Int. J. Pharm. Investigation, 2023; 13(4):735-746.
https://www.jpionline.org

Review Article

COVID-19 Current Management and Strategies for Future Outlook

Nayeema Khowser Shaik[1], Nalluri Poojitha[1], Kancharla Bhanu Sri Chandana[1], Maruvajala Vidyavathi[1,*], Sai Deepthi Rayadurgam Venkata[2]

[1]Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati, Andhra Pradesh, INDIA.
[2]Sri Padmavathi Medical College for Women, SVIMS, Tirupati, Andhra Pradesh, INDIA.

ABSTRACT

The highly infectious Corona Virus Disease 2019 (COVID-19) had spread and created a havoc worldwide due to lack of risk assessment and quick transmission. The outbreak created epicenters are still being reported daily. Different demographics, genetics, ethnicity, geography, ABO blood groups and HLA genotypes have significantly different rates of COVID-19 incidence, severity, and death. Because of this, finding a successful preventive approach has therefore been a primary focus, leading to the creation of large number of management strategies. In light of this, it had become essential globally, to develop COVID-19 vaccines, monoclonal antibodies and habitual activities like yoga, in order for everything to resume, as they had before the pandemic. Finally, it can now be observed the pre-pandemic normalcy. so, one should be prepared physiologically and psychologically to ponder about the future, of how to face this type of hurdles. However, it won't be feasible to evaluate the physical, social and economic effects of this global catastrophe Hence, by comprehending the past, the present and the emerging technologies for the future, this paper made an attempt to outline the clinical implications, treatment approaches like medicines, nutrients and lifestyle management and potential future therapeutic interventions for the control of century's advancing pandemic.

Keywords: ABO blood groups, Vaccines, Monoclonal antibodies, Biological changes, Antivirals, Immune boosters.

Correspondence:
Prof. Maruvajala Vidyavathi
Institute of Pharmaceutical Technology, Sri Padmavati Mahila Visvavidyalayam, Tirupati-517502, Andhra Pradesh, INDIA.
Email: vidyasur@rediffmail.com

Received: 07-04-2023;
Revised: 05-06-2023;
Accepted: 14-07-2023.

INTRODUCTION

The Novel Coronavirus, commonly known as the Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), is a zoonotic agent that causes the Coronavirus Disease 2019 (COVID-19).[1] A group of Rhinolophus bats are said to be the source of it, and it is supposed to have started in the city of Wuhan, People's Republic of China.[2] Since then, it has quickly spread around the globe, largely through personal contact and respiratory transmission. Clinical signs and symptoms of coronavirus disease included elevated body temperature, cough, headache, nausea, vomiting, anorexia, diarrhea, dyspnea and numerous organ dysfunctions. Many infected people, experienced only minor illness symptoms and recovered. Some patients experienced a progression of major side effects, such as sepsis, acute respiratory failure, metabolic acidosis, heart failure, renal injury and hypoxic encephalopathy, before passing away from their disease.[3-5] The patients in other asymptomatic cases, on the other hand, did not display any acute COVID-19 symptoms. They occasionally also have a slight fever, little to no exhaustion and no respiratory issues. These asymptomatic patients may, however, be SARS-CoV-2 carriers who spread the virus to other people's bodies.[5] Acute Respiratory Distress Syndrome (ARDS), immunological derangement, coagulopathy, septic shock and Multiple Organ Dysfunction Syndrome (MODS) are possible progressions in severe patients.[6] In order to raise general awareness among the public, an effort was made to highlight the molecular and biochemical changes that occur during COVID along with its management by treatment with drugs, drug delivery system, immune booster and breathing exercises or yoga.

BIOLOGICAL CHANGES

During COVID-19 various biological changes in some of systems or systemic conditions of body were observed as given below:

Cardiac System

Cardiomyocyte damage, both direct and indirect, is a common symptom of COVID-19 infection. There are various types of injuries that can result in these conditions, including acute myocardial infarctions, heart failure, myocarditis, arrhythmias, cardiac arrests, sepsis, septic shock, and pulmonary emboli.

DOI: 10.5530/ijpi.13.4.091

However, the mechanisms underlying the phenomenon remain unresolved, a few hypotheses have emerged, including cardiac stress caused by hypoxia and respiratory failure, direct SARS-CoV-2 infection of ACE2 receptor-expressing myocardial cells and indirect changes brought on by systemic inflammatory response.[7] Therefore, the early detection of heart injury and quick intervention may be advanced through the measurement of cardiac damage biomarkers throughout the hospital stay in COVID-19 patients.[8] An injury to the heart was also caused by the advancement of atherosclerosis and increased plaque rupture vulnerability.[9] Additionally, cytokine storm and high intracellular calcium caused by hypoxia are alternative pathways that result in cardiac myocyte death.[10]

Segment Elevation Myocardial Infarction (STEMI) and magnified acute CV events[11-13] are associated to air pollution exposure and COVID-19 infection, respectively.[14,15]

Nervous System

Psychiatric and neurological disorders may raise the likelihood of acquiring COVID-19.[16-18] The risk of Alzheimer's disease is increased by one of the most significant factors of cognitive impairment, social exclusion as a result of isolation.[18] Delirium was a severe COVID-19 presentation in elderly people with a history of neuropsychiatric illness. These people thereafter showed signs of motor and cognitive abnormalities, including agitation, stiffness, abulia and alogia. C-Reactive Protein (CRP) levels in the blood also increased along with neurological and cognitive abnormalities.[19,20]

Hepatic System

Acute inflammation caused by pneumonia, along with COVID-19 drug toxicity, have resulted in liver damage in patients with COVID-19. Examples of direct liver assault include the effects of coagulopathy and endothelial aggressiveness in tiny intrahepatic arteries, as well as the direct cytopathogenic effects of SARS-CoV-2 on hepatocytes and cholangiocytes. Less than 10% of patients had significant liver damage (ALT more than 5 times higher than the usual value), while the majority of patients with abnormal AST/ALT readings exhibited a moderate rise between 1-2 times than normal values. Injuries to the liver were mild in 30% of individuals (between 2 and 5 times higher than the normal value).[21,22]

Diabetes

Hypertension and Type 2 Diabetes Mellitus (TDM2) are common conditions in COVID-19 patients. In roughly 10% of TDM2/COVID-19 patients, a SARS-CoV-2 infection may cause the production of hyperglycemic hormones (such glucocorticoids and catecholamines) as well as bouts of hypoglycemia (with increased pro-inflammatory monocytes and platelet reactivity).[13-15] Although there was no statistically significant difference in CRP or Troponin-I levels, in COVID-19 positive patients with or without diabetes tended to have greater levels of both. There is a possibility that this pattern indicates a higher risk of cardiac failure in patients with COVID-19.[16]

Coagulopathy

SARS-CoV-2 uses the Angiotensin-Converting Enzyme 2 (ACE-2) receptors on human cells, including endothelial cells, as part of an unusual mode of infection.[23] Clotting activation, which is commonly reported in patients with COVID-19,[24,25] is caused by binding to ACE-2 receptors on endothelial cells. These receptors induce localized inflammation, endothelial activation, tissue lesions and changes in cytokine release (Tumor Necrosis Factor [TNF]-, Interleukines [IL-1, IL-2 and IL-6]). In between 70 and 95% of individuals with severe COVID-19, there were several coagulation abnormalities observed, the most important of which included a moderate thrombocytopenia. Patients with and without COVID-19, there was no change in mortality with heparin use.[26]

Pregnancy

Comparing pregnant COVID-positive women to COVID-positive non-pregnant women, the likelihood of ICU admission is greater in the former group. The risk of haematological issues was higher in pregnant women with COVID-19 (16%) compared to pregnant women without COVID-19 (0%).[27]

BIOCHEMICAL PARAMETERS

The above effects in different important systems of body during COVID-19 lead to variations in the levels of different biochemical parameters as shown in Table 1.

GENETIC CHANGES

Patients who have recovered from COVID-19 may nevertheless endure long-term symptoms due to changes in gene expression brought on by the new coronavirus.[43] Individual vulnerability, severity, and consequences of COVID-19 can be explained in part by host genetic variables such as variations in the ACE, ACE2, TMPRSS2, TMPRSS2A, HLA genotype and ABO blood group.[44]

A genetically susceptible site has been discovered in severe COVID-19 patients with respiratory failure that is part of the 3p 21.31 gene cluster, which includes the genes SLC6A20, LZTFL1, FYCO1, CXCR6, XCR1 and CCR9.[45,46] Additionally, it has been discovered that low CXCR6 expression and elevated SLC6A20 expression in the population are dangerous.[47] HLA-B, an allele of the HLA genetic system, is susceptible to COVID-19 according to a different study.[48] Predicting strong binders across certain HLA alleles can make a contribution to development of an efficient COVID-19 vaccination with the proper epitope targets since COVID-19 vaccines may have a wide range of binding affinities with different HLA genotypes in different populations.[49] The SARS-VoV-2 susceptibility and post-infection survival may

Table 1: Effect of COVID-19 on levels of various biochemical parameters.

