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# AN OVERVIEW OF PATHOGENESIS, EMERGING THERAPIES, MULTI-ORGAN MANIFESTATIONS AND TECHNOLOGIES IN THE TREATMENT OF COVID-19

**Shweta Mittal*, Aman Sharma, Rohan Aggarwal, Meenakshi K. Chauhan**

*Delhi Institute of Pharmaceutical Sciences and Research, Mehrauli-Badarpur Rd, Sector 3, Pushp Vihar, New Delhi, India*

**Corresponding author: shwetamittal489@gmail.com*

## ABSTRACT

The worldwide expansion of the novel coronavirus (nCoV) was termed as a pandemic by the World health organization (WHO) on March 11, 2020. After the epidemic of Middle East respiratory syndrome coronavirus (MERS CoV) in the year 2012 and Severe Acute Respiratory Syndrome coronavirus (SARS CoV) in the year 2002, the nCoV is the third-largest pandemic occurring at a large scale and has high pathogenicity. Angiotensin-converting enzyme-2 (ACE-2) is found to be the main target receptor of nCoV which was also the target receptor of SARS CoV. The increasing cases of nCoV worldwide are mainly because of its high transmission from one human to another. The clinical symptoms may include fatigue, cough, fever, breathlessness which may be severe in elderly patients or those with compromised immune systems. Since, there is no confirmed treatment available for the management of nCoV, some antivirals and antimalarials along with other therapies are being investigated by several researchers. As there is no exhaustive description of the COVID-19 manifestations to multiple organs which makes it difficult for physicians to educate quickly for the highly infectious and lethal pathogen. Thus, it is required to determine the impact of COVID-19 on the central nervous system, cardiovascular system, the ocular and renal system of the patient. Also, the effect of COVID-19 on the lungs, gastrointestinal tract, cancer, pregnancy, and heart needs to be studied. In this article, we tried to summarize the pathogenesis, possible treatment strategies, and the impact of COVID-19 on different organs and conditions. Along with that, the impact of SARS CoV-2 on the pharma industry and scope of Ayurveda and innovations in the management of the pandemic has been focussed.

**Keywords:** SARS-CoV-2, COVID-19, Pandemic, Antivirals, Antimalarials, Convalescent plasma, Vitamin D3.

## 1. INTRODUCTION

WHO on February 11th, 2020 named the coronavirus disease as COVID 19 which was first identified in Wuhan, China. Based on taxonomy, phylogenyand established practices the novel coronavirus was also named as SARS CoV-2 by a study group of the international committee. CoV belongs to *Orthocorona-virinae* (subfamily) and *sarbecovirus* (subgenus) which is classified as 4 genera *i.e.* gamma, beta, delta, and alpha CoV [1]. The COVID 19 belongs to beta genera which are responsible for infecting mammals. In the past, there were 6 identified CoV which were susceptible to human, out of which 4 CoV (beta-CoV HCoV-OC43, beta-CoV HCoV-HKU1, alpha-CoV HCoV-NL63, alpha-CoV HCoV-229E) caused symptoms related to the common cold, low respiratory infections and were less pathogenic whereas the remaining 2 CoV (MERS CoV, SARS CoV) caused fatal and severe infections of the respiratory tract [2].

SARS CoV-2 is the agent accountable for coronavirus disease (COVID 19). It is a potentially fatal disease and distress for public health around the globe. The zoonotic basis of COVID 19 is suggested based on a large population infected in Wuhan City in China upon exposure to the animal market. The COVID 19 was named as SARS CoV-2 because it showed 79% similarity to the SARS-CoV in terms of the sequence of the genome [2].

The detailed mechanism of viral entry and binding still needs to be elucidated and the data present today may be somehow incomplete and lacking the understanding of mechanisms that is responsible for transmission among individuals. However, the mortality rate associated with SARS CoV-2 is only 3.4% in comparison to 35% and 9.6 % of MERS-CoV and SARS CoV respectively [3].

Since the pandemic of COVID 19 is increasing at a very fast pace, enhancing the patient's number and deaths,

there is a high need to study the possible effective treatments available, some of which are the administration of antivirals, antimalarials, monoclonal antibodies, etc. As of now, no treatment or vaccine is approved by the WHO and food and drugs administration (FDA) [4, 5]. Researchers are concentrating more on antimalarials such as hydroxychloroquine and chloroquine due to their inhibiting activity of the ACE-2 receptor, which has a significant effect on the spread of SARS CoV-2. Reports of successful therapy with antivirals like remdesivir, ritonavir, and lopinavir are also published. More work on the therapeutic and diagnostic approaches to the production of drugs and vaccines is required. Thus, this review apart from pathogenesis and treatment therapies underlines the studies on numerous multi-organ damage which might happen due to illness with SARS-CoV-2 along with the effect of the virus on cancer and pregnant patients. The role of emerging therapies and technology has also been discussed.

## 2. DATA COLLECTION

In this review, keywords like COVID, hydroxyl-chloroquine, remdesivir, opinavir, organ damage, treatment, SARS CoV-2, interferons, clinical therapies, pandemic, manifestations, virus were searched in databases and internet such as Medline, Google Scholar, Scopus, Systematic review, Pub Med, NCBI and Web of science to study the published papers over last few years. Out of the 125 papers, 106 papers were selected to incorporate the key findings of this paper.

## 3. PATHOGENESIS

SARS CoV-2 is found to be a single-stranded RNA virus with a positive sense. It belongs to the genus beta coronavirus [1, 6]. It is found to be closely linked to two SARS-like CoV derived from a bat, but on the other hand, it was found to be distant from MERS CoV in phylogenetic analysis (Table 1) [7, 8]. COVID 19 is classified under the subfamily *orthocoronavirinae* and is included as the seventh member in the coronavirus family [1].

