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Review Article

Therapeutic approaches to tackle COVID-19: An overview

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ABSTRACT

Background: A series of an acute atypical respiratory disease occurred during December 2019 in Wuhan, China, that quickly metamorphosed as a pandemic, spreading across the globe, leaving more than 104,911,186 infected and more than 2,278,579 dead, in its wake within a year. This Novel Coronavirus, was also called Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) and the disease was called Coronavirus Disease 19 (COVID-19). On 30^{th} January 2020, The World Health Organisation (WHO) Director-General, declared the novel coronavirus outbreak, a public health emergency of international concern and flagged off WHO's highest level of alarm.

Objectives: To elaborate the various drug therapies used in trials and vaccines available for COVID-19 across the globe.

Materials and Methods: We compiled the literature searches under a single heading and scrutinized over 154 articles, for extracting data on the various pharmacotherapeutic approaches available to treat COVID-19.

Conclusion: Despite wide and varied treatment guidelines being available, the cure or prevention is still elusive for COVID-19. The categoric efficacy of vaccines must be proved to tackle the fast-mutating coronavirus.

Key findings: Current medical management is largely supportive with no targeted therapy available. Several drugs including lopinavir-ritonavir, remdesivir, antibiotics, hydroxychloroquine, steroids, anticoagulants, and antidiabetic drugs like metformin have been tried in clinical trials. Vaccines targeting the three different components of SARS-CoV-2 viruses, in different phases of clinical trials world-wide, have been made available.

1. Introduction

"Let hope be the antidote to fear. Let solidarity be the antidote to blame. Let our shared humanity be the antidote to our shared threat" – Tedros Ghebreyesus on the current COVID-19 pandemic (Director General of the WHO). The world has been struck by the little-known entity of corona virus that has evolved itself into a new 'AVATAR' and is claiming lives and smothering down people with the COVID-19 illness, bringing the world to an unprecedented pause. Evidently, this is a time of extraordinary uncertainty and a time when fear occupies the minds of all mankind. It is also a time when all of humanity have put aside their differences and unified against a single adversary. Although these are challenging circumstances, our solidarity provides promise of eventual triumph. The undeniably destructive novel coronavirus disease (COVID-19) has currently infected more than 153 million people globally and claimed more than 32 lakh lives as of May 1^{st} 2021. Being a new disease entity, it is the lack of a proven remedial agent, that is- a drug or vaccine, that elevates anxiety in the population. Tackling an unknown entity is like shooting ahead of a duck. Mankind is trying to find a cure as prevention with the available drugs in

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hand [vide Figure 1]. Each physician and therapist are trying to halt the progress of the disease and achieve a cure with extension of prior knowledge albeit, empirical. The quest for a definitive remedy arose with the ever-increasing volume of victims of COVID-19. The search for the drug for COVID-19, has left no stone unturned. The experiences of the Spanish Flu back in the 1920's and the related documented literature could give us a jumpstart for finding a suitable therapeutic regimen. Coincidentally, the use of hydroxychloroquine could put a damper on the COVID-19 infection, both prophylactically and therapeutically. Hence, this review looks at the literature search that provides data on drugs to counteract COVID-19, across the world.

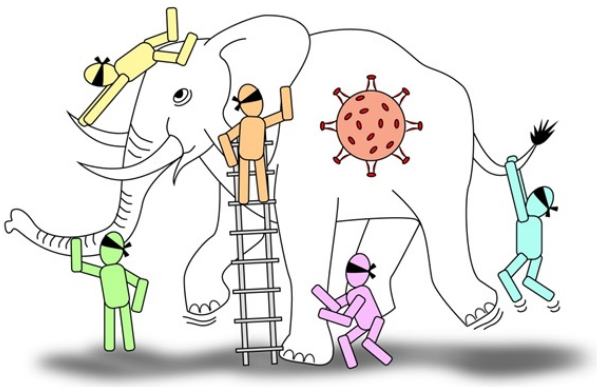

Fig. 1: Schematic illustration of analogy of 'Elephant with 5 blind man and the public understanding of Coronavirus'

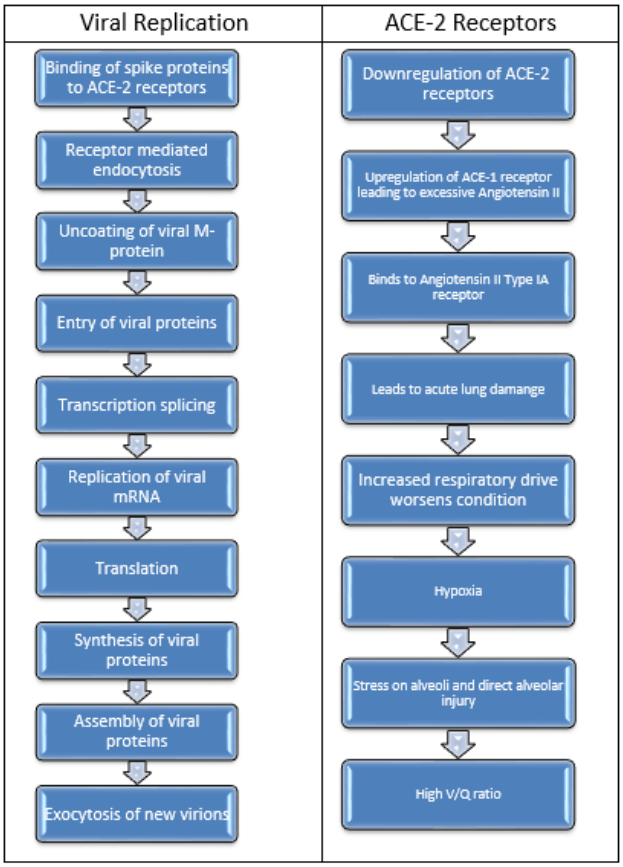

Chart 1: Chart showing viral replication and down regulation of ACE-2 receptors in developing hypoxia

