they have high risk-benefit ratio to the population like that of radiation exposure and other cross infections, their use has been limited only to the early stage of diagnosis by the medical community.

3.3. Diagnostic kits for COVID-19

In order to have quick and accurate diagnosis of COVID-19, many companies have started to produce diagnostic kits based on various techniques like RT-PCR [27], Immunoassays, and CRISPR based technologies [17]. ELISA is also used for diagnosis of COVID-19 [28]. On comparing the molecular diagnostic methods based on the time taken for diagnosis RT-PCR takes much time (around 2–6 h), followed by CRISPR based test and Immunoassay based test (around 1 h for CRISPR based test and within 15 min for Immunoassays) [17]. Shown in Table 2 are the list of kits available for diagnosis worldwide [29,30]. Based on the sensitivity of the diagnostic kits, it was found that antibody mediated testing i. e, use of IgM/IgG based ELISA kits showed good sensitivity of 87.3% [31]when compared to other diagnostic methods which are based on nucleotide markers [32].

From Table 2 it is evident that more number of kits are developed based on RT-PCR followed by immunological assays. But CRISPR based technologies also have several advantages over RT-PCR which includes low cost, lesser time consumption and no bulky instruments required. APTAMER, another highly specific approach can also be used for detection of SARS CoV-2. Thus this work suggest that scientific community could focus more on developing CRISPR and APTAMER based diagnostic kits.

4. COVID 19 testing through environmental samples

Other than direct human to human transmission, the SARS CoV2 spread can be attributed to contact with virus contaminated inanimate objects, hence it is necessary to monitor the spread in environmental point of view. The number of cases of both symptomatic and asymptomatic patients are increasing day by day all over the world. Despite transmission through liquid droplets, the detection of this virus in faecal contaminations is also being observed in many countries. Hence, monitoring environmental samples can help us to know more about the disease transmission and also can give an idea on future contamination problems. Nowadays many researchers have started focussing towards this and there is an urgent need to monitor environmental samples of water, air and sewage as they can be indicators in finding the circulation

Table 2
Diagnostic Kits based on Nucleic Acid Markers and Protein Markers.

Diagnostic Kits based on Protein Markers		
Method	Developer	Kit name
Lateral flow Immuno Assay	Guangzhou Wondfo Biotech	Wondfo SARS-CoV-2 antibody test (15 min)
	Innovita Biological Technology	SARS-CoV-2 antibody assay (15 min)
	Jiangsu Medomics Medical Technologies	SARS-CoV-2 rapid combined IgM/IgG antibody test kit (15 min)
	Mammoth Biosciences	SARS-CoV-2 DETECTR (CRISPR + Lateral flow based kit) (20 min)
	Sona Nanotech	Rapid SARS-CoV-2 antigen detection test (5–15 min)
	Biomerica	Rapid POC IgM/IgG antibody test (10 min)
	Sugentech	SGTi-flex COVID-19 IgM/IgG (10 min)
	Xiamen Amon Med Biotechnology	COVID-19 IgM/IgG test kit (Colloidal Gold) (10 min)
Chemiluminesence Immuno Assay	Snibe Diagnostics	MALGUMI 2019-nCoV IgM/IgG kit (30 min)
Solid phase Immunochromatography	Zhejiang Orient Gene Biotech	COVID-19 IgG/IgM Rapid Test
Diagnostic Kits based on Nucleic Acid Markers		
RT-PCR	Chinese National Institute for Viral Disease Control and Prevention	New Coronavirus nucleic acid assay
	US Centres for disease Control and Prevention (CDC)	CDC 2019-nCoV real time reverse transciptase PCR diagnostic panel
	University of Hong Kong	Real-Time reverse transcriptase PCR assays
	BGI Group (Beijing)	Real-time fluorescent RT-PCR kit for detecting 2019-nCoV
	Hong Kong University of Science and Technology	On-site rapid molecular diagnostic system based on Shenzhen Shineway Technology (microfluidic PCR test) (40mins)
	Novacyt, Primerdesign	Novel Coronavirus Strain 2019-nCoV (Within 2 h)
	Thermo Fisher Scientific	TaqMan 2019-nCoV Assay kit (Research purpose only)
	Biomeme	Biomeme COVID-19 Go-Strips (Research purpose only)
	Agency for Science Tecnology and Research (A*STAR), MiRXES	Fortitude Kit 2.0
	TIB Molbiol also via Roche Diagnostics	SARS-CoV-2 RdRP or N gene CE-IVD 7 virus Respiratory Panel multiplex RT-PCR
CRISPR Based Diagnostics	Crispr Biotech	Ultrasensitive, rapid and portable corona virus SARS-CoV-2 sequence detection (Within 1 h)
	Sherlock Biosciences	Rapid CRISPR based tests for SARS-CoV-2 and other pathogens (Within 1 h)

of virus in human communities. When Vincent et al. (2020) tried to study the environmental surveillance of SARS CoV-2 around infected patients, it was found that, though the viral genome was not detectable, its traces were found in environmental sample of one of those patients [33]. While monitoring sewage samples, it is observed that, SARS CoV-2 is being detected in untreated waste waters in many parts of the world but proper disinfection treatments can reduce their traces and concentrations to a greater extent. Warish et al. (2020) tried to monitor these viral infections in a catchment area in Australia and had reported that the viral RNA copies of SARS CoV-2 showed positive for two detections in the untreated waste water in that catchment area [34]. Live SARS CoV2 were isolated from faecal samples of infected persons [35], this increases the probability of finding infectious SARS CoV2 in hospital sewage water and from household sewage of infected patients. There is also an evidence for spread of SARS corona virus during the 2003 outbreak through domestic waste water, that aerosolized water droplets contained corona viruses from a damaged sewage pipe in a residential apartment, resulted in a cluster of cases, affected through a community who were thought to be affected by this incident in Hong Kong [36]. Even though, the waste water treatment plants may ensure the decontamination of treated water, there is a hazard of water borne virus spread through improper domestic sewage management and transport systems. The solution to avoid this problem will be establishment of decentralised water treatment and decontamination systems in hospitals and at least decontamination of household sewage before release into the centralised waste water management system. According to a new waste water worker guidance released by U.S.Occupational Safety and Health Administration (OSHA) in February 2020, the current disinfection technologies used in Waste water treatment plants, such as oxidation with hypochlorous acid or peracetic acid, and inactivation by UV irradiation, are expected to be effective in protecting wastewater workers, as well as the public, from coronavirus [37]. Use of chlorine proposed to be the cheapest method in inactivation of coronavirus in water [38].

In the study conducted by Ong et al. it is proven that the toilet area and other fomites in one of the patients' room resulted positive for SARS CoV2 contamination before routine cleaning. Only one sample collected from surface of front shoe wore by staff showed positive. They have concluded possibility of contamination is through droplets from respiratory tracts which would have displaced as aerosols and because of faecal shedding [39]. J. Wang et al. revealed that proper disinfection and routine cleaning could decrease the risk of SARS CoV 2 contamination in hospitals [40]. S. Farida et al. experimented the air borne transmission of COVID-19 virus which indicated that all the air samples collected by them resulted negative [41]. Another study by Joshua et al. examined the mode of transmission of viral particles in the environment. Surface samples were taken from common room, toilet and personal items used by confirmed and suspected patients. Air samples were collected from inside and outside of patient's room, in hallways and on staffs performing sampling. Almost all the surface and air samples resulted positive for the virus. This study suggested that viral aerosols are transported somehow from the patient. The flow of air, in and out of the room plays a major role in transmission [33]. The duration of infectivity and persistence of SARS CoV2 was reported in various inanimate objects like printing and tissue papers – 3 h, wood and cloth - 1 day, smooth surfaces like glass – 3 days, stainless steel and plastic – 6 days, surgical masks – 7 days. It is also notable that SARS CoV2 is stable at a wide pH range of 3–10 and at low temperature and humidity [42]. Therefore, surface decontamination of frequent touching places and floors must be carried out regularly. Heat can be applied for heat stable reusable medical equipments, since SARS CoV2 is reported to be inactivated by heating up to 56 °C for 30 min and Ultra violet ray exposure for a period of 60 min was also proved to be effective in virus inactivation. The surface decontamination can be carried out with lipid solvents like ethanol (>75%), isopropanol (>70%), formaldehyde (>0.7%), sodium hypochlorite (>0.21%), providone iodine (>0.23%), or hydrogen peroxide (>0.5%) [43].

5. Molecular pathogenesis - combat between COVID-19 & host cells

5.1. Pathology of COVID-19

SARS CoV-2 infects humans by gaining entry into the body mostly through the T-zone i. e, through eyes, nose and mouth. The presence of spike glycoproteins on the surface of SARS – CoV – 2 enables the viruses to enter host cells. The spike glycoproteins have two subunits; S1 and S2. S1 subunit of the glycoprotein, similar to SARS-CoV binds to ACE 2 receptor, a carboxypeptidase (E.C. 3.4.17.23), present on the surface of the cell, specifically in cells that are found in the lung and in the GI track and the other subunit, S2, fuses with the cell membrane [44]. ACE2 (Fig. 3) is a zinc metalloprotease whose activity increases up to 10 fold in presence of monovalent ions like Chlorine and Fluorine [45]. Angiotensin-I, a peptide hormone, is produced by the action of renin on angiotensinogen. Angiotensin-I is then converted to Angiotensin-II by an enzyme called angiotensin converting enzyme (ACE). The carboxypeptidase activity of ACE2 is best found by its hydrolytic activity over its high affinity substrates, Angiotensin-II, Apelin-13 and Dynorphin A 1–13 [45]. The K_M value for Angiotensin-II by ACE2 is 2 μM.

The reaction catalyzed by ACE2 is as follows Eq. (2):

$$Angiotensin - II + H_2O \rightarrow Angiotensin\ 1 - 7 + L - Phenylalanine \qquad (2)$$
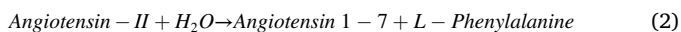
The product Angiotensin 1-7 is a vasodilator, whereas the Angiotensin-II is a vasoconstrictor. Patients are treated with ACE inhibitors and AT receptor blockers which are common types of high blood pressure medication. Recent studies have reported that the blood pressure medication can potentially increase the concentration of ACE 2 receptors on the surface of the cell. ACE 2 generates angiotensin from Angiotensin-II which then binds to Mas receptor and shifts the balance from vasoconstriction to vasodilation [44]. It was already found that the SARS-CoV exhibited its infection by binding to the ACE2 as its receptor [46]. A similar mechanism is observed in the case of SARS-CoV 2 [47, 48]. The structure of ACE2 shows a negatively charged ridge surrounding the catalytic site of this enzyme. This negatively charged ridge contributes as the docking site for the S1 domain of the viral spike protein or Receptor Binding Domain (RBD) of SARS-CoV [49]. Binding of viral spike protein with ACE 2 receptor is shown in Fig. 4. Being most affected organ, the lungs, once after the infection by SARS-CoV 2 there was a decrease in expression of ACE2 and thus resulting in resulting in accumulation of Angiotensin-II resulting in acute respiratory distress syndrome and fulminant myocarditis [50]. Apart from infecting lungs,
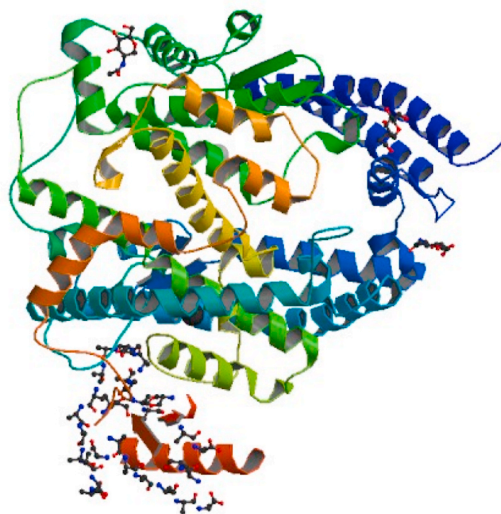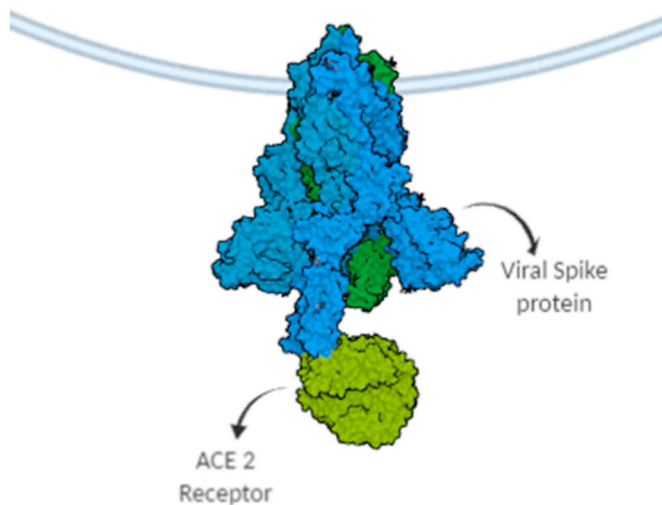