CoV is enveloped and named on the foundation of its appearance as that is due to 9-12 nm long spikes on the surface [11]. Four main structural proteins are present on the envelope encoded by the coronaviral genome. One of the proteins is the spike (S) protein which binds to the ACE-2 receptor and facilitates successive fusion between the envelope and host cell membranes to aid viral entry into the host cell [12]. S protein is further divided into 2 subunits *i.e.* S1 and S2. The other three proteins are nucleocapsid (N), small envelope (E), and protein matrix (M). The RNA based metagenomic next-generation sequencing showed that the complete genome of COVID 19 is 29,881 nucleotides long [13]. After the genomic investigations, it may be concluded that COVID 19 may be bat originated [14]. Fig. 1 shows the SARS CoV-2 structure.

**Table 1: Similarity of Covid-19 to bat, SARS CoV, and MERS CoV [9, 10]**

| Strain | Similarity to Covid-19 |
|---|---|
| Bat derived: bat-SL-CoVZXC21, bat-SL-CoVZC45 | 88-89% |
| MERS CoV | 50% |
| SARS CoV | 79% |

The SARS CoV-2 transmission from one individual /cross-species to another is due to the binding of its S-protein to the receptor ACE-2 present in the humans' respiratory region and this receptor was also used as a source of entry by SARS CoV [15]. S1 and S2 are two subunits of the viral S protein. The subunit S1 utilizes the receptor-binding domain (RBD) to estimate the cellular tropism and range of the host of the virus whereas subunit S2 is responsible for mediating the fusion between the two membranes of the host and the virus by utilization of two heptad repeats (HR) domains *i.e.* HR1 and HR2 [16]. Pp1ab and pp1a are the 2 poly-proteins translated by the viral RNA after it is fused and released into the human membrane. The 2 poly-proteins encode proteins (non-structural) and lead to the formation of a complex called RTC (replication transcription complex) which replicates continuously and releases RNAs (subgenomic) which encodes structural proteins and accessory proteins [17]. Buds of the virus are formed by the assembling of envelope proteins, nucleocapsid, genomic RNA, Golgi, and endoplasmic reticulum [18]. Then, the virus is fused with the human membrane and is released. Thus, the critical step for the entry of the virus is the binding between the human receptor ACE-2 and viral S protein.

The viral disease shows some common symptoms which can also help in the diagnosis of the infection but as the infection worsens, the patient shows clinical symptoms as observed in a chest CT scan. Table 2 shows common and clinical symptoms as observed in different patients of COVID 19. The symptoms further

can be classified into respiratory and systemic disorders as shown in Fig. 2.

Also, the results of the examination by the laboratory showed that patients also had an increased number of leukocytes, abnormal findings respiratory system, [8] increased erythrocyte sedimentation rate, increased d-dimer concentration, severe pneumonia, leukopenia-leukocyte count estimated 2.91×109 cells/L, RNA aemia accompanied with acute cardiac injury and ground-glass opacities [21]. Also, the chemokine and cytokines levels are found to be high that included macrophage inflammatory protein 1-α (MIP-1α), interferon-gamma- induced protein (IP-10), tumor necrosis factor α (TNF α), interleukins (IL)1-beta, IL1RA, IL7, IL8, IL9, IL10, monocyte chemoattractant protein-1 (MCP-1), and granulocyte colony-stimulating factor (GCSF) [22]. AlsoSARS CoV,MERS CoV, and SARS CoV-2 show some common features but the SARS CoV-2 show some features that can be used to distinguish it from MERS CoV and SARS CoV [23, 24] as shown in Table 3.

**Table 2: Symptoms of SARS CoV-2 [19, 20]**

| Common symptoms | Clinical symptoms |
|---|---|
| Fever, cough | Pneumonia |
| Fatigue | RNAaemia |
| Sputum production | Acute respiratory distress syndrome |
| Headache | Grand glass opacities |
| Myalgia | Acute cardiac injury |
| Upper airway congestion | Kidney failure |
| Diarrhea | |
| Haemoptysis | |
| Dyspnoea | |
| Lymphopenia | |

**Table 3: Common and distinguishing features of SARS CoV-2 [22-24]**

| Common | Distinguishing |
|---|---|
| Fever | Rhinorrhoea |
| Dry cough | Sneezing |
| Dyspnoea | Sore throat |
| Bilateral ground-glass opacities (chest CT Scan) | Infiltration in the upper lobe of the lung as seen in chest radiographs |
| | Gastrointestinal symptoms (diarrhea) |