2. Know thy Enemy

The coronavirus pandemic is thought to have originated from a seafood market in Wuhan, China in early December 2019. It soon spread rapidly between humans and is now a worldwide pandemic. The Coronavirus Study Group of the International Committee on Taxonomy of Viruses has renamed the novel coronavirus as Severe Acute Respiratory Syndrome Coronavirus-2, (SARS-CoV-2) due to its similarity with SARS-CoV. SARS-CoV was responsible for high mortality, causing acute respiratory distress syndrome in the early 2000s.[1,2] SARS-CoV-2 variants have different amino acid sequences and it was noted that Type A and the mutated Type C are common in Europe and the USA, while Type B is mainly found in East Asia.[3] Genome sequencing and phylogenetic analysis, revealed that similar to the SARS virus, the COVID-19 virus also binds to the angiotensin converting enzyme 2 (ACE2) receptors using its spike proteins, to enter the cells.[4,5] This explains the respiratory epithelial damage and respiratory symptoms of COVID-19 as ACE2 is found in abundance in lungs, heart, kidneys and small intestine. [Chart 1][6–8]

The primary means of transmission of this disease is direct person-to-person transmission as airborne transmission, especially by microdroplets. It is believed that infected individuals tend to be more contagious during the primary stages of their infection, essentially because viral RNA levels taken from upper respiratory specimens have been found to be highest in individuals at the onset of symptoms and generally decrease as the disease progresses.[6–10] Studies have concluded the mean incubation period to be 5.2 days and the combined case fatality rate to be 2.3%.[11] Ideally, pneumonia-like symptoms with fever, dyspnoea, and dry cough were first to be reported in those infected with the virus in Wuhan. The respiratory symptoms can be very divergent, from minimal cough to severe ARDS.[12] Generalized symptoms such as headache, abdominal discomfort, and malaise were also reported.[13] The clinical features have been graded and shown in [Table 1]. These laboratory findings also explain the reason for increased incidence of thrombosis and pulmonary embolism in patients with severe disease. Mian et al. has classified the common symptoms of this disease into mild, moderate, and severe.[14]

Table 1: Clinical features of SARS CoV2

Mild disease	Severe disease	Critical disease	Asymptomatic
Dry Cough	Fever	Respiratory failure	Ageusia
Fever	Tachypnoea	Fever	Anosmia
Sore throat	Dyspnoea	Decreases blood oxygen saturation	Non-specific abdominal pain
With or without nasal congestion		Septic shock	
Generalized body aches		Multiple organ failure	
Headache			
Malaise and fatigue			

2.1. Laboratory findings

Severe disease include elevated D-dimer and fibrinogen levels, prolonged prothrombin time and lymphopenia (mainly reduced peripheral T cells). Increased plasma concentrations of proinflammatory cytokines (interleukin (IL)-6, IL-10, granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1α, and tumor necrosis factor (TNF)-α) are also associated with Covid. Lymphopenia, neutrophilia, elevated serum alanine aminotransferase and aspartate amino transferase, lactate dehydrogenase, elevated high C reactive protein and high ferritin levels are also found in these patients. Respiratory symptoms (shortness of breath, cough, sneeze, and dyspnoea), GIT [diarrhoea, griping pain, nausea, vomiting] and Neurological [anosmia, ageusia, headache and body ache] have been reported.

2.2. Silent hypoxemia (Happy Hypoxic)

Covid is indeed a baffling phenomenon where long-standing respiratory pathology plays a vital role. Hypoxemia is a decrease in partial pressure of oxygen in blood. A few patients proceed without serious illness or even shortness of breath in spite of low blood oxygen levels. But these patients end-up with serious consequences at a later stage.

Cytokine storm is the phenomenon of excessive or uncontrolled release of anti-inflammatory cytokines. COVID-19 has been related with Cytokine Storm Syndrome (CSS) and Cytokine Release Syndrome (CRS). A thorough knowledge regarding the cytokine system and associated immunomodulatory therapy, paves a better method for improving the clinical outcomes of patients with severe acute infections.[15] Cytokines are group of diverse proteins secreted by the cells as part of signal transduction. Interferons are cytokines, with a major role in innate immunity to viruses in particular, and also other pathogens. Interleukins are immune system regulators that control immune cell differentiation and activation. Interleukins may be either pro or anti-inflammatory. Findings from few studies have shown that death in Covid could be due to the systemic spread of inflammation associated with cytokine storm.[16] Rubor, calor, dolor and 'functio laesa' are hallmarks of acute inflammation. Cytokine storm, the resulting inflammation and associated tissue edema causes a rise in extravascular pressures and also decreased tissue perfusion [vide. Figure 2]. This affects not only the lungs but leads to multi-organ failure among COVID-19 patients, adding to the severity of the disease. Cytokine induced apoptosis and infiltration of the lung tissues with the inflammatory cells cause severe lung damage and finally Acute Respiratory Distress Syndrome features.[17] Protein synthesis, folding, maturation and finally the transportation of proteins are carried out in the Endoplasmic Reticulum (ER). Endoplasmic reticular stress causes either misfolding of proteins or unfolding of the proteins, and this results in initiation of proinflammatory and hyperinflammatory reactions. There have been studies showing that the coronavirus spike protein induces and augments ER stress and this is evidenced by high level of ER stress markers. This initiation of proinflammatory and hyperinflammatory reactions causes cytokine storm.[18]

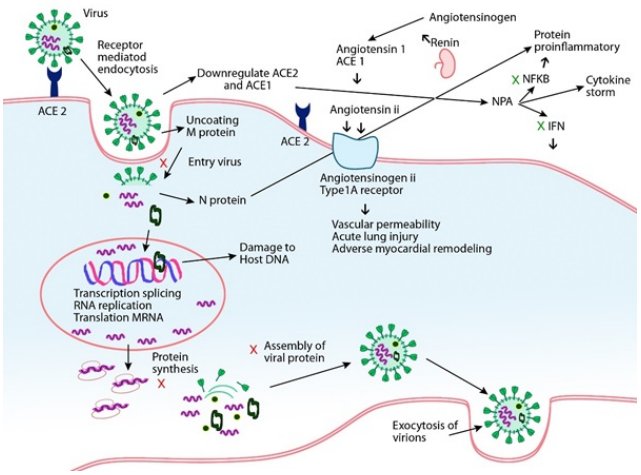

Fig. 2: Mechanism of SARS-CoV-2 viral entry, replication and role of ACE2 on pathogenesis

3. Asymptomatic Carriers

The proportion of patients who have been diagnosed as asymptomatic carriers have been varying depending upon

the age and the immune system of the individual. The variation in age could be due to the increased prevalence of underlying conditions in old age groups. There are few studies that show that children are less likely to show clinical symptoms compared to adults. Studies conducted during the initial phase of the pandemic among the people of the United States and China, reported that many cases were asymptomatic and lacked symptoms at the time of testing; but many among these people later developed symptoms. It has also been found that the viral load among the asymptomatic carriers is very less. Keeping a track of the different dimensions of presentation by an infected person and also the asymptomatic patients, it is apparent that the disease is potentially fatal. Studies and data analysis from hospitals have clearly echoed that mortality is higher among the elderly and those with comorbidities especially diabetes, hypertension, coronary artery disease, and chronic respiratory diseases.[19]