Fig. 4. Interaction between viral spike protein (Cyan-Blue color) and human ACE 2 receptor (Light green color) (PDB ID: 7A94). Image created using Bio-Render. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

SARS-CoV 2 found to infect digestive tract and nervous system. The infection in digestive or the GI tract is due to the high expression of ACE2, which became evident by the detection of SARS-CoV 2 in the fecal sample from patients [51]. Even a patient was found to be infected with SARS-CoV 2, where the virus was identified at the CSF sample, indicating that virus has the ability to cross the Blood Brain Barrier and infect the Central Nervous System [52]. The atomic level inspection of the binding of viral protein with the ACE2 was studied by Jinghua Yan et al. where by the important interactions between the amino acids of SARS-CoV 2 and ACE 2 for successful binding was described in Table 3 below:

Since immune cells play an important role against viral infections, overexpression of ACE in myeloid derived cells could be a promising approach for therapeutic manipulation, including the upregulation of immune cells to fight against COVID 19. Medications which causes an increase in Chloride ion concentration may also be a good choice to treat the infected people, since the activity of the ACE2 increases in presence of Chlorine and Fluorine. There is another protein called transmembrane serine protease, TMPRSS2, present adjacent to ACE 2. TMPRSS2 facilitate the entry of virus by two separate mechanisms. After the S1 subunit binds to the receptor on cell surface, TMPRSS2 activates the glycoprotein and cleaves ACE 2. TMPRSS2 also acts on the S2 subunit, causing an irreversible conformational change, activating it, and promoting fusion of the virus to the cell membrane. The mRNA of the virus then enters the cell [44].

Fig. 3. Structure of ACE2 (PDB ID: 1R42).

Table 3
Residues involved in binding of SARS-CoV2 and its receptor ACE2.

Location	Type of Interaction	SARS-CoV 2	ACE2
Interface of bound S1 and ACE2	H-Bond and Salt Bridge	A475	S19
		N487	Q24
		E484	K31
		Y453	H34
α3 of C-Terminal Domain	Ionic interaction	K417	D30
α1'/β1′ loop and β2'/η1′ loop	H-Bond	G446, Y449, G496, Q498, T500 and G502	D38, Y41, Q42, K353, D355
Further virus receptor packing	Hydrophobic interaction	Y489, F486	F28, L79, M82, Y83

5.2. Host cells response

In healthy adults, during the first week of incubation period the viral load is high which leads to increased number of leucocytes, immature neutrophils and erythroid cells [53,54]. The virus also affects the alveolar macrophages. The cytokine level increases in plasma [55]. The viral load gradually decreases on the second week due to the increased production of IgG and IgM antibodies against the virus. But in older people, person with comorbidities and low immunity have persistent lymphocytopenia especially hyperactivated CD4 and CD8 T cells [56], thrombocytopenia, diminished antibody production and prolonged viral shedding [55,57]. The expression of ACE2 receptor which is attached in the cell membranes of lungs, heart, kidneys and intestines is also high [54]. The C-reactive protein increases due to the inflammation. The prothrombin time increases which leads to increased D-dimer level [58]. The procalcitonin level increases due to the bacterial super infection [57]. The progressive stages of infection was depicted in Fig. 5 *(Image created using BioRender.com)*.

5.3. Histopathology

A hazy opacity called ground-glass opacity (GGO) was appeared in the lungs of infected patients [54]. The type II pneumocytes which is involved in the secretion of surfactants are deformed and damaged leading to the closure of alveoli [53]. Acute respiratory distress syndrome was observed due to the formation of hyaline membrane [53, 58]. The HA synthase 2 is upregulated during inflammation and it helps in the extrusion of hyaluronan (HA) from the cell surface which leads to the collection of clear jellies in the lungs [59]. The pulmonary edema causes congestion in the lungs leads to overlaid bacterial pneumonia [53]. The lymph nodal enlargement in the roots of the lungs and pleural effusion was observed [55,57]. The cytopathogenic effect and cilia dysfunction was also observed in the lungs. The gastrointestinal symptoms such as diarrhea, nausea and vomiting was observed in some patients because of highly expressed ACE2 receptor in intestinal epithelial cells [60]. Other than gastrointestinal symptoms liver damage is observed which leads to increased level of alanine aminotransferase (ALT), aspartate aminotransferase (AST), lactate dehydrogenase (LDH), creatine kinase and bilurubin [57,58,60,61]. The liver injury might be due to direct viral infection, necrosis caused by inflammatory agents of immune system or due to underlying diseases but is not well understood [62]. The Cerebro Spinal Fluid (CSF) tested positive cases are rarely observed in severely infected person and the pathogen attack with respect to central nervous system (CNS) is still unclear [52]. The person with underlying diseases like hypertension, cardiovascular diseases or diabetes develops severe injury in myocardial cells (Sufang Tian, Yong Xiong, Huan Liu, Li Niu, Jianchun Guo, Meiyan Liao, 2018; Zheng, Ma, Zhang, & Xie, 2020). The elevated level of troponin I protein is observed. The myocardial cell damage is also observed in patients without any underlying diseases which is due to inflammatory response of immune
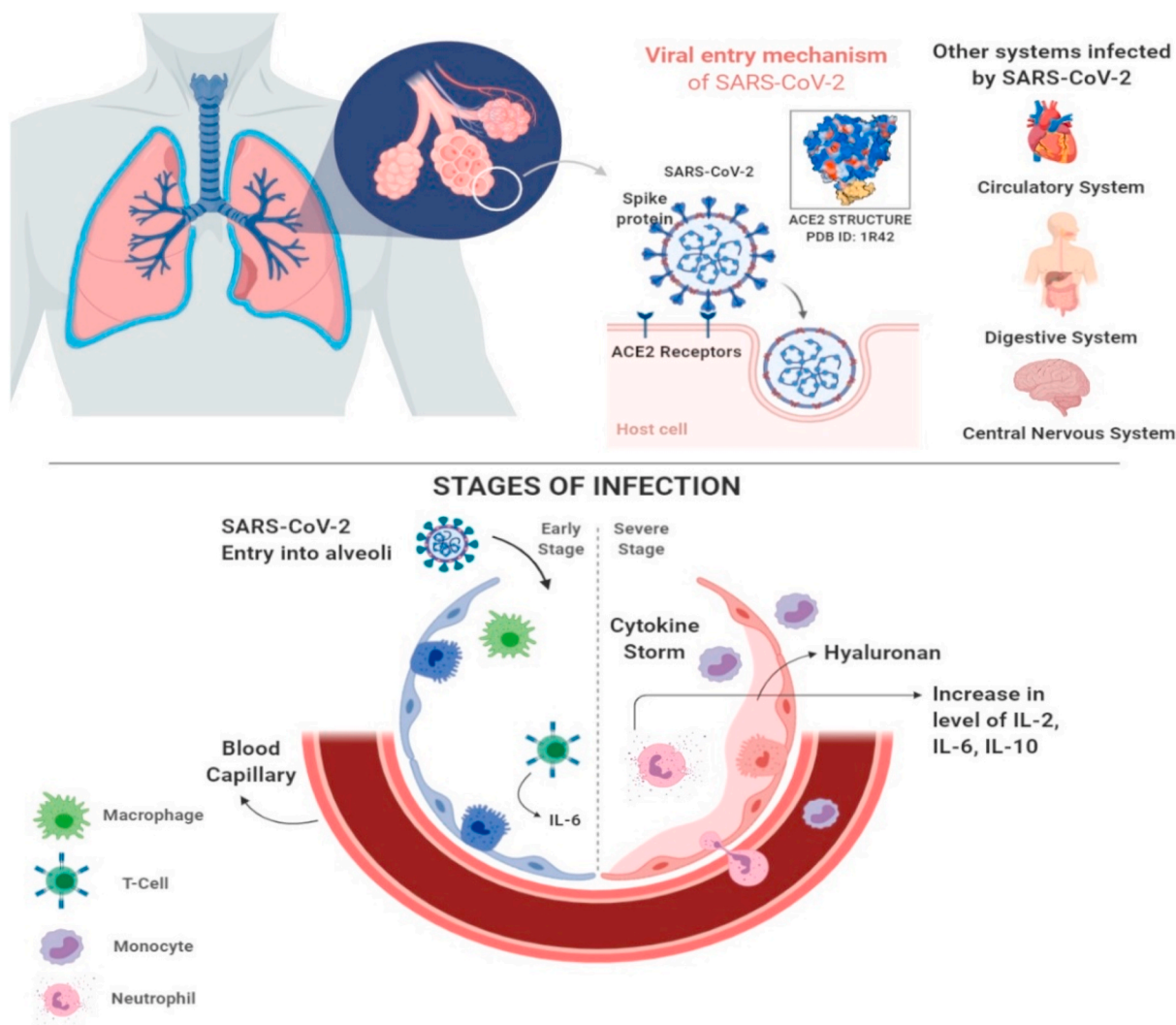

Fig. 5. Progressive stages of COVID-19 infection in Human Alveoli.

system or due to the use of anti-viral drugs [63].

6. Treatments for COVID-19

The treatment of COVID-19 is aimed in two different dimensions, (a) Antiviral based, (b) Host Based. The Drug development process should orderly possess the following three stages, (1) the broad-spectrum antiviral drugs which have been already existing to treat other viral infections has to be investigated using standard assays. This ensures the effect of these drugs on the following basis such as viral production and plaque formation of living cells and on the cytopathy. (2) The second is to screen the chemical libraries which contain a wide range of information about the compounds or databases. The obtained large number of compounds can be rapidly tested through high throughput screening and further assessed by antiviral assays. (3) The third is to reformulate new precise drugs based on the characteristics of the genome and biophysical understanding of the particular coronavirus. This method can become a clinically valuable treatment selection but it usually takes several years to procure a reliable therapy [64]. SARS-CoV-2 pertains to a vast family of positive-sense single-stranded RNA beta coronavirus which also contains SARS-CoV and MERS-CoV [65]. This genome encodes structural proteins (spike glycoprotein), non-structural proteins (such as RNA dependent RNA polymerase, papain-like protease, helicase and 3-chymotrypsin like protease) and accessory proteins. The spike glycoproteins are indispensable for the viral entry into the cell by inaugurating the virus-cell interactions and the four enzymes of non-structural proteins play a crucial role in the viral lifecycle are the desirable targets to develop an antiviral drug [66].