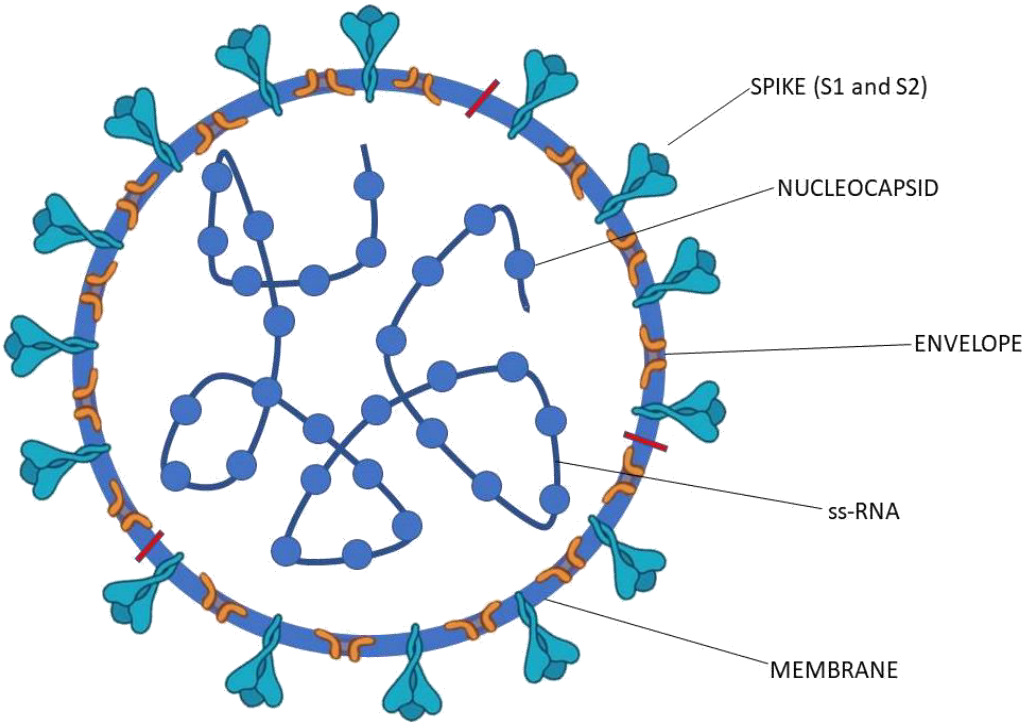



**Fig. 1: Structure of SARS CoV-2**

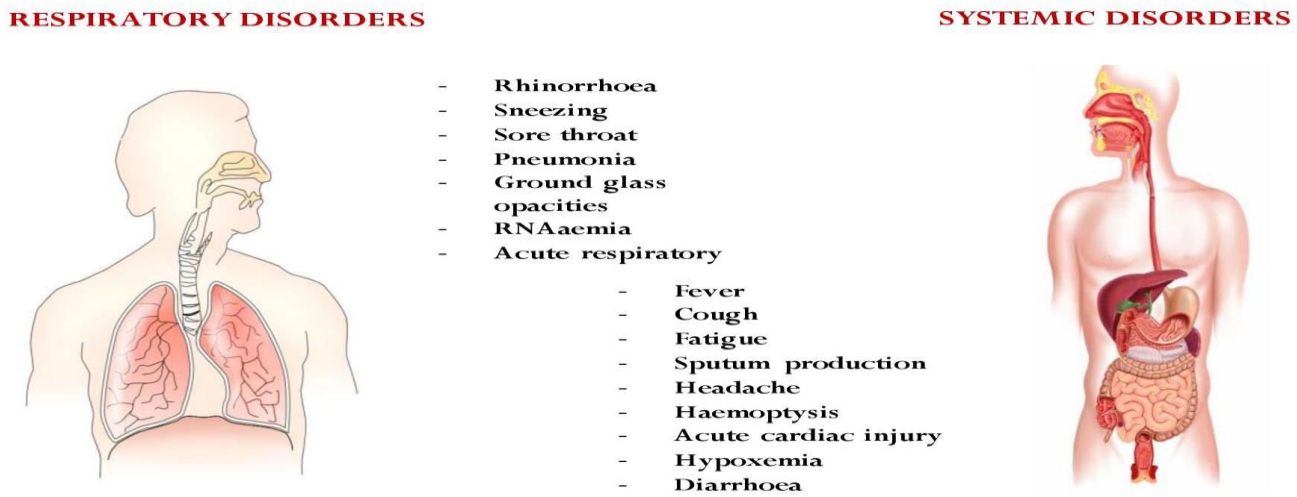



**Fig. 2: Disorders due to SARS CoV-2.**

## 4. TREATMENT THERAPIES UNDER CONSIDERATION

The transmission of the caused infection from one human to another has directed to patient isolation and a variety of treatments have been given to these patients. No antiviral or COVID 19 infection vaccine is available for possible infection treatment in humans [25]. However, remdesivir has been approved by the FDA for emergency use. The treatment available is administering antivirals with broad-spectrum properties like HIV-protease inhibitors and Nucleoside analogs. This may weaken the infection of viruses before the exact treatment is available [25]. Potential Broad-spectrum antiviral agents that could be used in the COVID 19 therapy which includes ritonavir, favipiravir, neuraminidase inhibitors/nucleoside analogs, remdesivir, umifenovir, chloroquine, hydroxychloroquine, DNA synthesis inhibitors (tenofovir, disoproxil, lamivudine) [13]. Some of the drugs that have shown some activity against COVID 19 in clinical studies are explained below in table 4. Recent guidelines by the national institute of health (NIH) suggested against the use of any drug as more data is required to prove their efficacy but some studies have shown their potential effect.