Sl. No.	Parameter	Status
Hepatic system		
1.	Alanine Transaminase (ALT)/Aspartate Transaminase (AST) levels.[28,29]	Increase
2.	Alkaline phosphatase.[30]	Increase
3.	Total bilirubin level.[31-33]	Increase
4.	Gamma glutamyl transferase.[34]	Increase
5.	Serum albumin.[35-39]	Decrease
Circulatory system.		
6.	Creatinine.	Increase
7.	Lymphocyte count.	Decrease
8.	Prothrombin time.[40]	Increase
9.	C-Reactive Protein (CRP).[41]	Increase
10.	Transaminase.	Increase
11.	Lactate dehydrogenase.[43]	Increase
12.	Cytokines.[41]	Increase
13.	Blood Urea Nitrogen.	Decrease
14.	Platelet count.[40]	Decrease
15.	Fibrinogen concentration.[42]	Increase
16.	D-dimer levels (with Low Molecular Weight Heparin).	Increase
Nervous system		
17.	Brain Natriuretic Peptide (BNP).	Increase
Cardiac system		
18.	Cardiac troponin (cTn).[44]	Increase
19.	Angiotensin converting enzyme-2 (ACE-2).	Increase
20.	C-reactive protein (CRP).[40]	Increase
21.	Procalcitonin.[43]	Increase
22.	Leukocyte count.[41]	Increase
Diabetes mellitus		
23.	Haemoglobin A1C (HbA1C).	Increase
24.	Serum ferritin.[42]	Increase
Pregnancy		
25.	Haemoglobin.	Decrease
26.	Lymphocyte count.	Increase

be correlated with ABO blood types. Blood type "O" is slightly protective, but blood type "A" is associated with a greater incidence of COVID-19.[50,51] A 1-base pair (bp) insertion in the DPP7 transcription may have a monogenic effect for COVID-19 patients who are asymptomatic.[47] The IFITM3 gene's rs12252 C-allele homozygosity and the severity of the COVID-19 illness are associated, and individuals who are CC-homozygote have a 6.37-fold higher risk of developing the disease.[52] Correlations between the COVID-19 variable recovery and prevalence rates and the ratio of the ACE 1/D allele frequency and regional variations of the ACE 1/D variant have been found.[53-56]

Treatment

After confirmation of diagnosis of COVID disease and observation of results of different biochemical tests the treatment is followed with a definite protocol. The treatment protocol consisted of following class of drugs.

Antivirals

Remdesivir

Against RNA viruses such as Coronaviruses and Flavisviridae, Remdesivir is a potent inhibitor of RNA polymerase. It is a monophosphate prodrug that metabolises to an active C-adenosine nucleoside triphosphate analogue.[57] With EC_{50} and EC_{90} values of 0.77 and 1.76 M, it has exceptional *in vitro* activity against several coronaviruses, including SARSCoV2. It was believed that COVID-19 might be treated when it initially started to spread.[58,59] Remdesivir is being tested with a single 200 mg loading dosage and a daily 100 mg infusion. However, treatment with remdesivir is not advised for those whose estimated glomerular filtration rate is less than 30 mL/min.[60] Reactions at the infusion site, gastrointestinal dysfunction, and hepatic malfunction (elevated transaminase levels) have all been connected to Remdesivir therapy's side effects.[61]

Favipiravir (FPV)

Favipiravir is a pyrazine carboxamide derivative that has been shown to be an effective against coronavirus, bunyavirus, flavivirus, filoviruses, and the Ebola virus.[62] This prodrug suppresses RdR and is proven to inhibit SARS-CoV-2 (EC_{50} = 61.88 M: CC_{50} = over 400 M).[63] This treatment helped to decrease the SARS-CoV-2 presence in nasal secretions.[64] In a study, FPV also demonstrated the control of inflammatory mediator and pneumonia advancement in COVID[65,66] with improved lung histology.[67-69]

Chloroquine and Hydroxychloroquine

It is a legitimate anti-malarial medication that is also used to treat autoimmune diseases. In an *in vitro* study, chloroquine was shown to be highly effective in preventing SARS-CoV-2 infection in host cells at the entry and exit stages.[68] However, the current use of these drugs to combat COVID-19 has recently been considered risky due to adverse events such as life-threatening arrhythmias, drug rash and hepatitis. Azithromycin (500 mg daily for 5 days) and Hydroxychloroquine (400 mg twice on day 1 and 200 mg twice daily for 5 days) showed QTc prolongation, which may instigate arrhythmia and sudden cardiac death, in COVID-19, as determined by the results of the experiment.[69]Since it prolongs the QT interval, hydroxychloroquine should be used with caution,

especially in those with co-morbidities and those who take such medications.[70]

Lopinavir/Ritonavir (LPV/RTV)

In order to be successful against SARS-CoV, LPV/RTV, the approved anti-HIV medications that specifically target the HIV protease[71] and are anticipated to act on the viral 3-chymotrypsin-like protease.[72] When LPV/RTV treatment is started within 10 days of the beginning of symptoms, virus shedding was dramatically reduced[73] and when combined with IFN- or RBV, COVID-19 patients' health was improved with lower mortality rates.[74,75]

Sofosbuvir/Daclatasvir

NS5A and NS5B polymerase inhibition is the mechanism through which the antiviral drugs sofosbuvir and daclatasvir to prevent viral RNA replication.[76,77] Since SARS-CoV-2 shares RNA replication processes with other RNA viruses, it may be possible for Sofosbuvir and Daclatasvir to effectively block SARS-CoV-2 replication when used together.[78,79]

Ritonavir-Boosted Nirmatrelvir (Paxlovid)

Nirmatrelvir, an orally accessible protease inhibitor, is effective against MPRO, a viral protease that cleaves the two viral polyproteins and is crucial for viral replication,[80] also proven to be antiviral against all coronaviruses.[81] Ritonavir co-administration raised the Nirmatrelvir concentrations to the desired therapeutic range The COVID-19 treatment Guidelines Panel (the Panel) suggests using Nirmatrelvir 300 mg with Ritonavir 100 mg (Paxlovid) orally twice daily for 5 days in non-hospitalized patients with mild to moderate COVID-19 aged 12 years and weighing 40 kg who are at high risk of disease progression. Patients who have hepatitis, abnormal liver enzyme tests, or pre-existing liver problems should use this medication with care.[82]

Molnupiravir

Due to Molnupiravir's potent antiviral activity against SARS-CoV-2, the FDA has given an Emergency Use Authorization (EUA) for its use in the treatment of mild to moderate COVID-19. This is because Molnupiravir is an oral prodrug of beta-D-N4-hydroxycytidine (NHC), which has a significant antiviral effect.[83,84] Molnupiravir has a low risk for genotoxicity, according to FDA's assessment of the data on genotoxicity that are currently available.[85] Concerns have also been raised about Molnupiravir's potential impact on the frequency of SARS-CoV-2 mutations. Molnupiravir has been linked to foetal harm in animal studies.

Interferons

A family of cytokines called interferons have antiviral effects both *in vivo* and *in vitro*. The Food and Drug Administration (FDA) has approved the interferon beta-1a for the treatment of COVID-19 and relapsing types of multiple sclerosis. The COVID-19 Treatment Guidelines Panel (the Panel) does not recommend systemic interferon beta for the treatment of COVID-19 hospital patients (AI). The Panel advises against treating hospitalised COVID-19 patients with interferon alfa or lambda outside of a research study (AIIa).[86]

Monoclonal Antibodies (MAB'S)

The Food and Drug Administration (FDA) has granted EUAs to five anti-SARS-CoV-2 MAB medicines, including:

Bamlanivimab +Etesevimab

Due to the Omicron VOC's significantly decreased in vitro sensitivity to Bamlanivimab and Etesevimab, these neutralising MABs bind to a variety of overlapping epitopes in the spike protein RBD of SARS-CoV-2. It is not anticipated that Bamlanivimab with Etesevimab would provide any therapeutic benefits for patients with Omicron infection as its distribution in the United States has been stopped.[87]

Bebtelovimab

This recombinant human protein neutralises MAB and binds to the advanced SARS-CoV-2 protein. There are no clinical efficacy data on the use of Bebtelovimab in patients at high risk for developing severe Omicron subvariants, despite the fact that it still has *in vitro* activity against all circulating subvariants of COVID-19.[88]

Casirivimab+Imdevimab

These human MABs are recombinant, and they bind to nonoverlapping epitopes on the spike protein RBD of the SARS-CoV-2 virus. It is unlikely that Casirivimab and Imdevimab would provide any therapeutic benefit to patients with Omicron infection because the Omicron VOC's *in vitro* susceptibility has been considerably reduced and its dissemination has been stopped.[89]

Sotrovimab

This MAB contracted SARS-CoV in 2003. The Panel no longer recommends treating COVID-19, and Sotrovimab distribution has stopped.[90-92] Although it targets an epitope that both SARS-CoV and SARS-CoV-2 share in the RBD of the spike protein, the Omicron BA 2 subvariant is immune to it.[93]

Table 2: Vaccines obtained in Emergency Use Listing.

Sl. No.	Name of Vaccine	Emergency Approval Date
1	The Pfizer/BioNTech COVID-19 vaccine.	31 December 2020
2	The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines.	16 February 2021
3	The Janssen/Ad26.COV 2.S vaccine.	12 March 2021
4	The Moderna COVID-19 vaccine (mRNA 1273).	30 April 2021
5	The Sinopharm COVID-19 vaccine.	7 May 2021
6	The CoronaVac vaccine.	1 June 2021
7	The Bharat Biotech BBV152 COVAXIN vaccine.	3 November 2021
8	The Nuvaxovid (NVX-CoV2373) vaccine.	20 December 2021

Tixagevimab+Cilgavimab

The non-overlapping epitopes on the spike protein RBD of SARS-CoV-2 are where these anti-SARS-CoV-2 recombinant human MABs bind. The FDA updated the EUA to authorise a dose of 300 mg each of the anti-cancer drugs ixagevimab and cilgavimab, which is expected to continue to work against all subvariants, including Omicron.[93-95]

Tocilizumab

When critical SARS-CoV-2 patients experience a cytokine storm, which is an increase in pro-inflammatory cytokines, Tocilizumab, a monoclonal antibody made from recombinant anti-human interleukin (IL)-6 receptor, stops subsequent inflammatory cascades from occurring.[96] Therefore, it may be able to save individuals with severe COVID-19.[97]

Vaccines

Another way of constricting COVID-19 is its prevention by vaccination. The approved vaccines listed under the Emergency Use Listing (EUL)[98] as of 2022 are shown in Table 2.