6.1. Anti-viral based targets

The viral-based treatment drugs are remdesivir, chloroquine, nitazoxanide, oseltamivir, darunavir, favipiravir, mefloquine [64,65,67,68]. The antiviral based treatment has gained much attention than the other due to the lack of reliable drugs that can deliver a desirable effect. The drugs such as lopinavir/ritonavir which significantly treated SARS-CoV and MERS-CoV are unsuccessful in the treatment of SARS-CoV-2 because of the absence of C2 catalytic pocket in which these drugs bind and it pertains to the class of cysteine protease family wherein the former belongs to the aspartic protease family [66]. Remdesivir (phosphoramidate prodrug of adenine derivative analogue which results in the premature termination of nascent viral RNA chain by incorporating with it) and chloroquine (an anti-malarial drug which rises the endosomal pH needed for virus/cell fusion) have shown the most promising impact against the SARS-CoV-2 in in-vitro with the very minimal half-maximal effective concentration of $EC_{50} = 0.77$ μM and $EC_{50} = 1.13$ μM respectively [65,69]. It is also evident that purine derivative analogues block the RNA dependent RNA polymerase enzyme of SARS-CoV-2 and even intravenous mode of remdesivir (GS-5734) which is a purine derivative analogue drug had recovered a patient with SARS-CoV-2 [66]. Some other drugs which also have anticoronal activity in in-vitro cell lines are ribavirin, penciclovir, cepharanthine, selamectin, galidesivir, disulfiram, imatinib and griffithsin [65–68]. But at present no drugs had been confirmed in the treatment of SARS-CoV-2 and all these drugs are used as supportive medications. The efficacy and safety of these drugs need to be confirmed in further clinical trials to treat SARS-CoV-2. We recommend the combination of drugs can be used to function more effectively against the SARS-CoV-2. The combination of drugs should be selected depending on all the possible mechanism of the virus attack. The nucleoside analogues, neuraminidase inhibitors and protease inhibitors with antibiotic treatment can be a promising combination in the treatment of SARS-CoV-2. Since the cocktail of drug treatment has shown some positive effect in the treatment of SARS-CoV-2, combinations of drugs paves a promising way to combat the virulence of SARS-CoV 2 [70].

6.2. Host-based treatment - stem cell treatment to COVID-19 patients

The important systems that are affected due to COVID-19 infection are respiratory and the cardiovascular system. The pathology of COVID-19 towards respiratory and cardiovascular system is due to the expression of ACE2, the receptor for COVID-19, leading to acute myocardial injury [63]. The respiratory system being the most affected, therapies are being developed for it. Using a histopathology report generated through biopsy of a 50 year old man, it was found that there exist a bilateral diffuse alveolar damage with cellular fibromyxoid exudates [56]. Stem cell therapy helps in curing and controlling the disease. Notably, Mesenchymal stem cells are used at this condition. Mesenchymal stem cells are less immunogenic and are capable of producing paracrine soluble factors, particularly anti-inflammatory factors like Interleukin-1 receptor antagonist, Interleukin-10, Prostaglandin-E_2 and some antimicrobial factors. Mesenchymal stem cells have been reported to be a potent remedy for acute lung injury [71]. Their various alveolar repair mechanism is shown in (Fig. 6). Patients affected with COVID-19 i. e, cases from critically severe to non-severe, were transplanted with mesenchymal stem cells as infusions and showed a very good pulmonary recovery thereafter. Administration of MSCs showed to normalize the abnormality in the white blood cells and the lymphocyte count to normal [72,73]. These mesenchymal stem cells were found not to be infected by the virus and showed a long term effect in anti-inflammatory factors production which is very much essential for the recovery from COVID-19 disease [74].

6.3. Host-based treatment - nanoparticles assisted treatment of COVID -19

Since the outbreak of novel coronavirus began in the late 2019, researchers have been reporting various treatment methods to fight against COVID – 19. One among them is the use of nanoparticles. Nanoparticles are promising candidate for the treatment of viral infections due to its unique properties, which are unlike the properties of bulk materials of same composition [75]. The nanoparticles based mechanism for virucidal activity or viral inhibition varies virus to virus. Magnetic nanoparticles as antiviral agent has been tested against various highly infectious viruses like zika virus, HCV, H5N2 [76–78]. Similarly, an attempt has been made to evaluate the efficacy of nanoparticles against COVID 19 [79]. The scanning electron microscopic image of SARS-CoV-2 (Fig. 7) isolated from a patient in the U.S revealed that the virus consists of a structure at nanoscale which can be disrupted using nanoparticles along with infrared light treatment. Iron based nanoparticles could attach to SARS-CoV-2, disrupting its structure and thus inactivating the potency of the virus to get through and survive in the human body. This approach of using nanoparticles for detecting and neutralizing virus is called theranostic approach, which focuses on combining diagnosis and therapy with the same particle. In addition, nanoparticles can also be used for deactivating viruses by spraying on objects and surfaces on which the viruses attach themselves. One of the main reasons for the lack of real time application of nanoparticles for the treatment of COVID - 19 is their size. Because of its permeating nature, nanoparticles can seep through other parts of the body. Even though iron based nanoparticles could be directed with magnetic fields to target organs, such as lungs and other areas which are susceptible to respiratory problems after viral infection, the studies to show that these nanoparticles are not spreading into the kidney or the brain during treatment is still under research.

6.4. In silico studies on various drug targets against COVID-19

Molecular docking studies carried out by researchers demonstrated that the bioactive compounds present in plants have the efficacy to inhibit COVID 19 and ACE 2. The Table 4 shows the list of compounds derived from plant sources with anticoronavirus activity. The values of
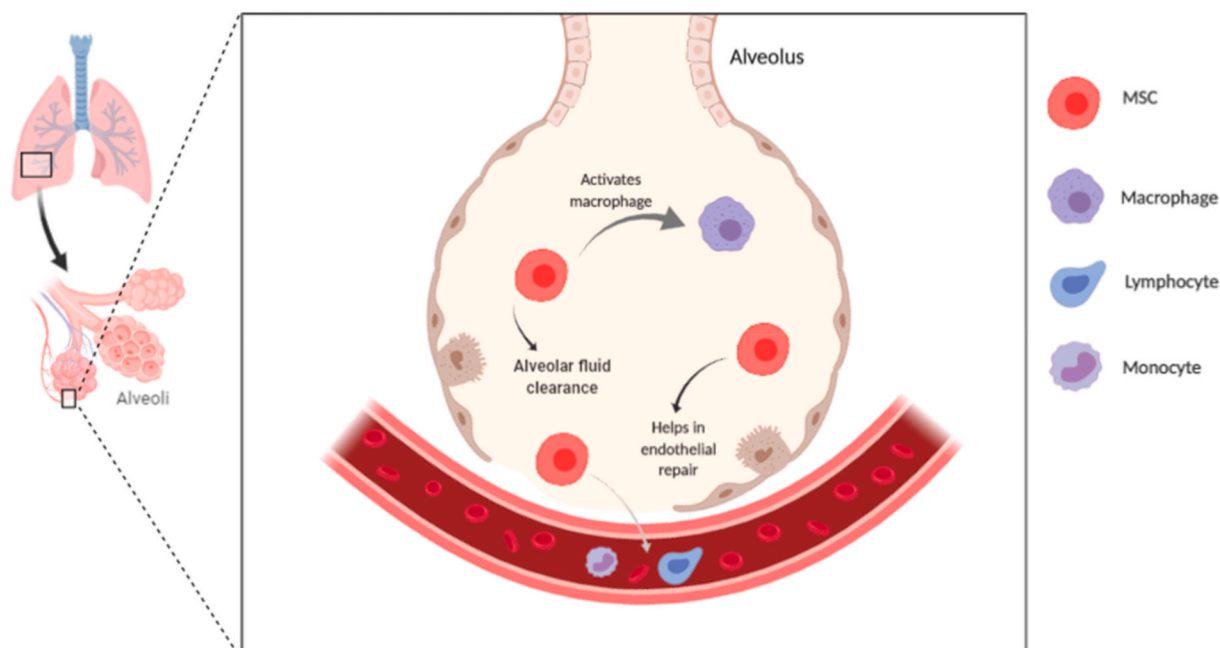
Fig. 6. Various alveolar repair mechanism exhibited by MSC. BioRender online tools were used to draw this image.
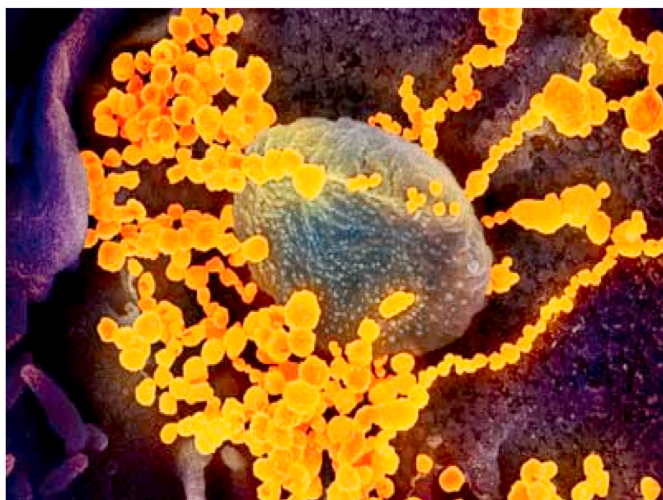

Fig. 7. Scanning electron microscope image of SARS-CoV-2 (round gold objects) emerging from the surface of cells cultured in the lab. (Source: NIAID – RML). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

Hesperidin, Rutin, Diosmin, Apiin and Diacetylcurcumin are in MolDock score [80], whereas the rest are the binding affinity scores of the molecules in Kcal/mol. The COVID-19 main protease, Papain like protease, RNA dependent RNA polymerase and ACE 2 protein were chosen as the main target in docking studies because inhibon of these targets results in inhibition of COVID 19 infection pathway. Compounds with lowest binding energies appeared to have the great potential to act as COVID 19 inhibitors. Plant based compounds having good binding affinity is a potential candidate for therapeutics against COVID 19 as they are components of dietary foods and biologically safe. Further in vivo and in vitro studies for the validation of plant derived compounds and drug design pave a way for these compounds in drug discovery and may represent potential options to treat SARS-CoV-2 infections.

6.5. Sterilization of personal protective equipment (PPE) using UV rays

Decontamination using UV rays is one among the physical methods that render harm to the viability of bacteria and virus by attacking their nucleic acid. During this pandemic situation, use of highly efficient and human-safe sterilization method is very much importance benefitting both the patients and health care workers. Among the various sterilization methods available, decontamination of PPE, like face shields, surgical masks, and N95 respirators, using ultraviolet germicidal irradiation (UVGI) as the high energy UV-C (254 nm) ray is found to be the most efficient one [91,92]. The UV-C rays were found to affect viruses like SARS-CoV, MARS-CoV [93]. In specific, use of mercury lamps for disinfection against bacteria and influenza virus was found to be effective since these lamps also produce Ozone and free radicals apart from UV-C [91,94]. Application of UV is relatively simple, avoids the use of chemicals and also less physical deformation was observed when UV irradiation was used rather than bleach, vaporized hydrogen peroxide and microwave irradiation [95]. Despite the advantages of UV method, the protocol by no means ensures complete sterilization or decontamination due to variation in the received dose by filtering faceplate respirators (FFRs) of different shape [96]. Studies related to UV decontamination is also limited by long time duration as higher dose is needed to inactivate virus on N95 FFRs compared to virus on gel or plate based media [97,98]. Ozone was also found useful in sterilization against SARS-CoV-2 [99].