**Table 4: Potential activity of antimicrobials and antivirals against the novel CoV**

| Drug and class | Mechanism of action | Evidence against SARS-CoV-2 |
|---|---|---|
| Chloroquine and Hydroxychloroquine (Antimalarial) | They show their antiviral activity by increasing the endosomal pH and low pH needed for virus/cell fusion This increase in endosomal pH alters the mechanism of endocytosis; for whichan acidic environment is required, so it blocks endocytosis in the intermediate stage which results in the failure of further transport of virions to the main site [26]. | • *In vitro* data in preclinical studies indicating activity against the virus [27].<br>• Reports suggesting chloroquine inhibiting the aggravation of pneumonia in patients infected [27].<br>• Hydroxychloroquine more potent antiviral activity than chloroquine as suggested in a study *in vitro* [28].<br>• Hydroxychloroquine when studied and compared in non-randomized, open-label trial studies (n = 26) with a control group (negative untreated), 70% of the patients treated were found to be cured virologically after 6 days in comparison to 12% in the control group [29].<br>• In a randomized parallel-group study with 62 SARS CoV-2 patients, after 5 days, there was a reduction in the recovery time of cough and fever when hydroxychloroquine (2.2 days) was administered in comparison to the standard treatment (3.2 days) [30].<br>• Efficacy and safety of both drugs against viruses being studied [31].<br>• The use of chloroquine and hydroxychloroquine against SARS CoV-2 is not yet approved, it requires more support and evidence |

| | | |
|---|---|---|
| | | from further clinical studies. Both drugs are not recommended by NIH due to lacking data in clinical studies and effects such as prolongation of QT interval need to be monitored [32].<br>• The solidarity trial arm of hydroxychloroquine has been stopped by WHO on 4th July 2020 because interim results of this trial show no effects on the mortality rate of COVID-19 patients. This result only depicts the treatment of hospitalized patients of COVID-19 and does not show any evidence against the use of hydroxychloroquine in pre and post prophylaxis [32]. |
| Ritonavir; Lopinavir (HIV protease inhibitors) | Acts by suppressing the activity of CoV by binding to an enzyme Mpro, required for CoV replication [33]. | • Data in preclinical studies indicating activity against the CoV [34].<br>• *Chu et al.* carried out a study in which lopinavir showed anti-SARS CoV activity *in vitro*. In clinical studies, they found that in 111 patients treated with ribavirin along with lopinavir, were on the lower risk of acute respiratory distress syndrome [34].<br>• Ritonavir and Lopinavir when administered to the infected patients (n = 199) in an open-label, randomized trial study, improvement in health was observed and treatment by both drugs was found similar in terms of clinical improvement, mortality, and duration of treatment [35].<br>• But both drugs are not recommended by NIH due to negative data obtained in trials and association of the drugs with serious arrhythmias [32].<br>• Solidarity trials of WHO has been stopped on Ritonavir/lopinavir. According to the interim results of the trial, this combination shows little or no effect on the mortality rate of COVID-19 patients [32]. |
| Remdesivir (Investigational nucleoside analogue) | It is a remdesivir triphosphate prodrug that inhibits RNA dependent RNA polymerase. Remdesivir triphosphate incorporates into RNA of the virus by competing with adenosine triphosphate and then terminates the synthesis of RNA. As the termination of the chain is not immediate, three nucleotides are added to escape the excision from the viral enzyme exoribonuclease [36,37]. | • It is approved for emergency use by the US- FDA.[38]<br>• Potent activity of remdesivir against novel CoV was found *in vitro* studies i.e. selective index (SI) > 129 and a half cytotoxic concentration (CC50) > 100 mcgM [36,39].<br>• Remdesivir was also able to inhibit replication and entry of bat, MERS, and SARS CoV in the epithelial cells in humans as suggested by the previous data [36,39].<br>• In a data of phase 3 study, an improvement in the mortality rate (8%) and recovery time (11 days) was observed in patients receiving remdesivir as compared to placebo (11% mortality and 15 days recovery time) [40].<br>• In a randomized study conducted by 'Gilead' involving 397 patients in which remdesivir was administered to patients for 5 and 10 days to determine the efficacy and safety of the drug. The patients who received the drug for 10 days showed more clinical improvement than to the patients with 5-day treatment [41].<br>• In a study with 53 patients, 68 percent of patients showed improvement clinically and required no oxygen. In cases of moderate to mild category patients, remdesivir has been recommended by NIH for administration for 5-10 days [41].<br>• The efficacy and safety of remdesivir against the virus are being studied. |
| Favipiravir (Investigational drug) | Inhibits synthesis of RNA of the virus by inhibiting RNA dependent RNA polymerase [42, 43]. | • Favipiravir efficacy was studied in an open-label, non-randomized trial involving 35 patients of SARS CoV-2, the median time for clearance of virus was less (4 days) in comparison to ritonavir and lopinavir (11 days). 91% improvement was observed in imaging of the chest with favipiravir whereas ritonavir and lopinavir showed only 62% improvement [44].<br>• Improvement by 88 percent was observed in patients when patients were treated with favipiravir and are approved for regulatory clearance for the treatment of the virus [44].<br>• Further efficacy of the drug is being studied [45]. |

## 5. RECENT STUDIES

Apart from the drugs that are showing immense potential in the treatment of COVID 19 as discussed above, there are some recent studies on vaccines, convalescent plasma, immune therapies, vitamin D that may also help in the treatment of SARS CoV-2.

### 5.1. Vaccines

SARSCoV-2 genetic sequence was published on 11 January 2020 and it triggered extreme worldwide research activity for developing a vaccine towards the COVID 19. As of 12 september2020, the world-wide COVID-19 vaccine research background presents 180candidates, of which 145 are presently at stages of the preclinical study. Table 5 shows some of the vaccines that have passed the pre-clinical stage [46].

### 5.2. Convalescent Plasma Therapy

Convalescent plasma therapy has the potential to combat against COVID 19 disease. Severe patients of COVID-19 can be treated from convalescent plasma recovered from the patients who successfully cope up with this disease. Several studies showed short hospital duration and mortality rates among patients who were treated with this therapy in comparison to other patients who were not treated by convalescent plasma. In 2014, the treatment of the Ebola virus disease from convalescent plasma was recommended by WHO during its outbreaks [47].