Pfizer-BioNTech COVID-19 Vaccine

The BNT162b2 vaccine, developed by BioNTech, relies on the use of nucleoside-modified mRNA (modRNA), which encodes a mutated version of the full-length spike protein found on the surface of the SARS-CoV-2 virus.[99] This immune response is triggered in response to the virus protein, protecting the body from infection. It is encapsulated in lipid nanoparticles.[100] The Food and Drug Administration (FDA) in the United States approved the Pfizer-BioNTech vaccine as the first COVID-19 vaccination for individuals aged sixteen and older.[101-103]

The SII/COVISHIELD and AstraZeneca/AZD1222 vaccines

It is an adenovirus vector from a chimpanzee that is recombinant and replication-deficient and that encodes the spike(S) glycoprotein of the SARS-CoV-2 virus. After being administered, a portion of the corona virus' genetic material is expressed and triggering an immunological reaction. Patients should not use covishield if they have low platelet counts in addition to venous and/or arterial thrombosis (thrombocytopenia). People with thrombocytopenia, anyone with a clotting condition, or those taking anticoagulant medication should use covishield with caution because, in these cases, intramuscular injections may result in bleeding or bruising.[104]

The Janssen/Ad26.COV 2.S vaccine

The Jcovden brand of the COVID-19 vaccine, manufactured by Johnson and Johnson, it is a viral vector vaccine that is based on a human adenovirus modified to carry the gene that produces the spike protein of the SARS-CoV-2 virus that causes COVID-19.[105] The body's immune system produces antibodies in response to this spike protein[106] with only one dose.

The Moderna COVID-19 vaccine (mRNA 1273)

The Spikevax brand of the Moderna COVID 19 vaccine (INN: elasomeran). is a mRNA vaccine made of lipid nanoparticle-coated nucleoside-modified mRNA (modRNA) that encodes the SARS-CoV-2 spike protein.[107-108] Australia is authorised for the use of other brand of a bivalent vaccination called Spikevax Bivalent Zero/Omicron[109]which contains elasomeran/elasomeran 0-omicron.[109]

Sinopharm BIBP COVID-19 vaccine

Sinopharm BIBP is one of two entire inactivated virus COVID-19 vaccines created by Sinopharm Beijing Institute of Biological Products is also known as BBIBP-CorV,[110] the Sinopharm COVID-19 vaccine, or BIBP vaccine.[111-113] The inactivated viral vaccines for COVID-19 CoronaVac and Covaxin, as well as BBIBP-CorV, have comparable technology.[114] The World Health Organization (WHO) suggested a gap of 3 to 4 weeks between dosages[115] of this vaccine.

The CoronaVac vaccine

Sinovac Biotech, a Chinese Company created CoronaVac, also known as the Sinovac COVID-19 vaccine, which is a whole inactivated COVID-19 vaccine. Similar to Covaxin and the Sinopharm BIBP vaccine,[116] is an inactivated-virus COVID-19 vaccine that uses conventional technologies. There are two dosages in the initial course. 4 weeks should elapse between dosages, according to the World Health Organization (WHO). Booster dose may be required after the initial course because preliminary data indicated that immunity dwindles quickly.[117]

The Bharat Biotech BBV152 COVAXIN vaccine

The Indian Council of Medical Research (ICMR)-National Institute of Virology collaborated with Bharat Biotech to create Covaxin, an indigenous COVID-19 vaccine (NIV). SARS-CoV-2 particles that have been chemically deactivated are present in the inactivated whole virus vaccination known as Covaxin. That implies they are no longer able to infect cells but can still activate the immune system to defend itself. It is advised to space out the two doses of the vaccine by 28 days. Covaxin's primary side effects were discomfort at the injection site, followed by headache, exhaustion and fever. There were no severe or fatal adverse effects reported with this vaccine.[117,118]

The Nuvaxovid (NVX-CoV2373) vaccine

The protein-based vaccination, Novavax has been given preliminary approval by the TGA for use in Australia. Part of the coronavirus spike protein is present in this kind of vaccine. Immunological system cells see the spike protein as a threat and start to mount an immune defence against it.[118]

Immune Boosters

Apart from treatment by different drugs and immune protection by vaccine, one can also get resistance power against viral attack by immune boosters in the form of nutrients as discussed below.

Vitamin D

A fat-soluble steroid hormone, vitamin D, is converted into the circulating precursor cholecalciferol, which improves innate cellular immunity by inducing the synthesis of anti-microbial peptides including cathelicidin and defensins.[119] Vitamin D insufficiency has been linked to both the likelihood and severity of COVID-19 infection. It has repeatedly been shown that COVID-19 patients have lower vitamin D levels than controls, with mean plasma concentrations that are only half as high.[120] Supplementing with vitamin D is suggested to improve immunity to COVID-19 and reduce death rates.[121] Upper respiratory tract infections are negatively correlated with serum 25-hydroxyvitamin D levels. The incidence and severity of viral infection are therefore known to be reduced by vitamin D supplementation.[118-120] Its supplementation may reduce pro-inflammatory cytokines in people with COVID-19, hence reducing mortality from acute respiratory distress syndrome.[121]

Vitamin C

To Neutralise Reactive Oxygen Species, Vitamin C works as an antioxidant (ROS), preventing oxidative damage and malfunction to biomolecules like proteins, lipids, and nucleotides.[122] In addition to avoiding viral infections, Vitamin C is lowering their duration and intensity and supporting respiratory defence mechanisms with antihistamine characteristics that can lessen flu-like symptoms.[123] Vitamin C supplementation is beneficial for those who are lacking in micronutrients and at risk of contracting COVID-19 infection because it helps to prevent and strengthen immune responses.[124]

Zinc

Due to its dual immunomodulatory and antiviral properties, zinc is thought to be a crucial component during COVID-19 infection.[125,126] In patients with COVID-19, it is a viable supportive treatment. to lower respiratory tract infections, and other symptoms of COVID-19.[127]

Omega-3 fatty acids

It is well known that the polyunsaturated fatty acids known as omega-3 fatty acids—which also include eicosapentaenoic and docosahexaenoic fatty acids—have advantageous effects on immunity and inflammation. Patients with COVID-19 may benefit from using omega-3 fatty acids to increase oxygenation.[128]

Herbal Immune Boosters

The plant-based compounds can also be used to boost the immunity, as given below.

Curcuma longa (Turmeric)

Curcumin exhibits a wide range of biological effects, such as antibacterial, antiviral, antifungal, antioxidant, and anti-inflammatory ones.[129] By preventing virus entry into cells, viral protease encapsulation, preventing virus reproduction and regulating a number of signaling pathways, it has an antiviral effect.[130] As a result, curcumin may be used as a supplement to fight against pathogenesis of COVID-19.

Cinnamomum cassia (Cinnamon)

The essential oils of cinnamon contain large amounts of cinnamonaldehyde, a naturally occurring bioactive molecule[131-133] with possible anti-inflammatory properties, so may be helpful in reducing lung hyperinflammation brought on by SARS-CoV-2.

Allium sativum (Garlic)

Allicin, the primary thiosulfate in fresh garlic extract, has demonstrated a range of health benefits as a result of its anti-inflammatory, antioxidant, and antiviral activities.[132] In order to prevent COVID-19, fresh garlic extract may be helpful.

Piper nigrum (Black pepper)

Black pepper's primary alkaloid, Piperine, which is derived from its ethanolic extract belongs to the family of compounds known as cinnamides. Since Piperine has a potent anti-inflammatory effect, it can be used to control the hyperinflammation in

COVID-19.[133] Piperine can therefore be utilised therapeutically or prophylactically to guard against the oxidative stress and hyperinflammation brought on by the COVID-19.

Zingiber officinale (Ginger)

SARS-CoV-2 was effectively combatted by ginger and its bioactive components. Ginger's bioactive components prevent SARS-CoV-2 entrance by blocking the spike (S) protein during infection.[134]

Azadirachta indica (Neem)

They have insecticidal, antibacterial, antiviral, larvicidal, antimalarial and spermicidal properties.[135,136] Methyl eugenol, oleanolic acid and ursolic acid, are derived from tulsi and neem, respectively, are natural bioactive substances that inhibit SARS-CoV-2 by binding to the spike glycoprotein, RNA polymerase, and/or its protease and preventing both viral attachment and reproduction.[136]

Herbal supplements of Selenium (Se)

Selenium is widely distributed in everyday foods such as corn, garlic, onion, cabbage, and broccoli. It is a necessary micronutrient is crucial for several physiological functions as well as the immune system. Supplementing with selenium may be beneficial in the fighting against COVID-19 due to its significant impact in reducing inflammation, boosting antioxidant status and innate immunity.[137-140]

Propolis

Propolis, which is produced by honeybees, has a variety of biological properties, including anti-microbial, anti-inflammatory, dermatoprotective, laxative, anti-diabetic, anti-tumor, and immunomodulatory activity.[140,141] Propolis can be used in conjunction with antiviral and immunomodulatory effects to help for prevention of COVID-19.

Probiotics

Bifidobacterium and *Lactobacillus* species are the most widely utilised probiotics, followed by *Streptococcus, Enterococcus, Bacillus,* and *Escherichia coli.*[142] The host's innate immune response is improved by these probiotics, which also have anti-inflammatory properties, and the enterocytes and gut involvement[143] can act as reservoirs for SARS-CoV-2 infection. To combat the pathogenesis of COVID-19, probiotics can be utilised as adjuvants and preventatives.