Keeping in mind the rapid infectivity of the virus, countries have been implementing ways to prevent further spread of this most dreaded viral entity through strict lockdowns, promoting the use of face masks, face shields, proper sanitisation, educating citizens about the importance of limiting social contact and encouraging appropriate personal hygiene. An infection with the COVID-19 virus has been found to induce protective antibodies. Studies have discovered SARS-CoV-2 specific CD4 and CD8 T cells in individuals who had recovered from the infection. This was also seen in individuals who received a trial of vaccines. This indicates that there is a possibility for lasting immunity against the virus. However, whether all infected individuals can produce the same magnitude of immune response remains unclear. There is no definitive proof that infection with COVID-19 induces lifelong immunity against this virus. Many clinical trials have been conducted to ascertain the definitive treatment for this disease, but to no avail. Although Remdesivir may be considered as curative therapy for COVID-19, symptomatic relief remains the mainstay of treatment.

4. Methods

Using PubMed Central Database and the keywords 'Covid Treatment' we got a humongous collection of 39260 articles, of which we have gone through around 1000 articles, divided among the authors. NCBI MeSH heading 'COVID–19' showed 18 articles, 'Corona viruses showed 73, 'Novel CoV' showed 15, 'Remdesivir' showed 3 articles, and 'SARS COV 2' showed 35 articles. For the literature search about vaccines, we searched under the MeSH heading 'COVID VACCINE' and short listed 8 articles and under 'SARS COV 2 VACCINE' we got 2 articles. To extend our literature search, we searched similar titles in Google Scholar also. No exclusion criteria have been used. No statistical analysis is done. Information has been gathered from 154 articles about the various drug trials/studies from different parts of the world, and also the developed and approved vaccines, to incorporate into this review article.

5. Drugs to the Rescue

A desperate race is on for providing the ultimate drug regimen that can effectively prevent, cure, and contain this horrendous disease. Curing the viral infection alone is not the mainstay of the fight against this virus. The disease spread and transmission has to be contained, to avoid devastating loss of life and economic strife in the near future. The economic strain and the ghastly death tales, has lured the drug discovery and clinical trial processes to be shortened and the drugs to be made available in the market, at the earliest. The process of expedited drug approval has a tremendous negative impact as people are left wondering about the safety of such drugs. Quenching people's worries about the safety and efficacy of these drugs is another major work task that has to be handled by the healthcare team. The drugs which have gained relevance in the therapy of COVID-19 are described in the tables [Table 2].

6. Antiviral Drugs

6.1. Remdesivir

Remdesivir is a SARS-CoV-2 nucleotide analog RNA polymerase inhibitor whose antiviral activity is remarkable. It is a prodrug. This drug inhibits viral replication by prematurely terminating the RNA transcription by binding with RNA dependent RNA polymerases. Initially during the outbreak, it has proved its activity against infected rhesus macaque models and was approved by the US FDA in ages >12 years/weight >40kg. Later under emergency use authorization, it has been approved for the use in weight >3.5kg also. Elevated alanine aminotransferase [ALT] levels and signs/symptoms of liver inflammation are criteria to stop the therapy. Use of remdesivir in patients with eGFR <30mL/min is not recommended. Intravenous administration of 200mg infusion over 30-120 min on day 1 followed by 100mg IV for further 5 (non- invasive mechanical ventilation) or 10 days (invasive mechanical ventilation/Extra Corporeal Membrane Oxygenation) is recommended.[20–22]

6.2. Lopinavir/Ritonavir

Lopinavir is a Human Immunodeficiency Virus -1 (HIV-1) protease inhibitor that is combined with ritonavir, a peptidomimetic molecule which inhibits the enzymes that metabolise lopinavir.[23] Randomised controlled trials have reported an additional benefit of reduced viral load with this drug.[24] Ivan et.al states that triple therapy with ribavirin has notably reduced the symptoms as well as

Table 2: Drugs used to treat COVID-19

Supportive Measures	**Enhancing-General Immunity**	
Antipyretics	Vitamin C supplements	Garlic
Antitussives	Vitamin D supplements	Ginger
Adequate Nutrition	Omega 3 supplements	Turmeric
Appropriate Hydration	Probiotic supplements	Green tea
Oxygen Therapy	Melatonin supplements	Ginseng
Proning	Zinc supplements	Cinnamon
Ventilator Support		Citrus fruits
Psychological Counselling		Black cumin
		Yogurt
		Red bell peppers
		Broccoli
		Spinach
		Almonds
		Sunflower seeds
		Papaya

duration of hospital stay in mild/moderate COVID-19 patients.[25] Lopinavir-ritonavir was given as 400/100mg orally. Nausea, vomiting, diarrhoea, hepatotoxicity were the adverse effects.[26]

6.3. Umifenovir (Aribdol)

Umifenovir (Arbidol) is approved in Russia and China for treating influenza infection. It is derived from indole carboxylic acid and was previously used against Ebola virus, Human Herpesvirus-8 (HHV-8), Hepatitis C etc.[23] The proposed action is by interfering with the hydrogen bonding network of phospholipids and blocking the virus-cell membrane fusion, thereby preventing viral entry. It is also a viral fusion protein haemagglutinin inhibitor.[23–27] With this background knowledge, in vitro studies by Dong et.al in SARS CoV-2 was fruitful and extended into the clinical trials of COVID-19 battle.[28] Wenyu et.al noticed there was considerable improvement in fever and accelerated cure time in patients treated with Arbidol as adjuvant therapy but not in their laboratory findings.[29] Deng et.al, in a retrospective cohort study, reported negative conversion rate of SARS CoV-2 and better Computed tomography (CT) scan results in combined use of umifenovir plus lopinavir-ritonavir than the lopinavir-ritonavir group.[30] In a retrospective study Lian et.al used 0.2g thrice daily, and few reported nausea and diarrhoea but none was serious to discontinue the therapy. They concluded nil improvement in prognosis and no increased viral clearance compared to the control group in non-ICU COVID-19 patients.[27] As the clinical trials have different opinions, further studies are needed to recommend its efficacy in n-CoV infection.