Convalescent plasma comes under passive antibody therapy in contrast to Vaccines which provide active immunity. Passive antibody therapy shows its action through viral neutralization or mechanism such as antibody-dependent cellular cytotoxicity or phago-cytosis might be involved. The passive antibody therapy is more effective when used in the prophylaxis or early stages of disease than for the treatment of disease. This alteration in the efficacy of passive antibodies might be due to the easy neutralization of inoculum by antibodies in early stages [48].

**Table 5: Vaccines in clinical phase development [46]**

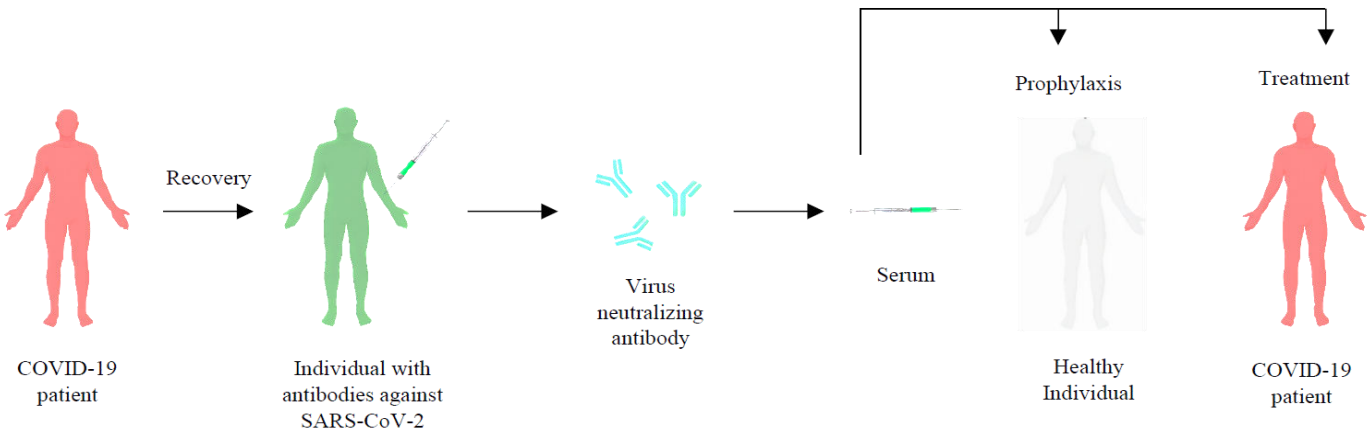
| Molecule Characteristics | Developers | Status (Phase) |
|---|---|---|
| mRNA-1273, LNP-encapsulated, encodes protein S. | Moderna | 2/3 |
| Adenovirus type 5 vector, protein S is expressed. | CanSino Biologicals | 1 and 2 |
| INO-4800, DNA plasmid, encodes protein S. | Inovio Pharmaceuticals | 1/2 |
| ChAdOx1 Non-replicating Viral vector. | Oxford university | 3 |
| BNT162-01, mRNA based. | Pfizer/Fosun Pharma/BioNtech | 1/2 |
| Inactivated + alum | Sinovac | 3 |
| Inactivated | Wuhan Institute of biological products | 1 |
| Inactivated | Sinopharm | 1/2 |
| Dynavax adjuvanted VLP derived from plant. | Medicago | 1 |
| mRNA | Walvax tech. | 1 |
| mRNA | Curevac | 1 |
| nCoVsaRNA- LNP | Imperial Institute | 1 |
| Adjuvant MF59 with protein spike stabilized by clamp molecule | Queensland university | 1 |
| Adjuvant advax with protein spike recombinant. | Medytox | 1 |
| Protein spike subunit (trimeric) | Dynavax/GSK | 1 |
| Adeno-based vector (non-replicating) | The research center of Gamaleya | 1 |
| Inactivated | Medical biology institute | 1 |
| GX-19 (Vaccine based on DNA) | Genexine | 1 |
| A vaccine based on nanoparticle of glycoprotein (recombinant) | Novavax | 1/2 |
| Inactivated-virion | Bharat tech | 1/2 |
| Plasmid of DNA | Cadila ltd. | 1/2 |
| Adjuvant plus plasmid of DNA | Takara/Anges | 1/2 |
| Dimer of RBD (protein - recombinant, adjuvanted) | Science Academy of China, microbiology institute | 1/2 |

*Liu et al.* carried out a study on five COVID-19 patients that were also suffering from acute respiratory distress syndrome (ARDS). In patients receiving Convalescent plasma, the SARS-CoV-2 antibody specific IgG binding titer was observed to be 1000 times higher than that obtained from 5 patients recovering from COVID-19 along with antiviral drugs. The primary outcome was that 4 out of 5 patients stabilized body temperature within 3 days. Viral studies within 12 days of transfusion were also found to be negative. After 37 days of transfusion, 3 patients were discharged out of 5 while 2 were in stable condition. The overall improvement in clinical status was observed [49].

*Duan et al.* carried out a study on 10 severe patients of COVID-19. Patients were treated with 200mL of Convalescent plasma with neutralizing antibody titers above 1:640 along with other antiviral drugs. The primary outcome was the safety of convalescent plasma transfusion and the secondary outcome was the clinical improvement within 3 days of transfusion. The results of the study showed that there was an increase in oxyhemoglobin saturation and an increase in lymphocyte count within 3 days of transfusion. Viral loads were undetectable in 7 patients out of 10 who had the previous viremia. Radiological tests showed varying degrees of lung absorption within 7 days of transfusion and no adverse effects were found [50].