6.6. Decontamination of facial mask by plasma generation

Facial masks plays an indispensable role in preventing the transmission of SARS CoV 2 but currently several countries are facing shortage of N95 masks which could affect health care workers as well as general public. There is an urge for reusing the masks after effective decontamination. Several research works are concentrating in decontamination of personal protection equipments by autoclave treatment, UV irradiation, hydrogen peroxide vaporisation and plasma generation. These works not only focus on improving decontamination efficiency but also tests the proper functionality of masks. Disinfection of contaminated masks by using ozone gas produced by DBD plasma generator was performed by Lee et al. In their work human coronavirus

Table 4
Various drug molecules identified using in silico approach to treat COVID-19.

Drug type	Name of the drug	Target	Binding energy (Kcal/mol) or MolDock score	Reference
Small Molecules	Darinaparsin	RNA Dependent RNAPolymerase	−82.52	[81]
		Nsp 9 replicase	−8.77	
		Nsp 15 endoribonuclease	−8.3	
		3CL Protease	−7.69	
		Papain Protease	−8.43	
		Furin (Host)	−7.23	
	CHEMBL127888	SARS-CoV-2 Main Protease	−104.89	[82]
	CHEMBL303543		−89.08	
	CHEMBL206650		−98.78	
	CHEMBL573507		−84.79	
Coenzyme	Flavin Adenine Dinucleotide (FAD)	Spike Glycoprotein	−11.089	[83]
	Coenzyme A		−11.555	
Rho kinase inhibitors	Fasudil/HA-1077	ROCK	–	[84]
	Y-27632	ROCK		
Anti-hypersensitive	Moexipril	ACE2 receptor	−13.24	[85]
Anti-hyper cholesterolemic	Rosavastanin	SARS-CoV-2 Main Protease	−12.30	
Antimalarial	Atovaquone		−8.145	
Antiretroviral	Darunavir		−14.03	
	Nelfinavir		−13.42	
	Lopanivir		−6.6 ± 0.3	[86]
Chemotherapeutic agent	Daunorubicin		−12.5	[85]
	Mitoxantrone		−13.81	
	Valrubicin		−7.2 ± 0.1	[86]
Anticancer agent	Carfilzomib	Proteasome	−13.8 ± 0.2	
Antibiotic	Streptomycin	SARS-CoV-2 Main Protease	−7.9 ± 0.4	
	Eravacycline		−7.7 ± 0.5	
	Talampicillin		−11.17	[87]
Anti-psychotic drug	Lurasidone		−11.17	
Antitumor drug	Rubetican	Type II Transmembrane Serine Protease	−9.47	
Anticonvulsant	Loprazolam	(TMPRSS2)	−9.31	
Anti-histaminic	Bepotastine	SARS-CoV-2 Main Protease	−10.63	[85]
Phytochemicals	Kempferol	COVID-19 Main Protease	−8.58	[88]
	Quercetin		−8.47	
	Luteolin-7-glucoside		−8.17	
	Demethoxycurcumin		−7.99	
	Naringenin		−7.89	
	Diallyl tetrasulfide	ACE2 receptor	−14.06	[89]
	Trisulfide,2-propenyl propyl		−14.01	
	Allyl disulfide		−12.84	
	Allyl trisulfide		−12.76	
	Allyl methyl trisulfide		−12.5	
	Hesperidin	COVID 19 Main Protease	−178.5910	[80]
	Rutin		−176.2740	
	Diosmin		−174.1260	
	Apiin		−171.0080	
	Diacetylcurcumin		−169.2550	
	5,7,3′,4′-Tetrahydroxy2'-(3,3-dimethyallyl) isoflavone	3- Chymotrypsin like cysteine protease	−29.57	[90]
	Myricitrin		−22.13	
	Methyl rosmarinate		−20.62	
	3,5,7,3′,4′,5′-hexahydroxy flavanone-3-O-beta-ᴅ-glucopyranoside		−19.10	

(HCoV-229E) was used as surrogate for SARS CoV-2 [100]. Ozone one of the powerful oxidizing agent has damaged the surface proteins which led to inability of virus attachment to the surface of mask. But the generated ozone gas did not affect the viral RNA. However their work proved there is no damage to structure of facial mask after treatment and they could be reused. Another study, by Kumar et al. experimented the efficiency of various techniques for sterilization which included low temperature hydrogen peroxide gas plasma treatment. Here 59% hydrogen peroxide liquid was used to generate plasma to remove *Vesicular stomatitis virus* as surrogate for SARS CoV-2. This work resulted in complete decontamination of virus coated mask [101]. Although hydrogen peroxide plasma treatment tends to be an effective method for decontamination, structure of mask gets affected after one cycle of treatment. Cold Atmospheric Plasma (CAP) produced using helium gas releases several Reactive Oxygen Species (ROS), Reactive Nitrogen Species (RNS), charged particles and other free radicals which could damage cell membrane, nucleic acids, and proteins present in virus. Chen et al. developed CAP devices for the purpose of sterilization and treatment of COVID 19. They explained the possible mechanisms for the destruction of virus by the species generated in CAP devices [102]. The plasma treatment sounds to better technique for sterilization of PPE and hence scientific community could concentrate on applicability of this technique to prevent the further spread of COVID 19.

6.7. Induction of acquired immunity against SARS CoV-2

6.7.1. Plasma therapy for SARS CoV-2

Acquired immunity can be expected to prevent or fight against the SARS CoV – 2 effectively. Convalescent plasma therapy is a passive mode of acquired immunity. The Convalescent plasma contains the neutralizing antibodies of SARS Cov 2 which is collected from the recovered patients of Covid 19. Recovery rate is also good in several

Table 5
Siddha based Poly Herbal Formulations against Viral Outbreaks.

Name of the disease	Name of Polyherbal formulation	List of Poly Herbs
Dengue Fever (Pitham suram)	Nilavembu kudineer	✓ Nilavembu (Andrographis paniculata), ✓ Vettiver (Vetiveria zizanioides), ✓ Vilamichu ver (Plectranthus vettiveroides), ✓ Chandanam (Santalum album), ✓ Peipudal (Trichosanthes cucumerina), ✓ Koraikilangu (Cyperus rotundus), ✓ Chukku (Zingiber officinale), ✓ Milaku (Piper nigrum) ✓ Parppadakam (Mollugo cervicana).
Swine Flu (Kabham Suram)	Kaba sura kudineer	✓ Nilavembu (Andrographis paniculata), ✓ Kanduparangi (Clerodendrun serratum), ✓ Chukku (dried ginger), ✓ Thippili (piper longum), ✓ Ilavangam (Syzygium aromaticum), ✓ Adathodai ver (root of Justicia beddomei), ✓ Cirukancori Ver (Tragia involucrate), ✓ Seenthil (Tinosporia cordifolia), ✓ Karpooravalli (Anisochilus carnosus), ✓ Koraikizhangu (Cyperus rotundus), ✓ Kostam (Costus speciosus), ✓ Akkara (Anacyclus pyrethrum), ✓ Vattathiruppi Ver (Sida acuta), ✓ Mulli Ver (Hygrophilla auriculata), ✓ Kadukkaithol (Terminalia chebula)
Immune boosters		✓ Decoction of de-skinned Ginger with honey. ✓ Soup of Kandankathiri (Solanum virginianum), Thoothuvalai (Solanum Trilobatum) and Aadathodai (Aadathoda Vasica) ✓ Thippili (Piper longum), ✓ Adi mathuram (Glycyrrhiza glabra) ✓ Palm Jaggery. ✓ Drink milk with a small amount of Pepper powder, turmeric power and Palm Jaggery

studies which accompanied with the use of other anti-viral drugs [103–105]. It is also notable in a particular study that though, convalescent plasma treatment stopped the viral shedding it could not prevent the mortality of 5 out of 6 severely affected patients who were infused with convalescent plasma at a later stage that is a median of 21.5 days after the detection of viral shedding [106]. Extensive use of convalescent plasma can be encouraged if the potential risks are carefully screened and studies on safety and efficacy of convalescent plasma therapy are done. The potential risks include cross infection of other viruses like HIV, hepatitis B and hepatitis C, allergic transfusion reactions, transfusion induced circulatory overload, transfusion related acute lung injury [107].

6.7.2. Vaccine for SARS CoV-2

Different approaches for vaccine development against SARS CoV-2 has been implemented which encompasses viral vector based vaccines, DNA & RNA based vaccines and the protein subunit and virus like particle vaccines [108]. The important component of the SARS CoV-2 that is being focused is the Spike protein, since it induces the generation of host's antibodies to neutralize them [109]. Hence both protein and nucleic acid based vaccine could provide a promising vaccine component against SARS CoV-2.

7. Promising control measure - traditional treatments for COVID-19

Explore the power of Herbs for Safe & Healthy Society - Though western method of treatments are being practiced to cure COVID-19, indigenous medicines are also tried by the respective nations to combat the disease. Globally, two most ancient medicinal practices are, Traditional Indian Medicine (TIM) and Traditional Chinese Medicine (TCM) which have strong philosophical and psychological base in respective geographical regions. Notably Traditional Chinese Medicine (TCM) were found to

treat the pneumonia caused by COVID-19 [110]. In TCM, ShuFengJieDu Capsules and Lianhuaqingwen Capsule are proposed to be a good drug candidate for the treatment [111,112]. Besides the goodness of TCM, it was also found that the use of bats to prepare medicinal compounds acts as a reason behind the zoonotic transmission of SARS-CoV-2 to humans [113,114]. Though, Traditional Chinese Medicine (TCM) is highly efficient and popular as Traditional Indian Medicine (TIM), the utilisation of TCM as a regular food habit is very less as compared with India. Both the practices operates based on the healthy life style as an integral part of human life. Their treatment is based on the proverb, "*Prevention is better than cure*". TIM is a cluster of 5 different medicinal practices, AYUSH: (a) Ayurveda, (b) Yoga and Naturopathy, (c) Unani, (d) Siddha and (e) Homoeopathy. The basic principle is based on the balance among five primordial elements: Earth, Water, Fire, Air and Space and among three humours: Vatham, Pitham and Kabham. A healthy individual will be having an equilibrium in humours whereas an imbalance in the equilibrium leads to a diseased state. Out of these, Siddha system of medicine (Traditional Tamil System of medicine) has its origin back to B.C 10,000 to B.C 4000. The Principles of siddha medicine says, 64 types of fever (suram) occurs because of the accumulation of humour - Kabham in the GI tract as a result of that there is a decrease in the humour – Pitham in the stomach and intestine called as Pitham suram. Siddha system aims to eliminate the root cause rather than treating the symptoms. A polyherbal formulation, "Nilavembu kudineer" has been proved against dengue and chikungunya virus [115,116]. Similarly, for swine flu as Kabham Suram, "Kaba sura kudineer" was used to treat the patients and was found to be efficient. In Tamil Nadu, India, during the dengue and swine flu outbreaks, Government of Tamil Nadu along with siddha medicine declared Nilavembu and Kaba sura kudineer decoction as preventive and controlling measure against the above said viral fever respectively. The recovery rate of the treatment was very high. The formulations are listed in Table 5. The natural immune system could be increased by immune boosters as listed below, which could probably

combat effectively against COVID-19. The attempts to try AYUSH based medicines as immune boosters and curative for COVID-19 are taking place in India [117].