Lactoferrin

The term "lactoferrin" refers to a safe and naturally occurring glycoprotein (Lf). It is necessary to prevent the virus from entering the body and proliferating.[144] By increasing T-cell activation, lowering interleukin levels like IL-6 and TNF-, and downregulating ferritin, it has immunomodulatory and antioxidant effects.[145] Additionally, it lessens the oxidative harm that H_2O_2 causes to the endothelial cells in the human umbilical vein.[146] As a result, it is used as a possible therapy and preventative approach for COVID-19.

Quercetin

Antiviral and anti-inflammatory effects can be found in the well-known antioxidant quercetin.[147] Synergistic antiviral and immunomodulatory effects are produced against COVID-19 when vitamin C is coupled with it.[148] Consequently, it can be considered as a possibility for COVID-19 therapy and prevention.

Yoga and Breathing Exercises

The predominant symptom of COVID-19 is 'decreased lung capacity'. So, from our ancient practices, the yogosannas can also be practiced for improving lung power further to decrease complication in COVID-19.

Some yoga exercises practiced to improve lung capacity are:

- **Anulom Vilom Pranayama or Alternate Nostril Breathing Technique of Yoga:** This breathing technique offers a multitude of advantages, including increasing memory, respiratory and cardiovascular health and blood pressure regulation.
- **Ustrasana (Camel pose):** Numerous benefits of this breathing technique include improved blood pressure control, respiratory and cardiovascular health, and memory enhancement.
- **Hasta Uttanasana (Raised arms pose):** Hasta Uttanasana is renowned for enhancing respiratory capacity and lowering exhaustion and fatigue. It reduces tension and enhances the body's blood circulation.
- **Bhujangasana:** This asana lessens lower back discomfort while also enhancing oxygenation of the body. In addition, it helps for blood circulation.
- **Paschimottanasana (Seated Forward Bend):** It works wonders to reduce tension and calm the neurological system by calming the mind. It also lessens tiredness.

Treatment Packages

Though, the above preventive and treatment strategies used or can be used, the following Table 3 treatment packages are being prescribed during COVID-19 treatment.

Future Prospectives

Different demographics, genders, ABO blood types, HLA genotypes, groups of people of a certain ethnicity, and

Table 3: Treatment packages prescribed during COVID-19 treatment.

Name of API (tablets)	Quantity	Frequency
Vitamin C	500mg	Twice a day
Zinc	50mg	Once a day
Vitamin D3	60000 IU	Weekly once for 4 weeks
B Complex	-	Once a day
Paracetamol	650mg	Twice a day
Cetirizine	10mg	Once at night
Ivermectin	12mg	Once a day after meals
Famotidine	40mg	Once before breakfast
Dose per day(package) Morning: Famotidine 40mg - Before breakfast -1 Vitamin C 500mg -1 Zinc 50mg -1 Paracetamol 650 mg - 1	Afternoon: B-Complex-1 Vitamin D3 60000 IU- 1 Ivermectin 12mg -1	Night: Cetirizine 10mg - 1 Vitamin C 500mg - 1 Paracetamol 650 mg - 1

geographical origins have significantly different rates of COVID-19 incidence, severity and death. Because of this, finding a successful preventive approach has therefore been a primary focus, leading to the creation of large number of management strategies. So, still there is a need to propose different strategies based on advanced technology, knowledge or information gained about virus.

Gene therapy

Gene therapy is one of the novel therapeutic approaches which employs genes or short oligonucleotide sequences as therapeutic molecules into cells to alter the phenotypes permanently. It is an approach to treat diseases either by modifying the expressions of specific genes or the rectification of abnormal genes. It can be accomplished by substituting the mutated gene with a new gene into the body. The major purpose of gene therapy is to introduce a functional gene into a person who has the deficiency of a specific gene and also to replace a missing enzyme to a patient who lacks a specific enzyme. Gene Therapy works by Gene Cloning, Carriers/ Vectors – like plasmids, Cosmides, phage virus, etc.

Airway cell gene expression could be altered by exposure to the SARS-CoV-2 spike protein.[59] The information about genetic expressions and the alleles that are involved for COVID-19's susceptibility opens up new possibilities for designing a gene therapy for the disease. Genes that are heavily associated with cancer, viral infections, and autoimmune illnesses have been silenced via the RNA interference (RNAi) method.[149,150] When siRNAs targeted to the SARS-CoV-2 genes are characterised and analysed *in vitro*, a suitable *in vivo* transport approach must be chosen[151] for the treatment of COVID-19. The created siRNA should be administered in this case via the pulmonary route, including inhalation, intranasal administration, and intratracheal aerosol delivery.[152] When combined with anti-mucosal medications, aerosol administration of lipidic, polymeric peptide, or inorganic siRNA derived nanocarrier systems may be able to overcome limitations such neutrophil and macrophage degradation.[153] Some of the molecular biology methods that can be used to manage illnesses like COVID-19 or pandemics include gene editing techniques like CRISPR-Cas12/13-based SHERLOCK, DETECTR, CARVER and PAC-MAN, ASO, antisense peptide nucleic acids, ribozymes, aptamers, and RNAi silencing treatments.[154] These techniques were developed with cutting-edge scientific developments.

Personalized Medicine in COVID-19

COVID-19 has already professed as a global pandemic and health emergency by the WHO, this enduring crisis has driven the progress of effective therapeutic agents thus resulted in testing of repurposed drugs. Currently, the speed of infection spread has partially halted through vaccination but, some of the breakthrough infections are reported even in fully vaccinated individuals. To deliver an optimized treatment, different biomarkers have been studied[154] and critical biomarkers can predict the severity of COVID-19.[155] The medications currently used to treat COVID-19 can cause more side effects. One treatment may not be appropriate for everyone due to these adverse effects being genetically unpredictable amongst different people. These considerations allow the personalised therapy to more potently lessen the existing epidemic.[155] The use of personalized medicine is also suggested for COVID-19 treatment.[156] Due to the heterogenicity in the host responses to the COVID-19 condensed and personalized treatment is essential to gain promising consequences. Through an extensive array of genomic and proteomic investigation, the identification of specific immune responses can be accomplished in segregating the population. This leads to more specific treatment and an improved response to the therapy. Clinical and paraclinical variables can be used to evaluate the dynamics of the illness and the likelihood that it will advance to more severe manifestations. Depending on when the condition first appeared, the goal would be to start the best possible treatment regimens. In this sense, managing COVID-19 patients ideally moves beyond the simplistic notion of "one disease, one treatment" and instead emphasises "a disease with a clinic-biological form, a particular kinetics, and therefore a particular treatment".[156]

Other Novel Drug Delivery Systems (NDDS)

Patients with severe forms may be admitted to the hospital at the beginning of the illness, when the viral phase is crucial, or, more usually, during the inflammatory phase, a week after

the illness begins.[157] Some of these people will have biological inflammatory signs that are more noticeable than others. Thus, in the management of the disease can be possible by some targeted Novel drug delivery systems to decrease side effects and future complications with the existing treatment strategies. The development of pulmonary targeted drug delivery systems using nanotechnology also emphasises the effective management of lung capacity.[158]

CONCLUSION

The COVID-19 pandemic is still having an adverse effect on the world, and its long-term effects are still not known. In this day and age, it is sad that there are still so many communicable diseases, but fortunately, they may be overcome. With the aforementioned sudden unfortunate situations in mind, people must strengthen their innate immunity to fight or resist against such diseases. To do this, people have been taking immune boosters and vaccines since birth and avoiding junk food, processed foods, and other things that affect or weaken human immunity. Identifying high-risk biomarkers, which may potentially offer possible targets for treatment, requires taking into account the link between the host genetic base and COVID-19. New therapeutic technologies that are rapid, accurate, stable, easy to manufacture, and target specific for surveillance and therapy are urgently needed, as shown by the emergence of the novel coronavirus.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