6.4. Sofosbuvir/Ribavirin

Ribavirin destabilizes viral RNA by its interference with polymerases, thus disturbing viral replication. Sustained virologic response can be achieved with <1000 mg of ribavirin, with an optimal dosage of 15 mg/kg. It also impedes the production of guanosine, which is important in preventing RNA degradation, by inhibiting inosine monophosphate dehydrogenase and so further leading to RNA degeneration. Sofosbuvir is converted into its active form, nucleoside triphosphate, after it is phosphorylated within the host cell. This nucleoside triphosphate then abolishes replication of RNA in the nascent viral genome because it competes with the nucleotides of the virus. In a study by Elfiky, a model was built for Wuhan COVID 19 RNA dependent RNA polymerase, and multiple anti-HCV drugs were tested against it. The most common adverse effects of sofosbuvir therapy are fatigue and headache.[31–33]

6.5. Favipiravir

Favipiravir has been developed in Japan for avian influenza since 2014.[34] It is a guanine analogue prodrug. After entering into the cells, it is immediately phosphorylated to active moiety (favipiravir ribofuranosyl phosphates), which then binds to the RNA dependent RNA polymerases and thereby inhibits viral replication.[23] It has been also used against Ebola and noroviruses and now experimented on SARS CoV-2. Many clinical trials were completed with impressive outcomes in China, Japan, Saudi Arabia, United States as well as India.[35] Dabbous et.al in a multicentric randomised trial compared favipiravir with chloroquine and noted a significant reduction in the duration of hospital stay and need for mechanical ventilation.[36] Favipiravir was compared with umifenovir in a randomised controlled trial and the duration of COVID-19 symptoms were notably shortened in favipiravir treated group.[37] The dose and

schedule were varied for each trial from 1600-1800mg on day 1 followed by 600-800mg on further days. Adverse effects like hyperuricemia, diarrhoea, transaminitis and decreased neutrophil counts were reported from different trials. As it has teratogenic potential, it is not recommended for use in women of child bearing age group.[35]

6.5.1. Hydroxycytidine (NHC)

NHC is a ribonucleoside analogue with antiviral property against influenza, Ebola, CoV, and Venezuelan equine encephalitis virus etc and has been well studied against MERS, SARS CoV and SARS-CoV-2 in vitro. Primary human respiratory epithelial cell culture studies showed reduced virus production without cytotoxic effects. They also claim potency against remdesivir resistant viruses too. NHCs prodrug (EIDD-2801) on mouse models significantly reduced SARS-CoV multiplication and spread.[38] To generalise this antiviral property, more studies in non-human primates needs to be conducted.

7. Antiparasitic

7.1. Chloroquine (CQ)/ Hydroxychloroquine (HCQ)

More than its antimalarial property, Chloroquine inhibits the production/release of interleukin 6 and tumour necrosis factor alpha. So, it has been intensively studied for its antiviral property against retroviruses, flaviviruses and coronaviruses.[39] Chloroquine and its analogue hydroxychloroquine have been tried in treatment of COVID-19 disease and both drugs increase the endosomal pH and thereby inhibit the fusion of viruses to the host cell. In addition to this, chloroquine inhibits glycosylation of the cellular ACE-2 receptor, and blocks the binding of Coronavirus to the cell receptor. Although few in vitro studies claim the antiviral property of chloroquine, clinical trials have contradictory reports. A study by Bhandari et.al reported early recovery in asymptomatic patients treated with HCQ than in the control (no treatment) group.[40] Another study showed decline in both symptoms as well as exacerbations of pneumonia and early reduction in viral load in HCQ treated COVID-19 positive patients.

Chief investigators of the RECOVERY (Randomised Evaluation of COVid-19 thERapY) trial, Peter Horby and Martin Landray, in June 2020, declared hydroxychloroquine has no more beneficial effect in hospitalized patients, mortality and duration of hospital stay.[41] A retrospective observational cohort study in New Jersey concluded that there is no survival benefit among hospitalized patients when treated with hydroxychloroquine alone or in combination with azithromycin. High dose (600mg twice daily for 10 days) has been associated with more severe toxicities than lower dose (450mg twice daily for day 1, followed by 450mg once daily for 4 days). Prolonged QTc interval (CQ>HCQ), ventricular arrhythmia, torsade de pointes are the few cardiac adverse effects mostly seen.[39] Co-administration with remdesivir is not recommended because chloroquine or HCQ may decrease the antiviral property of remdesivir.[42] When we look at the overall facts about the use of chloroquine/HCQ, it is limited to few countries because adverse effects outweigh the benefits.

7.2. Niclosamide, Ivermectin, Nitazoxanide

Niclosamide, through an unknown mechanism of anthelmintic action has now been redirected to antiviral action on SARS-CoV-2. Viruses like human rhinoviruses and influenza enters the host cell by acidifying the endosomal compartment. Niclosamide inhibits this endosomal acidification and disrupts the pH homeostasis and thereby prevents the fusion of viral envelopes to the host cell.[43] Similarly antiviral property of ivermectin against Human Immunodeficiency Virus (HIV), Influenza, West Nile etc has also been noted against SARS-CoV-2 in in vitro studies by Caly et al.[44] Another drug nitazoxanide is also studied in various clinical trials against Middle East Respiratory Syndrome Coronaviruses and showed its potential to limit viral entry while also reducing cytokines like interleukin 6 and tumour necrosis factor alpha.[45] So, more evidence from clinical trials are needed to prove its beneficial role in COVID-19.