8. Learning from experience – mitigation measures by various countries

China, being the first country to encounter this crisis has implemented some notable restrictions to control this outbreak. The nationwide lockdown, rapid isolation of confirmed cases, suspected cases, quarantining them, improving the rates of clinical management and diagnostic testing paved the way for the country to bring this crisis under control [69,118]. The aggressive implementation of this method by the country made it feasible to control the pandemic outbreak. While several other countries which adopted this method from China aren't able to control this viral infection due to the inadequate support from the government and lack of public responsibility. Besides this, some nations like South Korea, Singapore and Japan have shown tremendous control over this pandemic outbreak of SARS-CoV-2. These countries had a well-executed plan to meet this pandemic outbreak which may be due to the previous lessons from the SARS and MERS outbreak. The key control over this infectious disease is the earlier diagnosis. Keeping in mind that the earlier diagnosis is the only way to control this disease. South Korea had a diagnostic capacity of 5200 tests per day, the awareness message about SARS-CoV-2 was illustrated everywhere on the streets, public transports and through media. The South Korean Government also developed two mobile applications to continuously monitor and support the people. (i)The first application was developed for people arriving in South Korea from high-risk regions, they were continuously monitored by answering daily questions about their symptoms and also they were assisted with telecalling executives in case of development in symptoms for arranging diagnostic test through the application. (ii) The other application notifies public officials when someone from quarantine leaves the isolation zone. In addition to this, the government also strengthened this by "national mobile phone alert system" which cautions residents of the respective areas to be alert when a new case of SARS-CoV-2 is detected and also the alert system carries a link about the precise information about the last few areas where the patient had travelled through [119]. Use of GPS in monitoring the spread is a non-invasive technique and gives an ease to collect data, of which a valuable work done by the National Informatics Centre (NIC) of Indian Government is the launch of Aarogya Setu app for its subjects. This app development was initiated by the Department of Health and the database management is carried out by the Empowered Group 9. The Government of India made it mandatory to install the app to effectively monitor the pandemic, which resulted in about 114 million population of users as on 26th May [120] of which 72.76% of the users found it useful [121]. It's a contact tracing app that is based on crowdsourcing concept which uses the benefit of Bluetooth and GPS to track the movement of an individual in and around a containment zone. Apart from tracking, the app has self-medical evaluating option that benefits the user. While Singapore developed an innovative clinical diagnosis for earlier detection of infection and the Ministry of Health Department ensured public health through a video call. The private clinics in Singapore were also used to carry out a diagnostic test by providing physicians in private clinics with additional training to diagnose suspected individuals. In the case of suspected individuals showing respiratory symptoms, they were assisted with subsidized treatment and medications in that clinic. The government also covered all the health care expenses for individuals with a positive sign of the disease. This reduced the barriers for the individual and those people seeking help [122]. Japan followed PCR screening to test suspected individual in a rate of 6000 samples per day and also provided elderly people with social welfare facilities [123]. These control measures greatly reduced the spread of SARS-CoV-2 and brought complete control over the pandemic outbreak in these countries.

9. Looking through the COVID-19 lens for a sustainable new-modern society

As humans are running through a busy world with an increased population explosion, our focus is only on digitisation of the society and economic growth. Humans have also become greedy and started consuming excess foods and resources from environment and forgot to think about moving in a sustainable way. This rapid consumption has caused disturbance to the Mother Nature and many problems are being faced by humans because of this imbalance, including COVID-19 pandemic. In general, 2020 seems to be an unusual year as the pandemic COVID-19 has affected the way of living as well as the economic growth of people to a greater extent [124]. Many health care systems as well as industries are also facing a crucial period during this time. But in another point of view, when we look into the society through COVID-19 lens it can be seen that, this pandemic is also giving a new chance for humans to rethink on moving towards sustainable future and also a way for regaining the natural environment and to live in harmony with it. Humans should look deeply into the positive side of COVID-19. In recent times, the only focus of industries were about surviving on top but this pandemic gave a chance to think on sustainable ways of developing processes in industries. All food as well as water sectors should also take this as a chance to invent zero waste technologies so that the level of pollution can be controlled even after the situations have become normal. Replacing the fossil fuel sources by renewable energy based infrastructures in energy sectors can help them in achieving circular economy conditions. The transportation sectors should also take their next step towards electrification of transport systems so that the emission of pollutants into atmosphere can be controlled to a greater level. By adopting these transformations, an environment of zero carbon, zero emission and zero wastes can be achieved by humans and the climate change which is one of the biggest problems being faced by humans can also be mitigated [125]. Many changes are also being experienced because of COVID-19 as people have started relying more on online shopping, online education systems, tele medical diagnostics, e-commerce, e-banking facilities, etc. These digital transformations are necessary for societal running but maintaining a healthy living environment and proper mental health of humans is also an important part and a basic human right. Thus COVID-19 has made us to rethink about the current unsustainable environment and gave us an enlightenment for transition towards a sustainable new modern society [126]. Always the blessing of nature is a must for the humans to lead a proper and peaceful life and hereafter our focus should turn towards maintaining circular economy and providing a sustainable environment for the future.

10. Conclusion

In this review, epidemiology and pathology of COVID 19 has been discussed. The outbreak of COVID 19 pose major challenge to economic, medical and public health infrastructure of 199 countries and territories around the world and 2 international conveyances. Coronavirus pandemic have highlighted the need to reinforce public health capabilities, including disease control systems and health care workforce. Understanding the epidemiology and pathology of the virus holds a great promise for diagnosis and treatment of infection. Many research groups are focused towards developing a specific diagnostic kit for the detection of COVID 19 and it has been found that immunoassays and CRISPR technology are highly specific and could diagnose within short period of time. Several treatment methods have been proposed as supportive medication. Common laboratory findings include viral based treatment and host based treatment. But till date there is no specific treatment for COVID 19 and the development of supportive and symptomatic treatment is yet to be established. Prevention requires home isolation of suspected individuals and strict control measures have been followed at hospitals and health care centres to prevent infection from

one person to other. Continuing investigation of COVID 19 could lead to a novel and important discoveries, particularly concerning the human immune system, with real potential to fight against the disease. Moreover, there is a great chance of encountering new species of viruses in near future. Therefore, efforts should be made to devise a scientific approach to rapidly detect and evaluate the threat associated with viral infection whenever necessary. Specific training in disease surveillance and epidemic preparedness and response, strengthening healthcare systems worldwide, development of standard case management protocols for epidemic diseases could be a possible way to reduce mortality and morbidity due to pandemics.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2020.102120.

References

[1] 24 J.S. Kahn, K. Mcintosh, History and Recent Advances in Coronavirus Discovery, 223–227, https://doi.org/10.1097/01.inf.0000188166.17324.60, 2005.

[2] R.G. Webster, Wet markets - a continuing source of severe acute respiratory syndrome and influenza? Lancet (2004) https://doi.org/10.1016/S0140-6736(03)15329-9.

[3] M.S. Nassar, M.A. Bakhrebah, S.A. Meo, M.S. Alsuabeyl, W.A. Zaher, Middle East Respiratory Syndrome Coronavirus (MERS-CoV) infection: epidemiology, pathogenesis and clinical characteristics, Eur. Rev. Med. Pharmacol. Sci. 22 (2018) 4956–4961, https://doi.org/10.26355/eurrev_201808_15635.

[4] N. Zhu, D. Zhang, W. Wang, X. Li, B. Yang, J. Song, X. Zhao, B. Huang, W. Shi, R. Lu, P. Niu, F. Zhan, X. Ma, D. Wang, W. Xu, G.F. Gao, W. Tan, A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. (2020), https://doi.org/10.1056/NEJMoa2001017.

[5] WHO (World Health Organization), Statement on the Meeting of the International Health Regulations (2005) Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV), WHO Newsl, 2020.

[6] Y. Fan, K. Zhao, Z.L. Shi, P. Zhou, Bat coronaviruses in China, viruses. https://doi.org/10.3390/v11030210, 2019.

[7] A.M. Zaki, S. Van Boheemen, T.M. Bestebroer, A.D.M.E. Osterhaus, R.A. M. Fouchier, Isolation of a novel coronavirus from a man with pneumonia in Saudi Arabia, N. Engl. J. Med. (2012), https://doi.org/10.1056/NEJMoa1211721.

[8] S.P. Adhikari, S. Meng, Y.-J. Wu, Y.-P. Mao, R.-X. Ye, Q.-Z. Wang, C. Sun, S. Sylvia, S. Rozelle, H. Raat, H. Zhou, Epidemiology, causes, clinical manifestation and diagnosis, prevention and control of coronavirus disease (COVID-19) during the early outbreak period: a scoping review, Infect. Dis. Poverty. (2020), https://doi.org/10.1186/s40249-020-00646-x.

[9] N. van Doremalen, T. Bushmaker, D.H. Morris, M.G. Holbrook, A. Gamble, B. N. Williamson, A. Tamin, J.L. Harcourt, N.J. Thornburg, S.I. Gerber, J.O. Lloyd-Smith, E. de Wit, V.J. Munster, Aerosol and surface stability of SARS-CoV-2 as compared with SARS-CoV-1, N. Engl. J. Med. 2019 (2020), https://doi.org/10.1056/NEJMc2004973.

[10] WHO, Report of the WHO-China joint mission on coronavirus disease 2019 (COVID-19), Who 2019 (2020) 16–24.

[11] V. Colizza, A. Barrat, M. Barthélemy, A. Vespignani, Predictability and epidemic pathways in global outbreaks of infectious diseases: the SARS case study, BMC Med. 5 (2007), https://doi.org/10.1186/1741-7015-5-34.

[12] A. Flahault, Correspondence Has China faced only a herald wave of, Lancet 6736 (2020) 30521, https://doi.org/10.1016/S0140-6736(20)30521-3.

[13] G. Chowell, S. Blumberg, L. Simonsen, M.A. Miller, C. Viboud, Synthesizing data and models for the spread of MERS-CoV, 2013: key role of index cases and hospital transmission, Epidemics 9 (2014) 40–51, https://doi.org/10.1016/j.epidem.2014.09.011.

[14] M. Ely, R. Hardy, N.T. Longford, M.E.J. Wadsworth, Gender differences IN the relationship between alcohol consumption and drink problems are largely accounted for by body water 34 (1999) 894–902.

[15] T. Barr, C. Helms, K. Grant, I. Messaoudi, Opposing effects of alcohol on the immune system, Prog. Neuro-Psychopharmacol. Biol. Psychiatry (2015), https://doi.org/10.1016/j.pnpbp.2015.09.001.

[16] S.H. Mahassni, E.Y.I. Ali, The effects of firsthand and secondhand cigarette smoking on immune system cells and antibodies in Saudi Arabian males, Indian J. Clin. Biochem. (2018), https://doi.org/10.1007/s12291-018-0739-9.

[17] X.Z. Huajun Bai, Xiaolong Cai, Landscape Coronavirus Disease 2019 Test (COVID-19 Test) in Vitro - A Comparison of PCR vs Immunoassay vs Crispr-Based Test, 2019.

[18] F. Zhang, O.O. Abudayyeh, J.S. Gootenberg, C. Sciences, L. Mathers, A Protocol for Detection of COVID-19 Using CRISPR Diagnostics, 2020, pp. 1–8.

[19] L. Curti, F. Pereyra-Bonnet, C. Gimenez, An ultrasensitive, rapid, and portable coronavirus SARS-CoV-2 sequence detection method based on CRISPR-Cas12, BioRxiv (2020), https://doi.org/10.1101/2020.02.29.971127, 2020.02.29.971127.