A study conducted at Chongqing medical university involved five COVID 19 patients who suffered from advanced respiratory issues and had ABO-compatible convalescent plasma. The study showed an improvement in chest CT scan, nucleic acid results, laboratory reports, and clinical conditions. All the patients recovered with no adverse reactions that could be considered severe. All the patients survived and turned negative to COVID infection within 7 days of convalescent therapy. It was found that the patients had increased oxygen saturation, lymphocyte counts, and IgG and an improvement in chest CT scans and C reactive protein. IgM levels decrease quickly after the convalescent plasma therapy but IgG remains high in the blood to ensure safety. There was no evidence of adverse effects after 24 hours of administering CP. A case report from Chongqing medical university reported that there was a potential improvement in the condition of COVID patients who were on supportive care [50].

These studies showed that convalescent plasma therapy can be used in prophylaxis for vulnerable individuals (old age or individuals with chronic diseases) or for those who are in direct contact (health care professionals) with COVID-19 patients. One company Takeda, is preparing to generate antibody-based preparations against SARS-CoV-2 from Convalescent sera [51]. Fig. 3 shows the utilization of the Convalescent sera for COVID 19.




An individual recovers from COVID-19 and blood is drawn, screened for SARS-COV-2 neutralizing antibodies. These antibodies can be administered in prophylaxis to vulnerable individuals with other medical conditions, health care professionals who are in direct exposure with COVID-19.

**Fig. 3: Convalescent sera use in COVID 19**

Some of the other immune therapies that may some potential against COVID-19 and are being studied are shown in table 6. Apart from the above-stated drugs and adjunctive therapies, the utilization of corticosteroids, non-steroidal anti-inflammatory drugs, and inhaled pulmonary vasodilators are also being considered and is

under evaluation for the management of SARS-CoV-2. When COVID-19 patients are suffering from the syndrome of acute respiratory distress or refractory shock, therapy of corticosteroids can be taken into consideration [52]. The use of non-steroidal anti-inflammatory drugs in COVID-19 patients is under investigation by the FDA [53]. The temperature in the COVID-19 patients can be controlled by the administration of acetaminophen [53].

### 5.3. Role of Vitamin D3 to combat COVID-19

Studies showed that low levels of Vitamin D3 can increase the chances of respiratory tract infections [63]. Continuous supplements of Vitamin D3 can decrease antibiotic consumption and reduce the symptoms seen in patients who suffered frequently from respiratory tract infections [64].

Vitamin D3 shows its effect on the formation of inflammatory molecules known as cytokines [65]. Vitamin D3 increases the production of anti-inflammatory molecules and decreases the production of inflammatory molecules. "Cytokines storm" is a condition seen in critically ill patients of COVID-19 and Vitamin D3 might decrease its formation.

A recent report by TILDA (the Irish longitudinal study on aging) found that the deficiency of Vitamin D3 in those individuals who are obese and suffering from pre-existing lung disease makes them more vulnerable to COVID-19 [66].

There are currently several companies applying for clinical trials to develop medicines to tackle the rapid spread of COVID-19. Some of the undergoing clinical trials are shown in table 7.

**Table 6: Potential activity of antimicrobials, supportive, and adjunctive therapies against novel CoV**

| Drug and class | Mechanism of action | Evidence against SARS-CoV-2 |
|---|---|---|
| Azithromycin (Macrolides) | It acts as an immunomodulator which reduces the production of cytokine, thus regulating the inflammations related to viral respiratory infections. It reduces neutrophils chemotaxis, inhibits hypersecretion of mucus, and prevents the acceleration of neutrophil apoptosis [54]. | To prevent the superinfection of bacteria in six patients, azithromycin was given along with hydroxychloroquine in a non-randomized, open-label trial study (n =26), it was observed that the combination of the 2 drugs cured all the patients in comparison to 57% treatment with hydroxy-chloroquine [55]. |
| Tocilizumab (Monoclonal Antibody) | They bind to the receptors of interleukin-6 (IL-6) and inhibit its signaling activity. It induces the secretion of immunoglobulin and activates T-cell [56]. | When tocilizumab was combined with the therapy of SARS-CoV-2 in 21 patients, improvement in the percentage of lymphocyte, levels of C reactive protein, and clinical symptoms were observed. Efficacy against SARS-CoV-2 is being studied [57, 58]. |
| Siltuximab (Monoclonal Antibody) | | When administered intravenously to twenty-one SARS-CoV-2 patients, levels of CRP(C reactive protein) was found to decrease, the clinical condition improved. Efficacy against SARS-CoV-2 is being studied [45]. |
| Baricitinib (Monoclonal Antibody) | It inhibits Jason kinase that is responsible for regulating endocytosis (inhibition of alveolar type 2 related protein kinase) [59]. | It interferes with the endocytosis that is mediated by the receptor of SARS-CoV-2 in the alveolar type 2 cells of the lungs.[59] Efficacy against SARS-CoV-2 is being studied [45]. |
| Dexamethasone | It acts as an anti-inflammatory molecule and it can reduce the severity of ARDS which is a leading cause of death in COVID-19 patients [60]. | A clinical trial of Dexamethasone on COVID-19 patients. sponsored by Nuffield Department of Population Health at the University of Oxford shows that 28 days mortality rate reduces by one third among patients who are receiving invasive mechanical ventilation and it reduces by one fifth among patients who are receiving oxygen without invasive mechanical ventilation and no effect on |

| | | |
|---|---|---|
| | | mortality rate is seen in COVID- 19 patients who are not receiving any respiratory support [61]. |
| Interferon β 1a | It showed antiviral activity against SARS [62]. | Interferon α and β were studied and showed a positive response against CoV *in vitro* studies and animal models but they failed to show clinical response in humans [62].<br>This is a part of the solidarity trial conducted by WHO against COVID-19. |