REFERENCES

1. Bonilla-Aldana DK, Dhama K, Morales AJR.Revisiting the one health approach in the context of COVID-19: A look into the ecology of this emerging disease; advances in animal and veterinary sciences. 2020;8(3):234-37.
2. Das S, Das S, Ghangrekar MM. The COVID-19 pandemic: biological evolution, treatment options and consequences. Innov Infrastruct Solut. 2020;5(3):1-12. doi: 10 .1007/s41062-020-00325-8.
3. Sheng L, Wang X, Tang N, Meng F, Huang L, Li D. Clinical characteristics of moderate and severe cases with COVID-19 in Wuhan, China: a retrospective study. Clin Exp Med. 2021;21(1):35-9. doi: 10.1007/s10238-020-00662-z, PMID 32949308.
4. Kumar R, Singh V, Mohanty A, Bahurupi Y, Gupta PK. Corona health- care warriors in India: knowledge, attitude, and practices during COVID-19 outbreak. J Education Health Promot. 2021;10(44):1-8.
5. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, *et al.* Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in wuhan, China. J Am Med Assoc. 2020;323(11):1061-69. doi: 10.1001/jama.2020.1585, PMID 32031570.
6. Du Y, Tu L, Zhu P, Mu M, Wang R, Yang P, *et al.* Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. AmJ Respir Crit Care Med. 2020;201(11):1372-79. doi: 10.1164/rccm.202003-0543OC, PMID 32242738.
7. Akhmerov Akbarshakh ME. COVID-19 and the heart; circulation research; smidt Heart Institute. 2020;126:1443-55.
8. Lippi G, Lavie CJ, Sanchis-Gomar F. Cardiac troponin I in patients with coronavirus disease 2019 (COVID-19): evidence from a meta-analysis. Prog Cardiovascuar Dis. 2020;63(3):390-91.
9. Suwa T, Hogg JC, Quinlan KB, Ohgami A, Vincent R, van Eeden SF. Particulate air pollution induces progression of atherosclerosis. J Am Coll Cardiol. 2002;39(6):935-42. doi: 10.1016/s0735-1097(02)01715-1, PMID 11897432.
10. Hussein MH, Elshazli RM, Attia AS, Nguyen TP, Aboueisha M, Munshi R, *et al.* Asthma and COVID-19; different entities, same outcome: a meta-analysis of 107,983 patients. J Asthma. 2021:1-8.
11. Argacha JF, Collart P, Wauters A, Kayaert P, Lochy S, Schoors D, *et al.* Air pollution and ST-elevation myocardial infarction: A case-crossover study of the Belgian; ST- segment Elevation myocardial Infraction care registry 2009-2013. Int J Cardiol. 2016;223:300-5.
12. Akbarzadeh MA, Khaheshi I, Sharifi A, Yousefi N, Naderian M, Namazi MH, *et al.* The association between exposure to air pollutants including PM10, PM2.5, ozone, carbon monoxide, sulfur dioxide, and nitrogen dioxide concentration and the relative risk of developing STEMI: a case-crossover design. Environ Res.2018;161:299-303. doi: 10.1 016/j.envres.2017.11.020, PMID 29178978.
13. Frontera A, Cianfanelli L, VlachosK, Landoni G, Cremona G. Severe air pollution links to higher mortality in COVID-19 patients: the "double-hit" hypothesis. J Infect. 2020;81(2):255-9. doi: 10.1016/j.jinf.2020.05.031, PMID 32447007.
14. Wang A, Zhao W, Xu Z, Gu J. Timely blood glucose management for the outbreak of 2019 novel coronavirus disease (COVID-19) is urgently needed. Diabetes Res ClinPract. 2020;162:108118. doi: 10.1016/j.diabres.2020.108118, PMID 32179126.
15. Zhou J, Tan J. Diabetes patients with COVID-19 need better blood glucose management in Wuhan, China. Metabolism. 2020;107:154216. doi: 10.1016/j.metab ol.2020.154216, PMID 32220612.
16. Iqbal A, Prince LR, Novodvorsky P, Bernjak A, Thomas MR, Birch L, *et al.* Effect of Hypoglycemia on inflammatory Responses and the Response to Low-Dose endotoxemia in Humans. J Clin Endocrinol Metab. 2019;104(4):1187-99. doi: 10.1210 /jc.2018-01168, PMID 30252067.
17. Syeda Umme Fahmida M, Chowdhury PA, HakimA, Shahidul Islam M, Jahangir Alam Md, Azad A Kalam. Blood biochemical parameters for assessment of COVID-19 in diabetic and non-diabetic subjects: a cross-sectional study. IntJ Environ Health Res. 2021:1344-58.
18. Cipriani G, Fiorino MD. Access to care for dementia patients suffering from COVID-19. Am J Geriatr Psychiatry. 2020;28(7):796-7. doi: 10.1016/j.jagp.2020.04.009, PMID 32327300.
19. Friedler B, Crapser J, McCullough L. One is the deadliest number: the detrimental effects of social isolation on cerebrovascular diseases and cognition. Acta Neuropathol. 2015;129(4):493-509. doi: 10.1007/s00401-014-1377-9, PMID 25537401.
20. Beach SR, Praschan NC, Hogan C, Dotson S, Merideth F, Kontos N, *et al.* Delirium in COVID-19: a case series and exploration of potential mechanisms for central nervous system involvement. Gen Hosp Psychiatry. 2020;65:47-53. doi: 10.1016/j.genhosppsy ch.2020.05.008, PMID 32470824.
21. Phipps MM, Barraza LH, LaSota ED, Sobieszczyk ME, Pereira MR, Zheng EX, *et al.* Acute liver injury in COVID-19: prevalence and association with clinical outcomes in a Large U.S. cohort. Hepatology. 2020;72(3):807-17. doi: 10.1002/hep.31404, PMID 32473607.
22. Fix OK, Hameed B, Fontana RJ, Kwok RM, McGuire BM, Mulligan DC, *et al.* Clinical best practice advice for hepatology and liver transplant providers during the COVID-19 pandemic: AASLDexpertpanelconsensusstatement.Hepatology. 2020;72(1):287-304. doi: 10.1002/hep.31281, PMID 32298473.
23. Liu Z, Xiao X, Wei X, Li J, Yang J, Tan H, *et al.* Composition and divergence of coronavirus spike proteins and host ACE2 receptors predict potential intermediate hosts of SARS-CoV-2. J MedVirol. 2020;92(6):595-601. doi: 10.1002/jmv.25726, PMID 32100877.
24. Connors JM, Levy JH. COVID-19 and its implications for thrombosis and anticoagulation; Blood. 2020 ;135(23):2033-40.
25. Leisman DE, Deutschman CS, Legrand M. Facing COVID-19 in the ICU: vascular dysfunction, thrombosis, and dysregulated inflammation. Intensive Care Med. 2020;46(6):1105-8. doi: 10.1007/s00134-020-06059-6, PMID 32347323.
26. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARSCoV2 and non-SARS-CoV2. J Thromb Thrombolysis. 2021;51(4):1107-10. doi: 10.1007/s11239-020-02105-8, PMID 32246317.
27. Crossette-Thambiah C, Nicolson P, Rajakaruna I, Langridge A, Sayar Z, Perelta MR, *et al.* The clinical course of COVID-19 in pregnant versus non-pregnant women requiring hospitalisation: results from the multicentre UK CA-COVID-19 study. Br J Haematol. 2021;195(1):85-9. doi: 10.1111/bjh.17579, PMID 34132386.
28. Ponziani FR, Del Zompo F, Nesci A, Santopaolo F, Ianiro G, Pompili M, *et al.* Gemelli against COVID-19 group. Liver involvement is not associated with mortality: results from a large cohort of SARS-CoV-2-positive patients. Aliment Pharmacol Ther. 2020;52:1060-8.
29. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW; The Northwell COVID-19 Research Consortium, Barnaby DP, Becker LB, Chelico JD, Cohen SL, Cookingham J, Coppa K, Diefenbach MA, Dominello AJ, Duer-Hefele J, Falzon L, Gitlin J, Hajizadeh N, Harvin TG, Hirschwerk DA, Kim EJ, Kozel ZM, Marrast LM, Mogavero JN, Osorio GA, Qiu M, Zanos TP; Presenting Characteristics, Comorbidities, and Outcomes Among 5700 Patients Hospitalized With COVID-19 in the New York City Area; Journal of The American Medical Association; 2020; 323(20): 2052-9.
30. Ferm S, Fisher C, Pakala T, Tong M, Shah D, Schwarzbaum D, *et al.* Analysis of gastrointestinal and hepatic manifestations of SARS-CoV-2infection in 892 patients in Queens, NY. Clin Gastroenterol Hepatol. 2020;18(10):2378-9.e1. doi: 10.1016/j.cgh .2020.05.049, PMID 32497637.
31. Redd WD, Zhou JC, Hathorn KE, McCarty TR, Bazarbashi AN, Thompson CC, *et al.* Prevalence and characteristics of gastrointestinal symptoms in patients with severe acute respiratory syndrome coronavirus 2 infection in the United States: A multicenter cohort study. Gastroenterology. 2020;159(2):765-7.e2. doi: 10.1053/j.g astro.2020.04.045, PMID 32333911.