[20] X. Zou, J. Wu, J. Gu, L. Shen, L. Mao, Application of aptamers in virus detection and antiviral therapy, 10, https://doi.org/10.3389/fmicb.2019.01462, 2019.

[21] D. Ahn, I. Jeon, D. Kim, M. Song, S. Han, S. Lee, RNA Aptamer-Based Sensitive Detection of SARS Coronavirus Nucleocapsid Protein, 1896–1901, https://doi.org/10.1039/b906788d, 2009.

[22] W.Y. Wan, S.H. Lim, E.H. Seng, Cross-reaction of sera from COVID-19 patients with SARS-CoV assays, MedRxiv (2020), https://doi.org/10.1101/2020.03.17.20034454, 2020.03.17.20034454.

[23] S. Ee, F. Yong, D.E. Anderson, W.E. Wei, J. Pang, W.N. Chia, C.W. Tan, Y.L. Teoh, M.I. Chen, S. Vasoo, B. Ong, Y.S. Leo, L. Wang, V.J.M. Lee, Connecting clusters of COVID-19 : an epidemiological and serological investigation, Lancet Infect. Dis. 3099 (2020) 1–7, https://doi.org/10.1016/S1473-3099(20)30273-5.

[24] Z.B. Hu, C. Ci, [Screening and management of asymptomatic infection of corona virus disease 2019 (COVID-19)], Zhonghua Yufang Yixue Zazhi (2020), https://doi.org/10.3760/cma.j.cn112150-20200229-00220.

[25] H. Shi, X. Han, N. Jiang, Y. Cao, O. Alwalid, J. Gu, Y. Fan, C. Zheng, Radiological findings from 81 patients with COVID-19 pneumonia in Wuhan, China: a descriptive study, Lancet Infect. Dis. (2020), https://doi.org/10.1016/S1473-3099(20)30086-4.

[26] K. Wang, S. Kang, R. Tian, X. Zhang, X. Zhang, Y. Wang, Imaging manifestations and diagnostic value of chest CT of coronavirus disease 2019 (COVID-19) in the Xiaogan area, Clin. Radiol. (2020), https://doi.org/10.1016/j.crad.2020.03.004.

[27] 7 I. Disease, D.K.W. Chu, Y. Pan, S.M.S. Cheng, K.P.Y. Hui, P. Krishnan, Y. Liu, D. Y.M. Ng, C.K.C. Wan, P. Yang, Q. Wang, M. Peiris, L.L.M. Poon, Molecular diagnosis of a novel coronavirus (2019-nCoV) causing an outbreak of pneumonia, 1–7, https://doi.org/10.1093/clinchem/hvaa029, 2020.

[28] P.C.Y. Woo, S.K.P. Lau, B.H.L. Wong, H. Tsoi, A.M.Y. Fung, R.Y.T. Kao, K. Chan, J. S.M. Peiris, K. Yuen, Differential sensitivities of severe acute respiratory syndrome (SARS) coronavirus spike polypeptide enzyme-linked immunosorbent assay (ELISA) and SARS coronavirus nucleocapsid protein, ELISA for Serodiagnosis of SARS Coronavirus Pneumonia 43 (2005) 3054–3058, https://doi.org/10.1128/JCM.43.7.3054.

[29] C. Sheridan, Fast, portable tests come online to curb coronavirus pandemic. https://doi.org/10.1038/d41587-020-00010-2, 2020.

[30] C. Sheridan, Coronavirus and the race to distribute reliable diagnostics. https://doi.org/10.1038/d41587-020-00002-2, 2020.

[31] J. Xiang, M. Yan, H. Li, T. Liu, C. Lin, S. Huang, C. Shen, Evaluation of enzyme-linked immunoassay and colloidal gold- immunochromatographic assay kit for detection of novel coronavirus (SARS-Cov-2) causing an outbreak of pneumonia (COVID-19), MedRxiv (2020), https://doi.org/10.1101/2020.02.27.20028787, 2020.02.27.20028787.

[32] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, J. Pharm. Anal. 10 (2020) 102–108, https://doi.org/10.1016/j.jpha.2020.03.001.

[33] V.C.C. Cheng, S.C. Wong, J.H.K. Chen, C.C.Y. Yip, V.W.M. Chuang, O.T.Y. Tsang, S. Sridhar, J.F.W. Chan, P.L. Ho, K.Y. Yuen, Escalating infection control response to the rapidly evolving epidemiology of the Coronavirus disease 2019 (COVID-19) due to SARS-CoV-2 in Hong Kong, Infect. Control Hosp. Epidemiol. 2019 (2020), https://doi.org/10.1017/ice.2020.58.

[34] W. Ahmed, N. Angel, J. Edson, K. Bibby, J.W.O. Brien, P.M. Choi, M. Kitajima, L. Simpson, J. Li, B. Tscharke, R. Verhagen, J.M. Smith, J. Zaugg, L. Dierens, P. Hugenholtz, K. V Thomas, J.F. Mueller, First confirmed detection of SARS-CoV-2 in untreated wastewater in Australia: a proof of concept for the wastewater surveillance of COVID-19 in the community, Sci. Total Environ. (2020).

[35] W. Wang, Y. Xu, R. Gao, R. Lu, K. Han, G. Wu, W. Tan, Detection of SARS-CoV-2 in different types of clinical specimens, JAMA, J. Am. Med. Assoc. (2020) 29–30, https://doi.org/10.1001/jama.2020.3786.

[36] V. Naddeo, H. Liu, Editorial Perspectives: 2019 novel coronavirus (SARS-CoV-2): what is its fate in urban water cycle and how can the water research community respond? Environ. Sci. Water Res. Technol. (2020) https://doi.org/10.1039/d0ew90015j.

[37] U.S. Department of Labor, Occupational Safety and Health Administration, Guidance on Preparing Workplaces for COVID-19, Saf. Heal., 2020.

[38] 126 X. Wang, J. Li, M. Jin, B. Zhen, Q. Kong, N. Song, W. Xiao, J. Yin, W. Wei, G. Wang, B. Si, B. Guo, C. Liu, G. Ou, M. Wang, T. Fang, F. Chao, J. Li, Study on the resistance of severe acute respiratory syndrome-associated coronavirus, 171–177, https://doi.org/10.1016/j.jviromet.2005.02.005, 2005.

[39] S.W.X. Ong, Y.K. Tan, P.Y. Chia, T.H. Lee, O.T. Ng, M.S.Y. Wong, K. Marimuthu, Air, surface environmental, and personal protective equipment contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) from a symptomatic patient, JAMA, J. Am. Med. Assoc. 323 (2020), https://doi.org/10.1001/jama.2020.3227.

[40] J. Wang, H. Feng, S. Zhang, Z. Ni, L. Ni, Y. Chen, L. Zhuo, Z. Zhong, T. Qu, SARS-CoV-2 RNA detection of hospital isolation wards hygiene monitoring during the Coronavirus Disease 2019 outbreak in a Chinese hospital, Int. J. Infect. Dis. 94 (2020) 103–106, https://doi.org/10.1016/j.ijid.2020.04.024.

[41] S. Faridi, S. Niazi, K. Sadeghi, K. Naddafi, J. Yavarian, M. Shamsipour, N.Z. S. Jandaghi, K. Sadeghniiat, R. Nabizadeh, M. Yunesian, F. Momeniha, A. Mokamel, M.S. Hassanvand, T. MokhtariAzad, A field indoor air measurement of SARS-CoV-2 in the patient rooms of the largest hospital in Iran, Sci. Total Environ. 725 (2020) 1–5, https://doi.org/10.1016/j.scitotenv.2020.138401.

[42] A.W.H. Chin, J.T.S. Chu, M.R.A. Perera, K.P.Y. Hui, H. Yen, M.C.W. Chan, M. Peiris, L.L.M. Poon, Stability of SARS-CoV-2 in different environmental conditions, The Lancet Microbe 5247 (2020) 2004973, https://doi.org/10.1016/s2666-5247(20)30003-3.

[43] P.M. Duarte, V.P. de Santana, Disinfection measures and control of SARS-CoV-2 transmission, Glob. Biosecurity. 1 (2020).

[44] CEBM, Angiotensin converting enzyme (ACE) inhibitors and angiotensin receptor blockers in COVID-19. https://www.cebm.net/COVID-19/angiotensin-convertin g-enzyme-ace-inhibitors-and-angiotensin-receptor-blockers-in-COVID-19, 2020.

[45] C. Vickers, P. Hales, V. Kaushik, L. Dick, J. Gavin, J. Tang, K. Godbout, T. Parsons, E. Baronas, F. Hsieh, S. Acton, M. Patane, A. Nichols, P. Tummino, Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase, J. Biol. Chem. 277 (2002) 14838–14843, https://doi.org/10.1074/jbc.M200581200.

[46] A.J. Turner, J.A. Hiscox, N.M. Hooper, ACE2: from vasopeptidase to SARS virus receptor, Trends Pharmacol. Sci. 25 (2004) 291–294, https://doi.org/10.1016/j.tips.2004.04.001.

[47] Y. Chen, K. Shao, W. Qian, Asians do not exhibit elevated expression or unique genetic polymorphisms for ACE2, the cell-entry receptor of SARS-CoV-2, 1–13, https://doi.org/10.20944/preprints202002.0258.v2, 2020.

[48] M. Hoffmann, H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, T. S. Schiergens, G. Herrler, N.-H. Wu, A. Nitsche, M.A. Müller, C. Drosten, S. Pöhlmann, SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor, Cell (2020) 1–10, https://doi.org/10.1016/j.cell.2020.02.052.

[49] P. Prabakaran, X. Xiao, D.S. Dimitrov, A model of the ACE2 structure and function as a SARS-CoV receptor, Biochem. Biophys. Res. Commun. 314 (2004) 235–241, https://doi.org/10.1016/j.bbrc.2003.12.081.

[50] T.C. Hanff, M.O. Harhay, T.S. Brown, J.B. Cohen, A.M. Mohareb, Is there an association between COVID-19 mortality and the renin-angiotensin system - a call for epidemiologic investigations, Clin. Infect. Dis. (2020). https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa329/5811880.

[51] F. Xiao, M. Tang, X. Zheng, Y. Liu, X. Li, H. Shan, Evidence for gastrointestinal infection of SARS-CoV-2, Gastroenterology (2020), https://doi.org/10.1053/j.gastro.2020.02.055.

[52] T. Sun, J. Guan, Novel coronavirus and central nervous system Authors : Correspondence:, (n.d.). https://doi.org/10.1111/ene.14227.

[53] S. Tian, Y. Xiong, H. Liu, L. Niu, J. Guo, M. Liao, S.Y. Xiao, Pathological study of the 2019 novel coronavirus disease (COVID-19) through postmortem core biopsies, Mod. Pathol. 33 (2020) 1007–1014, https://doi.org/10.1038/s41379-020-0536-x.

[54] Y. Chen, L. Li, SARS-CoV-2: virus dynamics and host response, Lancet Infect. Dis. 20 (2020) 515–516, https://doi.org/10.1016/S1473-3099(20)30235-8.

[55] J. Liu, X. Zheng, Q. Tong, W. Li, B. Wang, K. Sutter, M. Trilling, M. Lu, U. Dittmer, D. Yang, Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV, J. Med. Virol. (2020), https://doi.org/10.1002/jmv.25709, 0–2.