8. Antibiotics

8.1. Azithromycin

Azithromycin a well-known macrolide antibiotic was put into use in the fight against COVID-19. Azithromycin fights various bacterial infections, mainly respiratory and dermatological infections and also sexually transmitted diseases. The antibacterial activity is by the 50S ribosomal subunit binding and thereby causing mRNA translation inhibition. There were claims that azithromycin had antiviral activity as well as immunomodulatory effects, apart from its routine antibacterial spectrum and hence could be protective against the Coronavirus if used in the early stages, when lung damage and fibrosis are minimal.[46] Literature search showed articles which enumerated that clarithromycin was effective against influenza virus infection.[47] Based on the findings from an animal study, it was hypothesized that prophylactic azithromycin was effective against Respiratory Syncytial Virus (RSV) in mice.[48] In a randomized trial published by Avraham Beigelman et al., there was a significant reduction in the morbidity and mortality of infants treated with azithromycin for RSV infection.[49]Synergistic activity of HCQ and azithromycin was elucidated in an invitro study by Julien Andraeni et al.[50] The SARS-CoV-2 spike proteins invade the lung tissue cells through the ACE2 receptors through glycosylation. Azithromycin produces ganglioside-mimicking effects thus attracting the spike protein and

binding to its ganglioside binding site. Azithromycin at the usual dose of 500mg OD for 3-5 days was preferred for antiviral activity also.[51] But of late, there has been an alert regarding use of azithromycin in the primary management of COVID-19 ue to a lack of significant benefit to patients.[52]

8.2. Cotrimoxazole

Cotrimoxazole is a combination of trimethoprim and sulfamethoxazole, which works by inhibiting dihydrofolic acid (DHFA) synthesis and also blocks tetrahydro folic acid (THFA) production. Both DHFA and THFA are required for bacterial proteins and nucleotide synthesis. Cotrimoxazole (CTX) in addition to being an excellent broad spectrum antibiotic, also has immunomodulatory actions.[53] The immunomodulatory effects of CTX, decrease the circulating levels of proinflammatory markers and thus reduce lung injury. Reduced in-patient mortality, reduced duration of hospital stays, and most importantly better outcome without the requirement of ventilatory support, have been seen with the use of CTX as an adjuvant therapy in COVID-19 affected patients. CTX with standard therapy proved to be more effective than standard therapy alone. Cytokine storm seen in COVID-19 patients was also reduced in patients on CTX plus standard therapy.[54–56]

8.3. Doxycycline

Doxycycline, a member of tetracycline group of antibiotics, binds to the 30S ribosomal subunit and thereby prevents protein synthesis. Earlier studies have also shown that doxycycline is capable of inflammatory cytokine production inhibition.[57] In a study conducted by Rothan et al in 2014, there was significant evidence that doxycycline had antiviral potency and as a result, inhibition of in vitro viral replication of dengue virus was noted. Doxycycline had a significant effect on all four dengue serotypes.[58] Earlier many studies have confirmed that Doxycycline has antiviral and also anti IL-6 and anti TNF production activity.[59] Keeping this in mind doxycycline was used in the treatment options of COVID-19 patients, as in Covid there is an increase in the levels of proinflammatory markers. In a case series analysis done by Mohammud M Alam et al. in New York, there was significant clinical outcomes in use of doxycycline in non-hospital settings. It was noted that there was a commendable decrease in the number of patients getting hospitalised and also reduction in mortality rates.[60] The potency of doxycycline to induce Zinc finger Antiviral Protein (ZAP) upregulation and its subsequent capacity to bind to viral mRNA is made use of against viral infections. It is by this action that doxycycline contributed in containing viral infections like Dengue, Zika, Ebola etc in the past.[61] More studies and clinical trials will be needed to ascertain the significance of doxycycline use in non-hospitalised covid patients, early mild covid infection and the resulting positive clinical outcomes.

9. Antithrombotics

The pathophysiology of COVID-19 is not yet fully studied. Evidence from post mortem reports suggests, viruses indeed directly damaged the type 1 and type 2 pneumocytes and alveolar endothelial cells. Later severe inflammatory reaction sets in the microvasculature of pulmonary vessels which ultimately cults in thrombosis. Similar endothelial damage and thrombi formation have been noted in other organs like the kidney, heart, brain etc. Therefore antithrombotics, like heparin, are clearly beneficial in managing cases; particularly in those patients with elevated D- dimer and fibrinogen and low antithrombin levels.[62] The treatment is moreover individualised and varies according to the various state level guidelines.

10. Corticosteroids

Use of corticosteroids has beneficial as well as deleterious effects on hosts during any acute infectious attacks. A well-known glucocorticoid compound - dexamethasone has been in the battle field since 1961 for many allergic/inflammatory diseases as it has shown high anti-inflammatory action when compared to others. The dexamethasone- glucocorticoid receptor complex will bind to specific genes to reduce the synthesis of pro inflammatory cytokines. Therefore, repurposing this to the battle of SARS-CoV-2, was necessary as it was showing promising results on the 'RECOVERY TRIAL-UK'. Mortality at 28 days on mechanically ventilated patients was less for those who received dexamethasone, than those who received standard care only.[63] Many trials were conducted across the globe which concluded that lower dose methylprednisolone/dexamethasone is beneficial than high dose, as high dose can aid in viral replication and increased risk of hyperglycaemia, secondary infections etc.[64]

11. Interleukin-6 Inhibitors

11.1. Sarilumab

Sarilumab, a human monoclonal antibody works by inhibiting the interleukin-6 (IL-6) pathway, and subsequently reduces pulmonary epithelial proinflammatory production. In an open label cohort study published by Emanuel Della-Torre et al., it was shown that sarilumab was associated with better recovery in Covid patients with minimal symptoms, but was not a promising option for severe illness.[65] There were also other trials in conjecture with this finding.[66]

11.2. Tocilizumab

Tocilizumab is a recombinant humanized monoclonal antibody. It has been efficiently used for treating cytokine

release syndrome associated symptoms as it binds to IL-6 receptors and finally decreases its production. As reduction in IL-6 levels is induced, further damage to lung tissues is prevented. In a retrospective cohort study done by Prof Giovanni Guaraldi et al., use of tocilizumab showed significant improvement in the mortality rates of COVID-19 ICU patients.[67] The recommended dose is 8mg/kg body weight up to a maximum of 800mg single IV dose, in combination with dexamethasone.[68]

11.3. Situximab

Siltuximab is an Interleukin-6 antagonist that was investigated in various clinical trials for its efficacy in managing COVID-19 patients. Currently Sylvant (Siltuximab) is being used in the treatment of Idiopathic Multicentric Castleman Disease (MCD). It is a recombinant human-mouse chimeric monoclonal antibody, that prevents IL-6 signaling by binding to both soluble and membrane bound forms of IL-6 receptors. Only limited data is available regarding the clinical trials and efficacy and safety of siltuximab as a therapeutic option in the management of COVID-19 patients.[68] A single dose of siltuximab is suggested as the half-life of the drug is 16.3 ± 4.2 days. 11mg/kg over 1 hour as an intravenous infusion is administered.[69]

12. Interleukin 1 Inhibitor

12.1. Anakinra

As discussed earlier, cytokine storm and cytokine release syndrome is a major part of the COVID-19 disease which causes multiorgan failure. Thus, treatment strategies aimed at reducing inflammatory marker levels in the circulation have gained prominence. Interleukin -1 inhibitors are one such immunomodulatory option. Anakinra, a recombinant IL-1 receptor antagonist has been studied in various clinical trials of SARS-C0V-2, especially ARDS associated with the illness.[70] In a prospective cohort study published by Emma J. Kooistra et al, anakinra was found to be highly efficacious in decreasing the clinical signs in COVID-19 patients.[71] Studies and trials will have to be carried out to prove the efficacy of anakinra as a therapeutic option.