32. Kulkarni AV, Kumar P, Tevethia HV, Premkumar M, Arab JP, Candia R, *et al.* Systematic review with meta-analysis: liver manifestations and outcomes in COVID-19. Aliment Pharmacol Ther. 2020;52(4):584-99. doi: 10.1111/apt.15916, PMID 32638436.
33. Xu L, Liu J, Lu M, Yang D, Zheng X. Liver injury during highly pathogenic human coronavirus infections. Liver Int. 2020;40(5):998-1004. doi: 10.1111/liv.14435, PMID 32170806.
34. Liu W, Tao ZW, Wang L, Yuan ML, Liu K, Zhou L, *et al*. Analysis of factors associated with disease outcomes in hospitalized patients with 2019 novel coronavirus disease. ChinMedJ (Engl). 2020;133(9):1032-8. doi: 10.1097/CM9.0000000000000775, PMID 32118640.
35. Pereira MR, Mohan S, Cohen DJ, Husain SA, Dube GK, Ratner LE, *et al.* COVID-19 in solid organ transplant recipients: initial report from the US epicenter. Am J Transplant. 2020;20(7):1800-8. doi: 10.1111/ajt.15941, PMID 32330343.
36. Iavarone M, D'Ambrosio R, Soria A, Triolo M, Pugliese N, Del Poggio P, *et al.* High rates of 30-day mortality in patients with cirrhosis and COVID-19. J Hepatol. 2020;73(5):1063-71. doi: 10.1016/j.jhep.2020.06.001, PMID 32526252.
37. Deng X, Liu B, Li J, Zhang J, Zhao Y, Xu K. Blood biochemical characteristics of patients with coronavirus disease 2019 (COVID-19): a systemic review and meta-analysis. Clin Chem Lab Med. 2020;58(8):1172-81. doi: 10.1515/cclm-2020-0338, PMID 32554832.
38. Puttegowda B, Shivashankarappa AB, Dutta S, Chikkamuniswamy R, Bhat P, Krishnan S, *et al.* Patterns of cardiovascular diseases in COVID-19 patients admitted to tertiary cardiac care centre. Indian Heart J. 2021;73(6):682-6. doi: 10.1016/j.ihj.2021.10.007 , PMID 34695446.
39. Malik SUF. Blood biochemical parameters for assessment of COVID-19 in diabetic and non-diabetic subjects: a cross-sectional study. Int J Environ Health Res. 2020;32(6):1344-58.
40. Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, *et al.* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature. 2020;579(7798):270-3. doi: 10.1038/s41586-020-2012-7, PMID 32015507.
41. Dimonte S, Babakir-Mina M, Hama-Soor T, Ali S. Genetic variation and evolution of the 2019novelcoronavirus. Public Health Genomics 24.1-2. 2021;24(1-2):54-66. doi: 1 0.1159/000513530, PMID 33406522.
42. Severe Covid-19 GWAS Group, Ellinghaus D, Degenhardt F, Bujanda L, Buti M, Albillos A, *et al.* Genomewide association study of severe COVID-19 with respiratory failure. N Engl J Med. 2020;383(16):1522-34. doi: 10.1056/NEJMoa2020283, PMID 32558485.
43. Ellinghaus D. The ABO blood group locus and a chromosome 3 gene cluster associate with SARS-CoV-2 respiratory failure in an Italian-Spanish genome- wide association analysis; 2020:1-26.
44. WangF, Huang S, Gao R, Zhou Y, Lai C, Li Z, *et al*. Initial whole-genome sequencing and analysis of the host genetic contribution to COVID-19 severity and susceptibility. Cell Discov. 2020;6(1):83. doi: 10.1038/s41421-020-00231-4, PMID 33298875.
45. Sakuraba A, Haider H, Sato T. Population difference in allele frequency of HLA-c*05 and its correlation with COVID-19 mortality. Viruses. 2020;12(11):1333. doi: 10.3390/ v12111333, PMID 33233780.
46. Prachar M, Justesen S, Steen-Jensen DB, Thorgrimsen S, Jurgons E, Winther O, *et al.* Identification and validation of 174 COVID-19 vaccine candidate epitopes reveals low performance of common epitope prediction tools. Sci Rep. 2020;10(1):20465. doi: 10.1038/s41598-020-77466-4, PMID 33235258.
47. Liu N. The impact of ABO blood group on COVID-19 infection risk and mortality: a systematic review and meta-analysis; Blood Revision. 2020;48:100785.
48. Valenti L, Villa S, Baselli G, Temporiti R, Bandera A, Scudeller L, *et al.* Association of ABO blood group and secretor phenotype with severe COVID-19. Transfusion. 2020;60(12):3067-70. doi: 10.1111/trf.16130, PMID 33009662.
49. Gómez J, Albaiceta GM, Cuesta-Llavona E, García-Clemente M, López-Larrea C, Amado-Rodríguez L, *et al*. The interferon-induced transmembrane protein 3 gene (IFITM3) rs12252 C variant is associated with COVID-19. Cytokine. 2021;137:155354. doi: 10.1016/j.cyto.2020.155354, PMID 33113474.
50. Delanghe JR, Speeckaert MM, De Buyzere ML. The host's angiotensin converting enzyme polymorphism may explain epidemiological findings in COVID-19 infections; Clinical chimica. Acta. 2020;505:192-3.
51. Hatami N, Ahi S, Sadeghinikoo A, Foroughian M, Javdani F, Kalani N, *et al*. Worldwide ACE (I/D) polymorphism may affect COVID-19 recovery rate: an ecological meta-regression. Endocrine. 2020;68(3):479-84. doi: 10.1007/s12020-020-02381-7, PMID 32542429.
52. Wu F, Zhao S, Yu B, Chen YM, Wang W, Song ZG, *et al.* A new coronavirus associated with human respiratory disease in China.Nature. 2020;579(7798):265-9. doi: 10.103 8/s41586-020-2008-3, PMID 32015508.
53. Lu G, Wang Q, Gao GF. Bat-to-human: spike features determining "host jump" of coronaviruses SARS-CoV, MERS-CoV, and beyond. Trends Microbiol. 2015;23(8):468-78. doi: 10.1016/j.tim.2015.06.003, PMID 26206723.
54. Siegel D, Hui HC, Doerffler E, Clarke MO, Chun K, Zhang L. Discovery and synthesis of a phosphoramidate prodrug of a pyrrolo[2,1-f][triazin-4-amino] adenine c-nucleoside (GS-5734) for the treatment of Ebola and emerging viruses. J MedChem. 2021;60:1648-61.
55. Al-Tawfiq JA, Al-Homoud AH, Memish ZA. Remdesivir as a possible therapeutic option for the COVID-19. Travel Med InfectDis. 2020;34:101615. doi: 10.1016/j.tmai d.2020.101615, PMID 32145386.
56. WangM, Cao R, Zhang L, Yang X, Liu J, Xu M, *et al*. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) *in vitro*. Cell Res. 2020;30(3):269-71. doi:10.1038/s41422-020-0282-0, PMID 32020029.
57. Sanders JM, Monogue ML, Jodlowski TZ, Cutrell JB. Pharmacologic Treatments for coronavirus disease 2019 (COVID-19): a review. Journal of Am Med Assoc. 2020;323(18):1824-36. doi:10.1001/jama.2020.6019, PMID 32282022.
58. Mehta N, Mazer-Amirshahi M, Alkindi N, Pourmand A. Pharmacotherapy in COVID-19; A narrative review for emergency providers. Am J Emerg Med. 2020;38(7):1488-93. doi:10.1016/j.ajem.2020.04.035, PMID 32336586.
59. Furuta Y, Gowen BB, Takahashi K, Shiraki K, Smee DF, Barnard DL. Favipiravir (T-705), a novel viral RNA polymerase inhibitor. Antiviral Res. 2013;100(2):446-54. doi:10.1016/ j.antiviral.2013.09.015, PMID 24084488.
60. Mc Cullough PA. Favipiravir and the need for early ambulatory treatment of SARS-CoV2 infection (COVID-19). Antimicrob Agents Chemotheraphy. 2020;17,64(12):e02017-20. doi:10.1128/AAC.02017-20.
61. Joshi S, Parkar J, Ansari A, Vora A, Talwar D, Tiwaskar M, *et al*. Role of favipiravir in the treatment of COVID-19. Int J Infect Dis. 2021;102:501-8. doi: 10.1016/j.ijid.2020.10.0 69, PMID 33130203.
62. Yamamura H, Matsuura H, Nakagawa J, Fukuoka H, Domi H, Chujoh S. Effect of favipiravir and an anti-inflammatory strategy for COVID-19. Crit Care. 2020;24(1):413. doi:10.1186/s13054-020-03137-5, PMID 32646499.
63. Takahashi H, Iwasaki Y, Watanabe T, Ichinose N, Okada Y, Oiwa A, *et al.* Case studies of SARS-CoV-2 treated with favipiravir among patients in critical or severe condition. Int J Infect Dis. 2020;100:283-5. doi:10.1016/j.ijid.2020.08.047, PMID 32829044.
64. Kaptein SJF, Jacobs S, Langendries L, Seldeslachts L, ter Horst S, Liesenborghs L, *et al*. Favipiravir at high doses has potent antiviral activity in SARS-CoV-2–infected hamsters, whereas hydroxychloroquine lacks activity. Proc Natl Acad Sci U S A. 2020;117(43):26955-65. doi:10.1073/pnas.2014441117, PMID 33037151.
65. cohen MS. Hydroxychloroquine for the prevention of COVID-19 - searching for evidence. N Engl J Med. 2020;383(6):585-6. doi:10.1056/NEJMe2020388, PMID 32492298.
66. FDA. FDA fact sheet -Hydroxychloroquine sulfate-COVID-19; 2020c. Available from: h ttps://www.fda.gov/media/136537/download.
67. Chandwani A, Shuter J. Lopinavir/ritonavir in the treatment of HIV-1 infection: a review. Therepeutics Clin Risk Manag. 2004;4:1023-33. doi:10.2147/tcrm.s3285.
68. Sisay M. 3CLpro inhibitors as a potential therapeutic option for COVID-19: available evidence and ongoing clinical trials. Pharmacol Res. 2020;156:104779. doi:10.1016/j. phrs.2020.104779, PMID 32247821.
69. Yan D, Liu XY, Zhu YN, Huang L, Dan BT, Zhang GJ, *et al*. Factors associated with prolonged viral shedding and impact of lopinavir/ritonavir treatment in hospitalised non-critically ill patients with SARS-CoV-2 infection. Eur Respir J. 2020;56(1):2000799. doi:10.1183/13993003.00799-2020, PMID 32430428.
70. Huang YQ, Tang SQ, Xu XL, Zeng YM, He XQ, LiY, *et al.* No statistically apparent difference in antiviral effectiveness observed among ribavirin plus interferon-alpha, lopinavir/ritonavir plus interferon-alpha, and ribavirin plus lopinavir/ritonavir plus interferon-alpha in patients with mild to moderate coronavirus disease 2019: results of a randomized, open-labeled prospective study. Front Pharmacol. 2020;11:1071. doi:10.3389/fphar.2020.01071, PMID 32765274.
71. Verdugo-Paiva F, Izcovich A, Ragusa M, Rada G. Lopinavir-ritonavir for COVID-19: a living systematic review. Medwave. 2020;20(6):e7967. doi:10.5867/medwave.2020.0 6.7966, PMID 32678815.
72. Diagnosis and treatment of pneumonia caused by new coronavirus (trail version 6) medical administration and hospital authority.www.nhc.gov.cn/yzygj/s7653p/2020 02/8334a8326dd94d329df351d7da8aefc2.shtml.
73. Bhatia HK, Singh H, Grewal N, Natt NK. Sofosbuvir: A novel treatment option for chronic hepatitis C infection. J Pharmacol Pharmacother. 2014;5(4):278-84. doi: 10.41 03/0976-500X.142464, PMID 25422576.
74. Abbaspour Kasgari H, Moradi S, Shabani AM, Babamahmoodi F, Davoudi Badabi AR, Davoudi L, *et al*. Evaluation of the efficacy of sofosbuvir plus daclatasvir in combination with ribavirin for hospitalized COVID-19 patients with moderate disease compared with standard care: a single-centre, randomized controlled trial. J Antimicrob Chemotheraphy. 2020;75(11):3373-8.
75. Elfiky AA. Ribavirin, remdesivir, sofosbuvir, galidesivir, and tenofovir against SARS-CoV-2RNA dependent RNA polymerase (RdRp): a molecular docking study. Life Sci. 2020;253:117592. doi: 10.1016/j.lfs.2020.117592, PMID 32222463.
76. Pillaiyar T, Manickam M, Namasivayam V, Hayashi Y, Jung SH. An overview of severe acute respiratory syndrome-coronavirus (SARS-CoV) 3CL protease inhibitors: peptidomimetics and small molecule chemotherapy. J Med Chem. 2016;59(14):6595-628. doi: 10.1021/acs.jmedchem.5b01461, PMID 26878082.
77. Owen DR, Allerton CMN Anderson AS, Aschenbrenner L, Avery M, Berritt S, *et al.* An oral SARS-CoV-2 M(pro) inhibitor clinical candidate for the treatment of COVID-19. Science. 2021;374(6575):1586-93. doi: 10.1126/science.abl4784, PMID 34726479.
78. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/ antiviral-therapy/ritonavir-boosted-nirmatrelvir--paxlovid-/.
79. Zhou S, Hill CS, Sarkar S, Tse LV, Woodburn BMD, Schinazi RF, *et al.* Beta-d-N4-hydroxycytidine inhibits SARS-CoV-2 through lethal mutagenesis but is also mutagenic to mammalian cells. J Infect Dis. 2021;224(3):415-19. doi: 10.1093/in fdis/jiab247, PMID 33961695.