**Table 7: Recent clinical trials for COVID-19 [67-81]**

| S. No. | Drug | Study |
|---|---|---|
| 1. | Isotretinoin | Assessment of the isotretinoin efficacy and safety in COVID-19 treatment: a clinical review. |
| 2. | Oseltamivir, favipiravir, and hydroxychloroquine | COVID-19: A randomized trial including hydroxychloroquine, favipiravir, oseltamivir. |
| 3. | Hydroxychloroquine | Hydroxychloroquine efficacy and safety towards COVID-19 for the population at risk. |
| 4. | Sevoflurane, propofol | Sedation with sevoflurane versus propofol in Patients With acute respiratory distress syndrome caused by COVID-19 infection. |
| 5. | Azithromycin, hydroxychloroquine or chloroquine, Interferon-Beta | Anti-Coronavirus treatments to keep COVID-19 from advancing. |
| 6. | Methylprednisolone, tocilizumab | Tocilizumab safety and efficacy in patients of COVID-19 in comparison to corticosteroids. |
| 7. | Lopinavir/Ritonavir, azithromycin, hydroxychloroquine | Medical Treatment safety and effectiveness against SARS CoV-2. |
| 8. | Remdesivir | Remdesivir (GS-5734™) antiviral action and safety evaluation in patients with moderate ailment (COVID-19) in comparison to standard. |
| 9. | Remdesivir | Adaptive COVID-19 treatment trial. |
| 10. | Sarilumab | Sarilumab safety and effectiveness evaluation in COVID-19 patients. |
| 11. | Nitric oxide | NO inhalation to check its effectiveness. |
| 12. | Infliximab | Safety and effectiveness are being determined. |
| 13. | Sirolimus | To determine its safety and efficacy. |
| 14. | Convalescent plasma | To determine the effectiveness of convalescent plasma. |
| 15. | Vitamin D3 | Evaluation of role of oral vitamin D3 against the virus. |

## 6. SARS COV-2 MANIFESTATIONS IN DIFFERENT ORGANS

A large number of patients of COVID-19 may have the risk of having a disability in their health. SARS CoV-2 effect on the eyes, brain, heart, lungs, kidney, GI tract needs to be studied and is shown in fig. 4. The section below discusses how COVID-19 is associated with damages of various organs and other issues related to it.

### 6.1. Central nervous system

The central nervous system (CNS) is responsible for maintaining homeostasis. The infection in the brain can be triggered when the virus enters the system through the nasal route [82]. Headaches, hypoplasia, hypogeusia, hyposmia are some of the symptoms manifested by COVID-19 patients [83]. These neuro disorders are due to the non-action of the immune system when any form of virus enters the CNS. Reports are suggesting that the damage of the brain can be considered as an outcome of SARS CoV-2. A case report mentioned that a woman aged 50 years infected with SARS CoV-2 also showed acute necrotizing encephalopathy in a tomography scan. It was stated that the virus caused a thalamus leakage *i.e.* leakage of the blood-brain vessel [84].

In another report, seizures and speaking inability were observed as neuro symptoms in a COVID-19 patient aged 74 years suffering from lung disease and Parkinson [85]. Some theories suggest that when the host immune system acts in response to the virus, cytokine storm is triggered in the brain by the virus which leads to the release of cytokines like chemokine ligand 9, 10, TNF α, IL-6,15, and these causes death of the cell and may

lead to induction of demyelination in the CNS [86]. Further studies are needed to unravel the potential connection between neurological disorders and COVID-19 to determine the invasion of the virus into CNS and to develop strategies for its prevention.