13. Other Monoclonal Antibodies

13.1. Mavrilimumab

Apart from IL-1 and IL-6 as inflammatory markers in Covid, there are also other proinflammatory markers found in the patients. A possibility of Granulocyte-Macrophage Colony Stimulating Factor (GM-CSF) being a hyperinflammatory mediator was also questioned and thus Mavrilimumab, a monoclonal antibody to GM-CSF receptor came into the moonlight for testing the proposed hypothesis.[72] In a prospective cohort study by Giacomo De Luca et al., treatment with Mavrilimumab single intravenous dose (6 mg/kg) showed significant clinical outcomes. Further studies will have to be conducted to confirm the findings and prove the efficacy of this drug.[73]

14. Kinase inhibitors

14.1. Janus kinase inhibitors: Baricitinib, ruxolitinib, tofacitinib

Janus Kinase (JAK) inhibitors block signalling, growth and survival of viruses on host cells by phosphorylating the Signal Transducer and Activator of Transcription (STAT) proteins. Moreover baricitinib has potential to directly interfere with viral endocytosis and prevent viral entry.[74] Adaptive COVID-19 Treatment Trial (ACTT), a large multinational randomised placebo control trial, used baricitinib (4mg once daily) in combination with remdesivir, and this combination showed less recovery time than placebo group of COVID-19 hospitalised patients. Later the US FDA recommended this combination in ages >2years old and among those requiring mechanical ventilation/ECMO/supplemental O2 therapy, but not otherwise except in clinical trials.[75] Adverse effects like reactivation of herpes, myelosuppression and transaminase elevation were noted. Baricitinib is not recommended in patients with eGFR <60 ml/min/1.73m2. Ruxolitinib also downregulates cytokine inflammation via selectively inhibiting JAK1/JAK2 and has been studied in a few clinical trials for example, Yang Cao et.al noticed improvement of lymphopenia and beneficial CT changes.[76] Tofacitinib is a selective inhibitor of JAK1/JAK3>JAK2 and blocks the cytokines like IL2, IL4, IL6, IL11 and interferons. There is no sufficient clinical trial data to report its use in SARS CoV-2.[77]

14.2. Bruton kinase (BTK) inhibitors: Ibrutinib, acalabrutinib, zanubrutinib

Role of Bruton Tyrosine Kinase (BTK) in inflammation - Toll like receptors recognises the viral RNA and initiates signalling through BTK dependent activation of nuclear factors(NF-κB), which signals for the mass production of inflammatory cytokines.[78] Very limited clinical trials with minimal sample size suggest their beneficial role in COVID-19. Treon et.al studied first generation BTK inhibitor- Ibrutinib and noted improved pulmonary function in hypoxic patients of COVID-19.[79] Acalabrutinib (second generation BTK inhibitor) which was approved for B cell malignancy is also proposed against SARS CoV-2 and a trial by Roschewski et.al reported clinical improvement in hospitalised patients.[66] Zanubrutinib a second generation BTK inhibitor has less toxicity than Ibrutinib and is a model drug for tackling inflammation but not yet studied in trials. More evidence from large clinical trials has to be conducted to support these facts.

15. Serine protease inhibitors: Nafamostat, camostat, gabexate- mesylate

Human coronavirus has trimeric transmembrane spike proteins which has two cleavage sites called S1/S2 and S2. Transmembrane protease serine 2 (TMPRSS 2) and cathepsin L and B help to cleave these domains and initiate the binding of S1 to ACE-2 on the host cell surface. Therefore, scientists now target the TMPRSS 2, as these could not undergo mutations as viral spike proteins. Drugs like Camostat, Nafamostat and Gabexate - mesylate approved for other diseases have potential to inhibit TMPRSS 2. Hoffmann et al in 2020 showed Camostat and Nafamostat have the potential to inhibit SARS-CoV 2 fusion to host cell membrane.[80] Different clinical trials with Camostat, Nafamostat, Upamostat with/without bromhexine hydrochloride, a Cathepsin L inhibitor, is in progress and a promising result in reducing multiorgan failure and deaths has to be established for licencing these drugs to treat COVID-19.

16. Anti Gout Drugs

16.1. Colchicine

Colchicine forms a complex with tubulin and inhibits the microtubular formation which are normally involved in cell division and signal transduction. This colchicine-tubulin complex inhibits the NLR P3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome formation, which has found a major role in Acute Respiratory Distress Syndrome/ Acute Lung Injury. It also binds to leukocyte membrane proteins that may hinder chemotaxis and phagocytosis. Schlesinger et. al in a review paper discussed various colchicine clinical trials. Although the outcome variables were different for each trial, there was an overall improvement in both symptomatic and laboratory findings. The dose of colchicine varied from 0.5mg to 1.5mg as twice/thrice daily. Minimal adverse reactions like gastro-intestinal troubles were also noted in some trials.[81]

16.2. Febuxostat

Febuxostat (FBX) is a non-purine xanthine oxidase (XO) inhibitor with anti-inflammatory, antioxidant, and anti-apoptosis effects like HCQ. In a clinical trial by Davoodi et.al, HCQ was compared with febuxostat in moderate cases on an outpatient basis. The symptomatic reduction, laboratory improvements and CT findings were found to be equally improving in both groups.[82]

17. Metformin

The recent past has attributed diabetes mellitus to be an inflammatory disorder and researchers noticed that people on metformin had a better chance of survival, triggering a thought that metformin may actually have a protective role in the treatment of COVID-19 patients by reducing the severity of infection and thereby reducing mortality. Metformin activates AMP-activated protein kinase (AMPK) in liver cells which upon activation, adds a phosphate group to the ACE 2 receptor. This brings about a structural change in this receptor, which could later hinder the binding of Coronavirus to the host cell. Very few clinical trials and retrospective studies show its benefits in COVID-19 disease outcome. Theoretical evidence is yet to be confirmed.[83]