80. Fischer WA, 2nd, Eron JJ, Jr, Holman W, Ralph Baric ER Duke, David Awohl, *et al.* A Phase 2a clinical trial of molnupiravir in patients with COVID-19 shows accelerated SARS-CoV-2RNA clearance and elimination of infectious virus. Sci Transl Med. 2021;14(628):eabl7430.
81. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for molnupiravir; 2021. Available from: https://www.fda.gov/media/155054/download.
82. Available from: https://www.covid19treatmentguidelines.nih.gov/therapies/antiviral-therapy/interferons/.
83. Public health emergency. Bamlanivimab/etesevimab; 2022. Available from: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/Bamlanivimab-etesevimab/Pages/default.aspx.
84. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for bebtelovimab; 2022. Available from: https://www.fda.gov/media/156152/download.
85. Public health emergency; 2022. REGEN-COV. Available from: https://www.phe.gov/emergency/events/COVID19/investigation-MCM/cas_imd/Pages/default.aspx.
86. Food and Drug Administration. Fact sheet for healthcare providers: Emergency Use authorization (EUA) of sotrovimab; 2022. Available from: https://www.fda.gov/media/149534/download.
87. Iketani S, Liu L, Guo Y, Liu l, jasper F-W, huang Y, Wang M, Luo Y, David D. Ho. Antibody evasion properties of SARS-CoV-2 Omicron sublineages. Nature. 2022;604(7906):553-56.
88. Takashita E, Kinoshita N, Yamayoshi S, Sakai-Tagawa Y, Fujisaki S, Ito M, *et al.* Efficacy of antiviral agents against the SARS-CoV-2 Omicron subvariant BA.2. N Engl J Med. 2022;386(15):1475-7. doi: 10.1056/NEJMc2201933, PMID 35263535.
89. Food and Drug Administration. Fact sheet for healthcare providers: emergency use authorization for Evusheld (tixagevimab co-packaged with cilgavimab); 2022. Available from: https://www.fda.gov/media/154701/download.
90. Planas D, Saunders N, Maes P, benhassine G, Florence, buchrieser C, *et al.* Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature. 2021;602(7898):671-75.
91. Cameroni E, Bowen JE, Rosen LE, Saliba C, Zepeda SK, Culap K, *et al*. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature. 2022;602(7898):664-70. doi: 10.1038/s41586-021-04386-2, PMID 35016195.
92. Liu B, Li M, Zhou Z, Guan X, Xiang Y. Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced Cytokine Release Syndrome (CRS)? J Autoimmun. 2020;111:102452. doi: 10.1016/j.jaut.2020.102452, PMID 32291137.
93. Zhang C, Wu Z, Li JW, Zhao H, Wang GQ. Cytokine release syndrome in severe COVID-19: interleukin-6 receptor antagonist tocilizumab may be the key to reduce mortality. Int J Antimicrob Agents. 2020;55(5):105954. doi: 10.1016/j.ijantimicag.2020.105954, PMID 32234467.
94. Available from: https://www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-vaccines.
95. Booth W, Cunningham E. Britain warns against Pfizer vaccine for people with history of "significant" allergic reactions.
96. Cabanillas B, Akdis CA, Novak N. Allergic reactions to the first COVID-19 vaccine: A potential role of polyethylene glycol? Allergy. 2021;76(6):1617-8. doi: 10.1111/all.14711, PMID 33320974.
97. Information for Healthcare Professionals on Pfizer/BioNTech COVID-19 vaccine. Medicines and Healthcare products Regulatory Agency (MHRA); 2020.
98. Comirnaty. United States Food and Drug Administration (FDA); 2021.
99. UK medicines regulator gives approval for first UK COVID-19 vaccine. Medicines and Healthcare products Regulatory Agency (MHRA); 2020.
100. Available from: https://www.seruminstitute.com/health_faq_covishield.
101. COVID-19 vaccine. Janssen. Therapeutic Goods Administration (TGA); 2021.
102. 'A Study of COV2 for the Prevention of SARS-CoV-2-Mediated COVID-19 in Adult Participants (ENSEMBLE)' at; 2022.
103. Moderna COVID-19 Vaccine- injection, suspension. Dailymed.2022.
104. FDA authorizes additional vaccine dose for certain immunocompromised individuals. United States Food and Drug Administration (FDA); 2021.
105. TGA grants provisional determination for the Moderna bivalent COVID-19 vaccine "Spikevax Bivalent Zero/Omicron". Therapeutic Goods Administration (TGA); 2022.
106. Xia S, Zhang Y, Wang Y, Wang H, Yang Y, Gao GF, *et al*. Safety and immunogenicity of an inactivatedSARS-CoV-2 vaccine, BBIBP-CorV: a randomised, double-blind, placebo-controlled, phase 1/2 trial. Lancet Infect Dis. 2021;21(1):39-51. doi: 10.1016/S1473-3099(20)30831-8, PMID 33069281.
107. The Sinopharm COVID-19 vaccine: what you need to know. World Health Organization; 2021.
108. Nguyen S. Coronavirus: Vietnam approves Sinopharm's vaccine, but will people take it? South China Morning Post; 2021.
109. Lahiri T, Li J. What we now know about the efficacy of China's Covid-19 vaccines. Quartz. 2021.
110. Hotez PJ, Bottazzi ME. Whole inactivate d virus and protein-based COVID-19 vaccines. Annu Rev Med. 2022;73(1):55-64. doi: 10.1146/annurev-med-042420-113212, PMID 34637324.
111. Interim recommendations for use of the inactivated COVID-19 vaccine BIBP developed by China National Biotec Group (CNBG), Sinopharm (Guidance). World Health Organization; 2021.
112. National Institutes of Health (NIH). Available from: https://irp.nih.gov/catalyst/29/4/covid-19-timeline-at-nih-may-june-2021;2021.
113. Available from: https://www.health.gov.au/initiatives-and-programs/covid-19-vaccines/approved-vaccines/novavax.
114. Gorman S, Buckley AG, Ling KM, Berry LJ, Fear VS, Stick SM, *et al*. Vitamin D supplementation of initially vitamin D-deficient mice diminishes lung inflammation with limited effects on pulmonary epithelial integrity. Physiol Rep. 2017;5(15):e13371. doi: 10.14814/phy2.13371, PMID 28774952.
115. D'Avolio AD, Avataneo V, Manca A, Cusato J, De Nicolò A, Lucchini R, *et al.* 25-hydroxyvitamin d concentrations are lower in patients with positive PCR for SARS-CoV-2. Nutrients. 2020;12(5):1359. doi: 10.3390/nu12051359, PMID 32397511.
116. Merzon E, Tworowski D, Gorohovski A, Vinker S, Golan Cohen A, Green I, *et al*. Low plasma 25(OH) vitamin D level is associated with increased risk of COVID-19 infection: an Israeli population-based study. FEBS Journal. 2020;287(17):3693-702. doi: 10.1111/febs.15495, PMID 32700398.
117. Lee JI, Burckart GJ. Nuclear factor kappa B: important transcription factor and therapeutic target. J Clin Pharmacol. 1998;38(11):981-93. doi: 10.1177/009127009803801101, PMID 9824778.
118. Hunt C, Chakravorty NK, Annan G, Habibzadeh N, Schorah CJ. The clinical effects of vitamin C supplementation in elderly hospitalised patients with acute respiratory infections. Int J Vitam Nutr Res. 1994;64(3):212-9. PMID 7814237.
119. Biaggio VS, Pérez Chaca MV, Valdéz SR, Gómez NN, Gimenez MS. Alteration in the expression of inflammatory parameters as a result of oxidative stress produced by moderate zinc deficiency in rat lung. Exp Lung Res. 2010;36(1):31-44. doi: 10.3109/01902140903061787, PMID 20128680.
120. Skalny AV, Rink L, Ajsuvakova OP, Aschner M, Gritsenko VA, Alekseenko SI, *et al*. Zinc and respiratory tract infections: perspectives for COVID-19. Int J Mol Med. 2020;46(1):17-26.
121. Razzaque MS. COVID-19 pandemic: can maintaining optimal zinc balance enhance Host Resistance?. Tohoku J Exp Med. 2020;251(3):175-81. doi: 10.1620/tjem.251.175, PMID 32641644.
122. Ischia J. High-Dose Intra Venouszinc (HDIVZn) as adjunctive therapy in COVID-19 positive critically ill patients: a pilot randomized controlled trial; 2020.
123. Barazzoni R, Bischoff SC, Breda J, Wickramasinghe K, Krznaric Z, Nitzan D, *et al*. ESPEN expert Statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection. Clin Nutr. 2020;39(6):1631-8. doi: 10.1016/j.clnu.2020.03.022, PMID 32305181.
124. Catanzaro M, Corsini E, Rosini M, Racchi M, Lanni C. Immunomodulators inspired by nature: a review on curcumin and echinacea. Molecules. 2018;23(11):2778. doi: 10.3390/molecules23112778, PMID 30373170.
125. Zahedipour F, Hosseini SA, Sathyapalan T, Majeed M, Jamialahmadi T, Al-Rasadi K, *et al*. Potential effects of curcumin in the treatment of COVID-19 infection. Phytother Res. 2020:n/a.
126. Rao PV, Gan SH. Cinnamon: A multifaceted medicinal plant. Evid Based Complement Alternat Med eCAM. 2014;2014:1-12. doi: 10.1155/2014/642942.
127. Lang A, Lahav M, Sakhnini E, Barshack I, Fidder HH, Avidan B, *et al*. Allicin inhibits spontaneous and TNF alpha induced secretion of proinflammatory cytokines and chemokines from intestinal epithelial cells. Clin Nutr. 2004;23(5):1199-208. doi: 10.1016/j.clnu.2004.03.011, PMID 15380914.
128. Bang JS, Oh DH, Choi HM, Sur B-J, Lim S-J, Kim JY, *et al*. Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1beta-stimulated fibroblast-like synoviocytes and in rat arthritis models. Arthritis Res Ther; 2009;11(2):R49.
129. Hilgenfeld R. From SARS to MERS: crystallographic studies on coronaviral proteases enable antiviral drug design. FEBS Journal. 2014;281(18):4085-96. doi: 10.1111/febs.12936, PMID 25039866.
130. Gupta SC, Patchva S, Aggarwal BB. Therapeutic roles of curcumin: lessons learned from clinical trials. The Am Assoc Pharm Sci J. 2013;15(1):195-218. doi: 10.1208/s12248-012-9,432-8.
131. Kumar A. Molecular docking of natural compounds from Tulsi (*Ocimum sanctum*) and neem (*Azadirachta indica*) against SARS-CoV-2 protein targets. Preprints. 2020. doi: 10.21203/rs.3.rs-27151/v1.
132. Dhanjal NIK, kaur SS, Prabhu KS, Prakash NT. Selenium supplementation through Se-rich dietary matrices can upregulate the anti-inflammatory responses in lipopolysaccharide-stimulated murine macrophages. Food Agric Immunol. 2017;2;28(6):1374-92. doi: 10.1080/09540105.2017.1343805, PMID 29563666.
133. Ca S, KK, RK. Ww F. Role Selenium HIV Infect. 2010;68, Nutrition reviews.
134. Dworkin BM. Selenium deficiency in HIV infection and the Acquired Immunodeficiency Syndrome (AIDS). Chem Biol Interact.1994;1;91(2):181-6. doi: 10.1016/0009-2797(94)90038-8, PMID 8194134.
135. Wolska K, Gorska A, Antosik K, Lugowska K. Immunomodulatory effects of propolis and its components on basic immune cell functions. Indian J Pharm Sci. 2019;81(4):575-88. doi: 10.36468/pharmaceutical-sciences.548.
136. Schreck Bird A, Gregory PJ, Jalloh MA, Risoldi Cochrane Z, Hein DJ. Probiotics for the treatment of infantilecolic: A systematic review. J Pharm Pract. 2017;30(3):366-74. doi: 10.1177/0897190016634516, PMID 26940647.