[56] Z. Xu, L. Shi, Y. Wang, J. Zhang, L. Huang, C. Zhang, S. Liu, P. Zhao, H. Liu, L. Zhu, Y. Tai, C. Bai, T. Gao, J. Song, P. Xia, J. Dong, J. Zhao, F.S. Wang, Pathological findings of COVID-19 associated with acute respiratory distress syndrome, Lancet Respir. Med. 2600 (2020) 19–21, https://doi.org/10.1016/S2213-2600(20)30076-X.

[57] J.F.W. Chan, S. Yuan, K.H. Kok, K.K.W. To, H. Chu, J. Yang, F. Xing, J. Liu, C.C. Y. Yip, R.W.S. Poon, H.W. Tsoi, S.K.F. Lo, K.H. Chan, V.K.M. Poon, W.M. Chan, J. D. Ip, J.P. Cai, V.C.C. Cheng, H. Chen, C.K.M. Hui, K.Y. Yuen, A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster, Lancet 395 (2020) 514–523, https://doi.org/10.1016/S0140-6736(20)30154-9.

[58] T. Singhal, A review of coronavirus disease-2019 (COVID-19), Indian J. Pediatr. 2019 (2020), https://doi.org/10.1007/s12098-020-03263-6.

[59] Y. Shi, Y. Wang, C. Shao, J. Huang, J. Gan, X. Huang, E. Bucci, M. Piacentini, G. Ippolito, G. Melino, COVID-19 infection: the perspectives on immune responses, Cell Death Differ. (2020), https://doi.org/10.1038/s41418-020-0530-3.

[60] S.H. Wong, R.N. Lui, J.J. Sung, Covid-19 and the digestive system, J. Gastroenterol. Hepatol. (2020), https://doi.org/10.1111/jgh.15047, 0–3.

[61] F. He, Y. Deng, W. Li, Coronavirus Disease 2019 (COVID-19): what we know? J. Med. Virol. 2019 (2020) https://doi.org/10.1002/jmv.25766, 0.

[62] P.S.-Y. Sufang Tian, Yong Xiong, Huan Liu, Li Niu, Jianchun Guo, Meiyan Liao, Pathological study of the 2019 novel coronavirus disease (COVID-19) through post-mortem core biopsies, Preprints (2020), https://doi.org/10.20944/preprints202003.0311.v1.

[63] Y.Y. Zheng, Y.T. Ma, J.Y. Zhang, X. Xie, COVID-19 and the cardiovascular system, Nat. Rev. Cardiol. (2020), https://doi.org/10.1038/s41569-020-0360-5.

[64] H. Lu, nCoV) 14 (2020) 69–71, https://doi.org/10.1002/jmv.25678.4.

[65] M. Wang, R. Cao, L. Zhang, X. Yang, J. Liu, M. Xu, Z. Shi, Z. Hu, W. Zhong, G. Xiao, Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro, Cell Res. 30 (2020) 269–271, https://doi.org/10.1038/s41422-020-0282-0.

[66] G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. 19 (2020) 149–150, https://doi.org/10.1038/d41573-020-00016-0.

[67] H.-H. Fan, L.-Q. Wang, W.-L. Liu, X.-P. An, Z.-D. Liu, X.-Q. He, L.-H. Song, Y.-G. Tong, Repurposing of clinically approved drugs for treatment of coronavirus disease 2019 in a 2019-novel coronavirus (2019-nCoV) related coronavirus model, Chin. Med. J. (2020), https://doi.org/10.1097/CM9.0000000000000797.

[68] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), Drug Discov. Ther. 14 (2020) 58–60, https://doi.org/10.5582/ddt.2020.01012.

[69] C.C. Lai, T.P. Shih, W.C. Ko, H.J. Tang, P.R. Hsueh, Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): the epidemic and the challenges, Int. J. Antimicrob. Agents 55 (2020) 105924, https://doi.org/10.1016/j.ijantimicag.2020.105924.

[70] The Times of India, Rajasthan doctors cure coronavirus patient with HIV drugs. https://timesofindia.indiatimes.com/city/jaipur/city-docs-cure-corona-patient-with-hiv-drugs/articleshow/74584859.cms, 2020.

[71] J.W. Lee, X. Fang, A. Krasnodembskaya, J.P. Howard, M.A. Matthay, Concise review: mesenchymal stem cells for acute lung injury: role of paracrine soluble factors, Stem Cell. 29 (2011) 913–919, https://doi.org/10.1002/stem.643.

[72] Z. Leng, R. Zhu, W. Hou, Y. Feng, Y. Yang, Q. Han, G. Shan, F. Meng, D. Du, S. Wang, J. Fan, W. Wang, L. Deng, H. Shi, H. Li, Z. Hu, F. Zhang, J. Gao, H. Liu, X. Li, Y. Zhao, K. Yin, X. He, Z. Gao, Y. Wang, B. Yang, R. Jin, I. Stambler, L. W. Lim, H. Su, A. Moskalev, A. Cano, S. Chakrabarti, K.-J. Min, G. Ellison-Hughes, C. Caruso, K. Jin, R.C. Zhao, Transplantation of ACE2- mesenchymal stem cells improves the outcome of patients with COVID-19 pneumonia, Aging Dis 11 (2020) 216, https://doi.org/10.14336/ad.2020.0228.

[73] B. Liang, J. Chen, T. Li, H. Wu, W. Yang, Y. Li, J. Li, C. Yu, F. Nie, Z. Ma, M. Yang, P. Nie, Y. Gao, C. Qian, M. Hu, Clinical remission of a critically ill COVID-19 patient treated by human umbilical cord mesenchymal stem cells, China (2020), https://doi.org/10.21203/rs.3.rs-19549.v1.

[74] S.H. Burstein, ur l P re, prostaglandins other lipid mediat, 106408, https://doi.org/10.1016/j.prostaglandins.2020.106408, 2020.

[75] L. Singh, H.G. Kruger, G.E.M. Maguire, T. Govender, R. Parboosing, The role of nanotechnology in the treatment of viral infections, Ther. Adv. Infect. Dis. 4 (2017) 105–131, https://doi.org/10.1177/2049936117713593.

[76] T.C. Chou, W. Hsu, C.H. Wang, Y.J. Chen, J.M. Fang, Rapid and specific influenza virus detection by functionalized magnetic nanoparticles and mass spectrometry, J. Nanobiotechnol. 9 (2011) 1–13, https://doi.org/10.1186/1477-3155-9-52.

[77] N. Delaviz, P. Gill, A. Ajami, M. Aarabi, Aptamer-conjugated magnetic nanoparticles for the efficient removal of HCV particles from human plasma samples, RSC Adv. 5 (2015) 79433–79439, https://doi.org/10.1039/c5ra12209k.

[78] T. Shelby, T. Banerjee, I. Zegar, S. Santra, Highly sensitive, engineered magnetic nanosensors to investigate the ambiguous activity of zika virus and binding receptors, Sci. Rep. 7 (2017) 1–8, https://doi.org/10.1038/s41598-017-07620-y.

[79] Nanowerk, Here's how nanoparticles could help us get closer to a treatment for COVID-19. https://www.nanowerk.com/nanotechnology-news2/newsid=54710.php, 2020.

[80] S. Adem, V. Eyupoglu, I. Sarfraz, A. Rasul, M. Ali, Identification of potent COVID-19 main protease (mpro) inhibitors from natural polyphenols: an in silico strategy unveils a hope against CORONA, Preprints (2020), https://doi.org/10.20944/preprints202003.0333.v1.

[81] T. Chowdhury, G. Roymahapatra, S.M. Mandal, In Silico Identification of a Potent Arsenic Based Approved Drug Darinaparsin against SARS-CoV-2: Inhibitor of RNA Dependent RNA Polymerase (RdRp) and Necessary Proteases, 2017, pp. 36–41.

[82] S. Pant, M. Singh, V. Ravichandiran, U.S.N. Murty, H.K. Srivastava, Peptide-like and small-molecule inhibitors against Covid-19, J. Biomol. Struct. Dyn. (2020) 1–15, https://doi.org/10.1080/07391102.2020.1757510, 0.

[83] D.C. Hall, H.-F. Ji, A search for medications to treat COVID-19 via in silico molecular docking models of the SARS-CoV-2 spike glycoprotein and 3CL protease, Trav. Med. Infect. Dis. (2020) 101646, https://doi.org/10.1016/j.tmaid.2020.101646.

[84] F. Abedi, R. Rezaee, G. Karimi, Plausibility of therapeutic effects of Rho kinase inhibitors against severe acute respiratory syndrome coronavirus 2 (COVID-19), Pharmacol. Res. 156 (2020) 104808, https://doi.org/10.1016/j.phrs.2020.104808.

[85] M.S. Ahmed, Identification of FDA approved drugs targeting COVID-19 virus by structure- based drug repositioning, Gene Regul. Metab (2002), https://doi.org/10.7551/mitpress/3215.003.0017.

[86] J. Wang, Fast identification of possible drug treatment of coronavirus disease -19 (COVID-19) through computational drug repurposing study, J. Chem. Inf. Model. 19 (2020), https://doi.org/10.1021/acs.jcim.0c00179.

[87] A.D. Elmezayen, A. Al-Obaidi, A.T. Şahin, K. Yelekçi, Drug repurposing for coronavirus (COVID-19): in silico screening of known drugs against coronavirus 3CL hydrolase and protease enzymes, J. Biomol. Struct. Dyn. (2020) 1–12, https://doi.org/10.1080/07391102.2020.1758791, 0.

[88] S. Khaerunnisa, H. Kurniawan, R. Awaluddin, S. Suhartati, Potential inhibitor of COVID-19 main protease (M pro) from several medicinal plant compounds by molecular docking study, Preprints (2020) 1–14, https://doi.org/10.20944/preprints202003.0226.v1.

[89] B.T.P. Thuy, T.T.A. My, N.T.T. Hai, L.T. Hieu, T.T. Hoa, H. Thi Phuong Loan, N. T. Triet, T.T. Van Anh, P.T. Quy, P. Van Tat, N. Van Hue, D.T. Quang, N.T. Trung, V.T. Tung, L.K. Huynh, N.T.A. Nhung, Investigation into SARS-CoV-2 resistance of compounds in garlic essential oil, ACS Omega (2020), https://doi.org/10.1021/acsomega.0c00772.

[90] M.T. ul Qamar, S.M. Alqahtani, M.A. Alamri, L.-L. Chen, Structural basis of SARS-CoV-2 3CLpro and anti-COVID-19 drug discovery from medicinal plants, J. Pharm. Anal. (2020), https://doi.org/10.1016/j.jpha.2020.03.009.

[91] A.E. Torres, A.B. Lyons, S. Narla, I. Kohli, A. Parks-Miller, D. Ozog, I.H. Hamzavi, H.W. Lim, Ultraviolet-C and other methods of decontamination of filtering facepiece N-95 respirators during the COVID-19 pandemic, Photochem. Photobiol. Sci. (2020), https://doi.org/10.1039/d0pp00131g.

[92] C.C.L.R.I. Theory Division, K.J. Card, D. Crozier, A. Dhawan, M. Dinh, E. Dolson, N. Farrokhian, V. Gopalakrishnan, E. Ho, E.S. King, N. Krishnan, G. Kuzmin, J. Maltas, J. Pelesko, J.A. Scarborough, J.G. Scott, G. Sedor, D.T. Weaver, UV sterilization of personal protective equipment with idle laboratory biosafety cabinets during the covid-19 pandemic, MedRxiv (2020), https://doi.org/10.1101/2020.03.25.20043489, 2020.03.25.20043489.