18. Pirfenidone

A pyridone derivative used for idiopathic pulmonary fibrosis is proposed to treat SARS CoV-2 because they can down regulate ACE-2 receptors directly, which prevents the viral entry into the host cells. Antifibrotic, anti-inflammatory and antioxidant properties of pirfenidone could theoretically show benefit against cytokine storms as well. More clinical trials and research have to be done to prove this hypothetical information.[84]

19. Chaperones

Chaperones are proteins designated to interact with partially or improperly folded polypeptides and facilitate their proper folding. Viruses are devoid of chaperones and they rely on their host chaperone system to sustain their life cycle. This could bring either a cytoprotective effect when the chaperones are overexpressed, leading to antiviral effect, or it could cause replication of viruses aided by Glucose-regulated Proteins (GRPs), calnexin and calreticulin etc. Chemical chaperones for example - tauroursodeoxycholic acid (TUDCA) and 4-phenyl butyric acid (4-PBA) exhibit antiviral property against SARS-CoV-2 according to few research articles. We have already discussed the cytokine storm during ER stress in the introduction part and handling this with 4-PBA, could bring down the severity and some animal studies have reported this.[85]

20. Convalescent plasma transfusion

Convalescent plasma transfusion (CPT) is an investigational drug under US FDA and is used in clinical trials under emergency use authorization. Since the 19th century, CPT has shown efficacy in SARS, MERS and Ebola viruses and recently extended on to SARS-CoV-2. Plasma of COVID-19 recovered patients with sufficient antibody titre is transfused as passive immunotherapy. Though transfusion dose or titre is not well studied, 2 doses of 400ml plasma, 24 hours apart, with Ig G antibody titre of 1:640 (ELISA) or 13 AU (Absorbance Unit)/mL9 (CLIA) or neutralising antibody titres of 1:80, is used in recipient within 3-7 days of symptom onset have been tried in few states of India. Symptomatic improvement was reported invariably from many trials. The reduction in viral load and increase in antibody titre during initial stage is also noted in some

trials.[86] Studies have shown that it has not been effective, and US FDA has not approved it yet.

21. Mesenchymal Stem Cells (MSC)

Treatment modalities in COVID-19 are aimed at the systemic inflammatory response caused by the infection. As discussed earlier, the systemic inflammatory response is due to various factors like cytokine storm, endothelial dysfunction and the resulting coagulation issues. Immunomodulation plays a very important role in treating this viral infection. Mesenchymal stem cells have been aptly called multipotent stem cells as they are capable of differentiating into different types of cells. They have remarkable immunomodulatory and immunoregulatory properties and thus they find a place among the therapeutic options for COVID-19 infection which flares by the process of cytokine storm. MSCs also induce regeneration/tissue repair. There have been preclinical studies demonstrating high levels of efficacy of MSCs in the management of Acute Respiratory Distress Syndrome (ARDS) and Acute Lung Injury (ALI).[87,88] MSCs modulate innate immune systems by inhibiting lymphocytic proliferation, suppressing dendritic cell maturation and also inhibiting Natural Killer (NK) cell activation. Inhibition of lymphocytic proliferation has also been observed with embryonic stem cells. Thus, the intravenous transplantation of MSCs is safe and effective for treatment of patients with COVID-19 pneumonia, as it not only decreases the inflammatory process but also helps in regeneration of the damaged lung tissue and can very much prevent death due to lung damage.[89–91] COVID-19 specific research and clinical trials are yet to be done on a large scale to validate this therapeutic option.

22. Chinese Herbal Treatments

During the COVID-19 pandemic, Jinhua Qinggan granule (JHQG) was extensively used in China. More than 85% of SARS-CoV-2-infected patients in China had received some form of Traditional Chinese Medicine (TCM) treatment. Studies reported the traditional medicines may have the capacity to target ACE2. Astragalus membranaceus, CurrPharmacol Rep Glycyrrhiza Uralensis, Saposhnikoviae Divaricata etc.[92] As there are only few studies conducted in TCM, the effectiveness and curability of the disease need further clarification.

23. Immunity Promoters

Despite above drugs/vaccines, many immunity boosters like Vitamin C, Vitamin D, Zinc, Turmeric, Yogurt, Sunflower seeds etc, are advocated in home care therapy and summarized in Table 3.

24. Vaccines out and in Pipeline

24.1. Covaxin

Bharat biotech, India developed this inactivated vaccine. COVAXIN with immunopotentiators are administered as 2 doses 28 days apart. It is a ready-to-use a vaccine with no sub-zero storage/reconstitution and the vial is stored at 2-8 degree Celsius. It entered phase 3 trial and on January 3^{rd}, 2021, DCGI-CDSCO granted emergency restricted use in India with 81% interim efficacy after receiving 2 doses of vaccination.[93] National Institute of Virology isolated Coronavirus from asymptomatic carriers, produced large stocks of the Coronaviruses, and then doused them with a chemical called beta-propiolactone which disabled the coronaviruses by binding to their genes. These inactivated corona viruses could no longer replicate, but their proteins and spike, remained intact. These inactivated viruses are then mixed with aluminium based adjuvant to stimulate immunity boost in the host.

24.2. Covid 19 Oxford Vaccine/Astrazeneca

Replication-deficient chimpanzee adenovirus vector (ChAdOx1), encoding the SARS-CoV-2 Spike (S) glycoprotein is produced in genetically modified human embryonic kidney (HEK) 293 cells. Two separate doses of 0.5 ml each is administered; the second dose being 4 to 6 weeks apart from the first dose (up to 12 weeks in overseas studies). It is recommended for use in ages >18 years because safety and efficacy are not established in the paediatric population. Side effects include generally feeling unwell, fatigue, chills or feeling feverish, headache, nausea, joint pain, or muscle ache.Feeling dizzy, decreased appetite, abdominal pain, enlarged lymph nodes and excessive sweating, itchy skin, or rash are the uncommon side effects. Increased risk of blood clots was reported and therefore few countries halted giving AstraZeneca vaccine. As the vaccine efficacy spiked from 76% to 81.3% upon second dose, WHO in March 2021, declared a statement to continue the vaccine as benefit outweighs the small percentage of risk.[94]

24.3. Covishield

Serum Institute of India, Pune partnered with University of Oxford along with British pharmaceutical, AstraZeneca and developed this recombinant vaccine - ChAdOx1 nCoV- 19 Coronavirus Vaccine. The vaccine was given among health care workers from January 2021 and for elderly from March 2021 under emergency restricted use authorization in India.