137. Lin L, Jiang X, Zhang Z, Huang S, Zhang Z, Fang Z, *et al*. Gastrointestinal symptoms of 95 cases with SARS-CoV-2 infection. Gut. 2020;69(6):997-1001. doi: 10.1136/gutjnl-2020-321013, PMID 32241899.
138. Rosa L, Cutone A, Lepanto MS, Paesano R, Valenti P. Lactoferrin: A natural glycoprotein involved in iron and inflammatory homeostasis. Int J Mol Sci. 2017;18(9):1985.
139. Ishikado A, Imanaka H, Takeuchi T, Harada E, Makino T. Liposomalization of lactoferrin enhanced its anti-inflammatory effects via oral administration. Biol Pharm Bull. 2005;28(9):1717-21. doi: 10.1248/bpb.28.1717, PMID 16141546.
140. Safaeian L, Javanmard SH, Mollanoori Y, Dana N. Cytoprotective and antioxidant effects of human lactoferrin against H2O2-induced oxidative stress in human umbilical vein endothelial cells. Adv Biomed Res. 2015;4:188. doi: 10.4103/2277-9175.164010, PMID 26605227.
141. Manjeet KR, Ghosh B. Quercetin inhibits LPS-induced nitric oxide and tumor necrosis factor-alpha production in murine macrophages. Int J Immunopharmacol. 1999;7:435-43.
142. Colunga Biancatelli RML, Berrill M, Catravas JD, Marik PE. Quercetin and vitamin C: an experimental, synergistic therapy for the prevention and treatment of SARS-CoV-2 related disease (COVID-19). Front Immunol. 2020;11.
143. Wang M, Wu Q, Xu W, Qiao B, Wang J, Zheng H, *et al.* Clinical diagnosis of 8274 samples with 2019-novel coronavirus in Wuhan. med Rxiv. 2020. doi: 10.1101/2020.02.12. 20022327. PPR:PPR112805.
144. Wang Y, Kang H, Liu X, Tong Z. Combination of RT-qPCR testing and clinical features for diagnosis of COVID-19 facilitates management of SARS-CoV-2 outbreak. J Med Virol. 2020;92(6):538-39. doi: 10.1002/jmv.25721, PMID 32096564.
145. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal. 2020;10(2):102-8. doi: 10.1016/j.jpha.2020.03.001, PMID 32282863.
146. Youngren-Ortiz SR, Gandhi NS, España-Serrano L, Chougule MB. Aerosol delivery of siRNA to the lungs. part 1: rationale for gene delivery systems. Kona. 2016;33:63-85. doi: 10.14356/kona.2016014, PMID 27081214.
147. Saw PE, Song EW. siRNA therapeutics: a clinical reality. Sci China (Life Sci).2019. doi: 10.1007/s11427-018-9438-y.
148. Berber B, Aydin C, Kocabas F, Guney-Esken G, Yilancioglu K, Karadag-Alpaslan M, *et al.* Gene editing and RNAi approaches for COVID-19 diagnostics and therapeutics. Gene Ther.2021;28(6):290-305. doi: 10.1038/s41434-020-00209-7, PMID 33318646.
149. Hacisuleyman E, Hale C, Saito Y, Blachere NE, Bergh M, Conlon EG, *et al*. Vaccine breakthrough infections with SARS-CoV-2 variants. N Engl J Med. 2021;384(23):2212-8. doi: 10.1056/NEJMoa2105000, PMID 33882219.
150. Zhou A, Sabatello M, Eyal G, Lee SS, Rowe JW, Stiles DF, *et al*. Is precision medicine relevant in the age of COVID-19? Genet Med. 2021;23(6):999-1000. doi: 10.1038/s41436-020-01088-4, PMID 33442027.
151. Demerle K, Angus DC, Seymour CW. Precision medicine for COVID-19: phenotype anarchy or promise realized? J Am Med Assoc. 2021;325(20):2041-2. doi: 10.1001/jama.2021.5248, PMID 33961002.
152. Wan S, Yi Q, Fan S, Lv J, Zhang X, Guo L, *et al.* Relationships among lymphocyte subsets, cytokines, and the pulmonary inflammation index in coronavirus (COVID-19) infected patients. Br J Haematol. 2020;189(3):428-37. doi: 10.1111/bjh.16659, PMID 32297671.
153. Yamada T, Sato S, Sotoyama Y, Orba Y, Sawa H, Yamauchi H, *et al*. RIG-I triggers a signaling-abortive anti-SARS-CoV-2 defense in human lung cells. Nat Immunol. 2021;22(7):820-8. doi: 10.1038/s41590-021-00942-0, PMID 33976430.
154. Luft T, Wendtner CM, Kosely F, Radujkovic A, Benner A, Korell F, *et al*. EASIX for prediction of outcome in hospitalized SARS-CoV-2 infected patients. Front Immunol. 2021;12:634416. doi: 10.3389/fimmu.2021.634416, PMID 34248931.
155. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, *et al*. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-4. doi: 10.1016/S0140-6736(20)30628-0, PMID 32192578.
156. Zimmer C, Corum J, Wee SL. Coronavirus vaccine tracker. The New York Times. ISSN 0362-4331. [retrieved Apr 9 2021].
157. Mallapaty S. China's COVID vaccines have been crucial - now immunity is waning. Nature. 2021;598(7881):398-9. doi: 10.1038/d41586-021-02796-w, PMID 34650240.
158. Kulkarni MS, Kakodkar P, Nesari TM, Dubewar AP. Combating the psychological impact of COVID-19 pandemic through yoga: recommendation from an overview. J Ayurveda Integr Med. 2022;13(2):100433. doi: 10.1016/j.jaim.2021.04.003, PMID 34172388.

Cite this article: Shaik NK, Poojitha N, Chandana KBS, Vidyavathi M, Venkata SDR. COVID-19 Current Management and Strategies for Future Outlook. Int. J. Pharm. Investigation. 2023;13(4):735-46.