[93] K. Bedell, A.H. Buchaklian, S. Perlman, Efficacy of an automated multiple emitter whole-room Ultraviolet-C disinfection system against coronaviruses MHV and MERS-CoV, Infect. Control Hosp. Epidemiol. 37 (2016) 598–599, https://doi.org/10.1017/ice.2015.348.

[94] W. Szeto, W.C. Yam, H. Huang, D.Y.C. Leung, The efficacy of vacuum-ultraviolet light disinfection of some common environmental pathogens, BMC Infect. Dis. 20 (2020) 1–9, https://doi.org/10.1186/s12879-020-4847-9.

[95] D.J. Viscusi, M.S. Bergman, B.C. Eimer, R.E. Shaffer, Evaluation of five decontamination methods for filtering facepiece respirators, Ann. Occup. Hyg. 53 (2009) 815–827, https://doi.org/10.1093/annhyg/mep070.

[96] K. Card, D. Crozier, A. Dhawan, M. Dinh, E. Dolson, N. Farrokhian, V. Gopalakrishnan, E. Ho, T. Jagdish, E. King, N. Krishnan, G. Kuzmin, J. Maltas, J. Mo, J. Pelesko, J. Scarborough, J. Scott, G. Sedor, E. Tian, D. Weaver, UV Sterilization of Personal Protective Equipment with Idle Laboratory Biosafety Cabinets during the Covid-19 Pandemic, MedRxiv, 2020, https://doi.org/10.1101/2020.03.25.20043489.

[97] C.C. Tseng, C.S. Li, Inactivation of viruses on surfaces by ultraviolet germicidal irradiation, J. Occup. Environ. Hyg. 4 (2007) 400–405, https://doi.org/10.1080/15459620701329012.

[98] D. Mills, D.A. Harnish, C. Lawrence, M. Sandoval-Powers, B.K. Heimbuch, Ultraviolet germicidal irradiation of influenza-contaminated N95 filtering facepiece respirators, Am. J. Infect. Contr. 46 (2018), https://doi.org/10.1016/j.ajic.2018.02.018 e49–e55.

[99] A.C.P. D, D.H.P. D, Ozone gas: scientific justification and practical guidelines for improvised disinfection using consumer-grade ozone generators and plastic storage boxes, J. Sci. Med. 2 (2020).

[100] J. Lee, C. Bong, P.K. Bae, A.T. Abafogi, S.H. Baek, Fast and easy disinfection of coronavirus-contaminated face masks using ozone gas produced by a dielectric barrier discharge plasma generator, MedRxiv (2020) 1–13.

[101] A. Kumar, S.B. Kasloff, A. Leung, T. Cutts, J.E. Strong, K. Hills, G. Vazquez-Grande, B. Rush, S. Lother, R. Zarychanski, J. Krishnan, N95 mask decontamination using standard hospital sterilization technologies, MedRxiv (2020), https://doi.org/10.1101/2020.04.05.20049346, 2020.04.05.20049346.

[102] Z. Chen, R.E. Wirz, Cold atmospheric plasma for COVID-19, Preprints (2020) 1–7, https://doi.org/10.20944/preprints202004.0126.v1.

[103] K. Duan, B. Liu, C. Li, H. Zhang, T. Yu, J. Qu, M. Zhou, L. Chen, S. Meng, Y. Hu, C. Peng, M. Yuan, J. Huang, Z. Wang, J. Yu, X. Gao, D. Wang, X. Yu, L. Li, J. Zhang, X. Wu, B. Li, Y. Yu, W. Chen, Y. Peng, Y. Hu, L. Lin, X. Liu, S. Huang, Z. Zhou, L. Zhang, Y. Wang, Z. Zhang, K. Deng, Z. Xia, Q. Gong, W. Zhang, X. Zheng, Y. Liu, H. Yang, D. Zhou, D. Yu, J. Hou, Z. Shi, S. Chen, Z. Chen, X. Zhang, X. Yang, The feasibility of convalescent plasma therapy in severe COVID-19 patients: a pilot study, MedRxiv (2020) 1–22, https://doi.org/10.1101/2020.03.16.20036145.

[104] J.Y. Ahn, Y. Sohn, S.H. Lee, Y. Cho, J.H. Hyun, Y.J. Baek, S.J. Jeong, J.H. Kim, N.S. Ku, J.S. Yeom, J. Roh, M.Y. Ahn, B.S. Chin, Y.S. Kim, H. Lee, D. Yong, H.O. Kim, S. Kim, J.Y. Choi, Use of convalescent plasma therapy in two covid-19 patients with acute respiratory distress syndrome in Korea, J. Kor. Med. Sci. 35 (2020) 2–9, https://doi.org/10.3346/JKMS.2020.35.E149.

[105] B. Zhang, S. Liu, T. Tan, W. Huang, Y. Dong, L. Chen, Q. Chen, L. Zhang, Q. Zhong, X. Zhang, Y. Zou, S. Zhang, Treatment with convalescent plasma for critically ill patients with severe acute respiratory syndrome coronavirus 2 infection, Chest 158 (2020), https://doi.org/10.1016/j.chest.2020.03.039 e9–e13.

[106] Q.L. Zeng, Z.J. Yu, J.J. Gou, G.M. Li, S.H. Ma, G.F. Zhang, J.H. Xu, W.B. Lin, G.L. Cui, M.M. Zhang, C. Li, Z.S. Wang, Z.H. Zhang, Z.S. Liu, Z.S. Liu, Effect of convalescent plasma therapy on viral shedding and survival in patients with coronavirus disease 2019, J. Infect. Dis. 222 (2020) 38–43, https://doi.org/10.1093/infdis/jiaa228.

[107] E.M. Bloch, S. Shoham, A. Casadevall, B.S. Sachais, B. Shaz, J.L. Winters, C. Van Buskirk, B.J. Grossman, M. Joyner, J.P. Henderson, A. Pekosz, B. Lau, A. Wesolowski, L. Katz, H. Shan, P.G. Auwaerter, D. Thomas, D.J. Sullivan, N. Paneth, E. Gehrie, S. Spitalnik, E.A. Hod, L. Pollack, W.T. Nicholson, L.A. Pirofski, J.A. Bailey, A.A.R. Tobian, Deployment of convalescent plasma for the prevention and treatment of COVID-19, J. Clin. Invest. 130 (2020) 2757–2765, https://doi.org/10.1172/JCI138745.

[108] M. Uddin, F. Mustafa, T.A. Rizvi, T. Loney, H. Al Suwaidi, A.H.H. Al-Marzouqi, A.K. Eldin, N. Alsabeeha, T.E. Adrian, C. Stefanini, N. Nowotny, A. Alsheikh-Ali, A.C. Senok, SARS-CoV-2/COVID-19: viral genomics, epidemiology, vaccines, and therapeutic interventions, Viruses 12 (2020) 1–18, https://doi.org/10.3390/v12050526.

[109] L. Du, Y. He, Y. Zhou, S. Liu, B.J. Zheng, S. Jiang, The spike protein of SARS-CoV - a target for vaccine and therapeutic development, Nat. Rev. Microbiol. 7 (2009) 226–236, https://doi.org/10.1038/nrmicro2090.

[110] Z. Wang, X. Chen, Y. Lu, F. Chen, W. Zhang, Clinical characteristics and therapeutic procedure for four cases with 2019 novel coronavirus pneumonia receiving combined Chinese and Western medicine treatment, Biosci. Trends. 14 (2020) 64–68, https://doi.org/10.5582/bst.2020.01030.

[111] K. Dhama, K. Sharun, R. Tiwari, M. Dadar, Y.S. Malik, K.P. Singh, W. Chaicumpa, COVID-19, an emerging coronavirus infection: advances and prospects in designing and developing vaccines, immunotherapeutics, and therapeutics, Hum. Vaccines Immunother. (2020) 1–7, https://doi.org/10.1080/21645515.2020.1735227, 00.

[112] H. Lu, Drug treatment options for the 2019-new coronavirus (2019-nCoV), Biosci. Trends. 14 (2020) 69–71, https://doi.org/10.5582/bst.2020.01020.

[113] A.J. Rodriguez-morales, K. Bonilla-Aldana, R. Tiwari, R. Sah, A.A. Rabaan, K. Dhama, COVID-19 , an emerging coronavirus Infection : current scenario and COVID-19 , an emerging coronavirus Infection : current scenario and recent developments – an overview, Pure Appl. Microbial. 14 (2020) 1–8.

[114] T.M. Wassenaar, Y. Zou, 2019_nCoV/SARS-CoV-2: rapid classification of betacoronaviruses and identification of Traditional Chinese Medicine as potential origin of zoonotic coronaviruses, Lett. Appl. Microbiol. (2020) 1–7, https://doi.org/10.1111/lam.13285.

[115] J. Jain, A. Kumar, V. Narayanan, R.S. Ramaswamy, P. Sathiyarajeswaran, M.S.S. Devi, M. Kannan, S. Sunil, Journal of Ayurveda and Integrative Medicine Antiviral activity of ethanolic extract of Nilavembu Kudineer against dengue and chikungunya virus through in vitro evaluation, J. Ayurveda Integr. Med. (2018) 1–7, https://doi.org/10.1016/j.jaim.2018.05.006.

[116] H. Chennai, T. Nadu, Siddha Medicine and Clinical Presentation of Dengue Fever at Tertiary Care Siddha Medicine and Clinical Presentation of Dengue Fever at Tertiary Care Hospital of Chennai, 2014. Tamil Nadu , India.

[117] I.T. Tanushree Pandey, PM Urges AYUSH Representatives, Ayurveda Doctors to Counter Rumours about Covid-19, 2020 (n.d.).

[118] 21 D. Sprott, The effect of human mobility and control measures on the COVID-19 epidemic in China, Block Caving – a Viable Altern, 1–9, https://www.golder.com/insights/block-caving-a-viable-alternative/, 2020.

[119] A.S. Braun, Commitment, transparency pay off as South Korea limits COVID-19 spread. https://www.euractiv.com/section/coronavirus/news/commitment-transparency-pay-off-as-south-korea-limits-covid-19-spread/, 2020.

[120] Government of India, Ministry of Electronics & Information Technology Electronics Niketan, CGO Complex New Delhi Aarogya Setu is now open source, 3–3, https://static.mygov.in/rest/s3fs-public/mygov_159050700051307401.pdf, 2020.

[121] P.B. Kodali, S. Kopparty, G.R. Kalapala, B. Haloi, How Indians responded to the arogya Setu app? Indian J. Publ. Health 64 (2020) 228–230. http://www.ijph.in/temp/IndianJPublicHealth646228-5902456_013822.pdf. (Accessed 13 September 2020).

[122] L.Y. Hsu, M.-H. Tan, What Singapore can teach the U.S. about responding to Covid-19. https://www.statnews.com/2020/03/23/singapore-teach-united-states-about-covid-19-response/, 2020.

[123] P.M. of J, Hi Cabinet, [COVID-19] government responses on the coronavirus disease 2019. http://japan.kantei.go.jp/ongoingtopics/_00013.html, 2020.

[124] S. Jain, COVID-19: A Strategic Opportunity for Sustainable Development, TERI, 2020. https://www.teriin.org/article/covid-19-strategic-opportunity-sustainable-development. (Accessed 13 September 2020).

[125] S. Ramakrishna, Guest editorial: circular economy and sustainability pathways to build a new-modern society, Dry. Technol. (2020) 1, https://doi.org/10.1080/07373937.2020.1758492, 0.

[126] S. Khetrapal, R. Bhatia, Impact of COVID-19 pandemic on health systems & sustainable development goal 3, Indian J. Med. Res. 151 (2020) 395–399, https://doi.org/10.4103/ijmr.IJMR.