24.4. Sputinik V/GAM-Covid-VAC

Gam-COVID-Vac is also a vector-based vaccine, developed by Gamaleya Research Institute of Epidemiology and Microbiology. In December 2020, this vaccine was distributed widely in countries like Russia, Argentina, UAE

Table 3: Supportive measures and general immunity boosters

Anti- Coronaviral Drugs					
Anti-Viral	**Anti-Parasitic**	**Anti-Microbials**	**Antithrombotic**	**Immunomodulatory drugs**	**Other drugs**
Remdesivir	Chloroquine/ Hydroxychloroquine	Cotrimoxazole	Heparin	IL-1 Inhibitors	Corticosteroid
Lopinavir/Ritonavir	Niclosamide	Doxycycline		IL-6 Inhibitors	Anti-gout drugs
Umifenovir	Ivermectin	Azithromycin		Kinase Inhibitors	Metformin
Ribavirin	Nitazoxanide			Serine Protease Inhibitor	Pirfenidone
Favipiravir				Mavrilimumab	Chaperones
N-4 Hydroxycytidine					Convalescent plasma therapy
					Mesenchymal stem cells
					Chinese herbal treatment

etc. It is given 2 doses 0.5ml IM, 21 days apart as recombinant adenovirus type Ad26 on day 1 and Ad5 on day 21. The vaccine is available in both 'freeze dried powder', which requires 2-8°C/36-46 °F refrigeration, as well as in 'ready to use solution' which is kept in home refrigerator at -18°C/0°F or lower. Phase 3 trial is still going on in Moscow, UAE, India, Venezuela and Belarus. Interim analysis reports show 91.6% efficacy against COVID-19. It also has approval in 60 countries as of April 2021.[95]

24.5. Johnson and Johnson Vaccine

This is a viral vector-based vaccine like AstraZeneca and Sputnik V. Human adenovirus type 26 is used here as well. Clinical trials began in June 2020, with an 85% efficacy in preventing severe COVID-19. The advantage over other vaccines is that this is a single dose vaccine and does not need to be frozen. Adverse effects are also similar to other vector-based vaccines like local injection site swelling and redness, fever and chills (<1 in 10 people). <1 in 100 people had sweating, muscle weakness, tremors, body pain, throat pain etc. Thrombocytopenia with blood clot formation was reported in <1 in 10,000 people. Vaccine was halted during the 2nd/3rd week of April 2021 as there were cerebral venous sinuses thrombosis following vaccination. Later, the vaccine fact sheet was revised with the addition of risk for thrombocytopenia-thrombosis syndrome (TTS), and vaccine administration was resumed.[96]

24.6. Pfizer-biontech Covid-19 Vaccine/BNT162b2

BNT162b2 is the first vaccine approved by the US FDA under emergency use authorization in Mexico. This vaccine is developed on the basis of novel technology that uses virus mRNA, which enters host cells to produce the specific spike protein/protein fragment. These specific spike protein/protein fragments in accordance with the mRNA will be present on their cells. When the vaccinated cells die, the Antigen Presenting Cell (APC) will take up these fragments and activate Helper T cells as well as other immune cells like B cells to produce target antibodies. Further trials are going on to extend its use in pregnant mothers and children. Very few local site reactions and mild-moderate adverse reactions have been reported. As the nanoparticles with mRNA of SARS CoV-2 are highly unstable, they need to be transported only in ultra-frozen temperature (-70°C/-94°F). Though the transport is cumbersome, its efficacy is 95%. It is given 0.5ml IM, 2 doses, 21 days apart.[97]

24.7. Moderna

It is an mRNA-based vaccine approved for emergency use in Canada and later in Israel, UK, Singapore. The vaccine is a modified mRNA and upon administration, it gets linked to endoplasmic reticulum and signals the cell to make specific spike protein-2P. It has stabilising mutations, by proline substitutions at 2 sites. When cells die, the proteins are shredded out, which are detected by our immune cells, and they produce the corresponding antibodies. Unlike Pfizer which needs ultra-cold freezing temperature, this vaccine requires 2-8°C/36-46 °F at refrigeration and can be stored up to 4 months at -20°C/-4°F.[94,95] 2 doses of 0.5ml intramuscularly, 4 weeks apart, with a booster dose 6-12 months later is the recommended regimen.

24.8. Novavax

Novavax is a recombinant nanoparticle vaccine which is produced by engineering a baculovirus with modified SARS CoV-2 spike protein. This virus infects the moth cells to develop spike proteins on their cells, which is taken and incorporated onto nanoparticles. The vaccine is adjuvanted with 'Saponin based Matrix-M' to enhance the immunity. The phase 3 UK trial shows 89.3% efficacy and is protective against the B.1.1.7 variant in the UK and B1.351 variant of

South Africa.[94,98] It is given 2 doses 0.5ml intramuscularly, 21 days apart.

24.9. Clover and Dynavax

Clover used trimer tag technology to develop this recombinant trimerized fusion proteins to develop this COVID-19 S-Trimer vaccine. S-Trimer of this vaccine is produced by mammalian cell-culture based expression system and Clover's phase 1 clinical trial used adjuvants from two companies - GlaxoSmithKline and Dynavax. In phase 1, both showed high levels of neutralising antibodies, safety as well as tolerability. Clover's partnership with GlaxoSmithKline has discontinued and S-Trimer antigen adjuvanted with CpG 1018 plus Alum has begun its global phase 2/3 clinical trial in March 2021. 2 doses, 21 days apart is given across the continents.[99]

24.10. Inovio Vaccine

It is a DNA plasmid vaccine, which is administered via CELLECTRA (hand held device), to the cells intramuscularly/intradermally. The administered vaccine (1mg/2mg) enters the human body and produces humoral and cellular responses in accordance with the surface antigen coding DNA. The stability of this vaccine in room temperature for up to a year makes this vaccine different from others. It is now in phase 2/3 of US trial mid stage and is yet to start late stage of phase 2/3.[98]

25. Conclusion

A drug must come to the succour in tackling COVID-19, which can be empirical, but a definite solace to the grappling situation with this little-known viral infection. Various combinations have been tried with rudimentary rationale, which have been successful at the time. The quest for the definitive therapy in COVID-19 is still elusive. This review has pooled the data of pharmacotherapeutic approaches into a single strand, to provide current mechanistic avenues to sort out the ultimate cure for COVID-19.

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27. Conflicts of Interest

None.

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