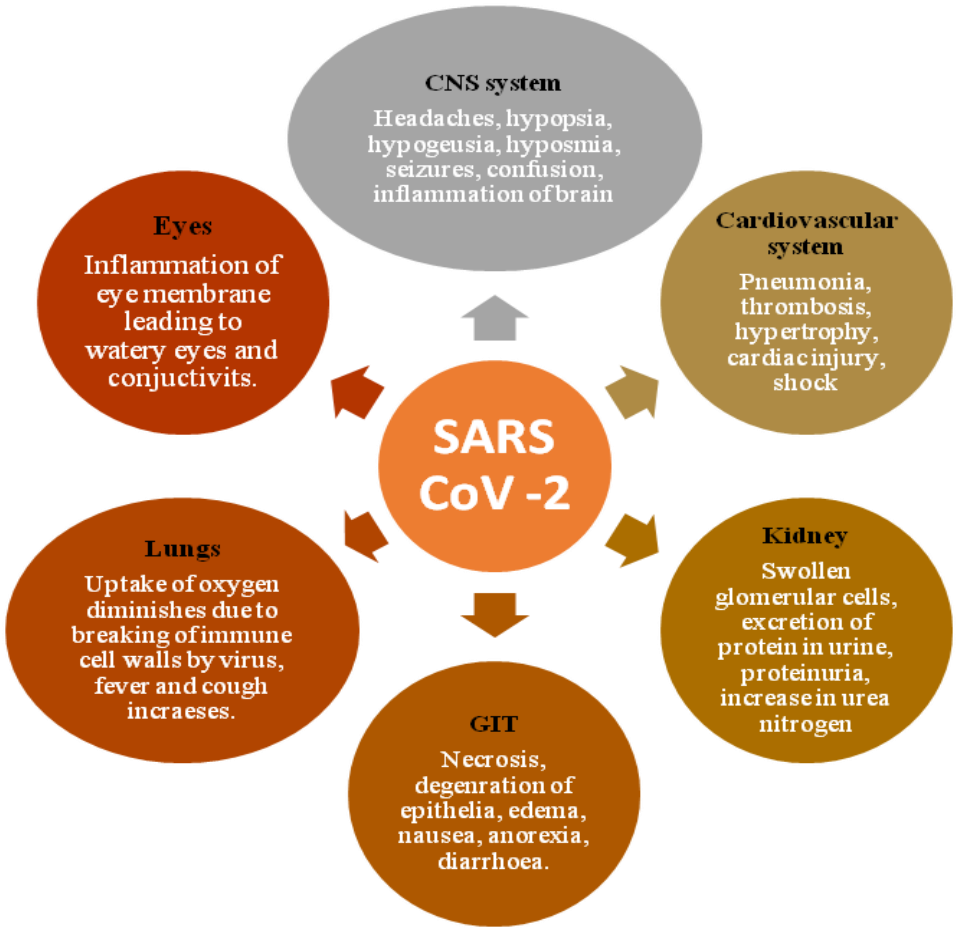



**Fig. 4: Effect of SARS CoV-2 on different human organs and systems**

### 6.2. Renal system

Patients of SARS CoV-2 are suffering from acute kidney injury as stated in some reports as the virus bind to the receptors of ACE-2 present in the kidney [87]. The binding between the virus and the receptor was found more in SARS-CoV-2 as compared to SARS CoV, thus acute kidney injury was more prominent in SARS CoV-2 [88]. It was found that in the COVID-19 patient, transmembrane protease serine 2 (responsible for proteolytic action and permits the entry of virus) along with ACE-2 was expressed in the cells of the kidney (proximal convoluted tubules). Kidney inflammation and injury also results due to pathways of apoptosis and inflammasome [89]. Consequently, follow-up research in patients is crucial to confirm that there are no existing COVID-19-derived conditions.

### 6.3. Cardiovascular system

The cardiovascular system is also impacted by COVID-19 due to the generation of pneumonia in the infected patients leading to heart attack due to arteries plaque deposition. Myocarditis or cardiac failure due to SARS CoV-2 is reported in several studies [90]. When the virus binds to the heart ACE-2 receptor, the normal function of the receptor deviates and the virus causes the myocardium inflammation leading to myocarditis. This deviation of the receptor may also fail multiple organs in humans due to an increase in cytokine storm and responses of inflammation [91]. The cells of the cardiac muscle are proliferated by the cytokine storm which ruptures the necrotic lipid core and results in myocardial infraction due to blood clots formation. In patients with SARS CoV-2, the myocardial injury may be due to impairment of the demand-supply of oxygen

as a result of high demand in cardiometabolic activity [92]. Reports also stated that during SARS CoV-2, levels of the troponin (heart muscle protein responsible for normal heart functioning) is elevated and this could be used as an abnormal parameter to diagnose the virus. A report from a Chinese center of disease control shows the death rate of 2.3% among COVID-19 patients, which increases to 5% for patients with cardiovascular disease [92]. The patients with comorbidities are more vulnerable to COVID- 19 and there are more chances of conversion from a mild case to severe one because extensive comorbidity is the hallmark of immune-deficiency.

### 6.4. Ocular system

Eyes can not only serve as a potential site for viral replication but also can lead to respiratory infection through extraocular sites. The latest studies have indicated that conjunctiva in the eye acts as an initial route to help enter the virus and spread the virus to other human organs [93]. The lacrimal system may also serve as a transmission route of the virus inside the human body because ACE-2 is present in the retina's retinal pigment epithelial cells. SARS-CoV-2 may penetrate droplet-shaped tears and spread the disease to different organs [94]. Symptoms related to eyes include chemosis, epiphora, and conjunctivitis, swelling of the conjunctiva in SARS CoV-2 acquired patients. In patients with SARS COV-2 infection, hematological abnormalities such as amplified level of neutrophils, Creactive protein, prolactin, white blood cells (WBC) can be seen as ocular associated symptoms [95]. Therefore, it can be concluded that the eyes can be a potential route of transmission for the virus.

### 6.5. Gastrointestinal tract system

GI symptoms exhibited by COVID-19 patients include anorexia, nausea, vomiting, abdominal pain, and bleeding. Elevated rates of dizziness, sore throats, headache, fever, fatigue, and breath shortness has been observed in patients with GI symptoms that suggest that GI symptoms be a part of the initial stage of COVID-19 infection. A study concluded that a neonate exhibited vomiting and milk refusal i.e. GI symptoms before any other COVID-19 symptoms [96]. Gastrointestinal disorders may also be involved as the viral particles were sequestered from the COVID-19 contaminated person's fecal matter. There is also the risk of liver damage in COVID-19 patients and the damage can be characterized by changes in the level of alanine amino transferase and aspartate aminotransferase liver enzymes [97]. Liver proliferation increase and markers associated with them were also found along with abnormalities in cytokines and apoptosis-related markers [98]. It can thus be concluded that liver manifestations must be taken into consideration while treating COVID-19 patients [99].

### 6.6. Respiratory system

A major site for COVID 19 infection, is the lungs and CT scans have shown the first few indicators of the infection. A study performed by Chen et al., in 99 COVID-19 patients with pneumonia has shown the abnormal phenomenon of Hb related biochemical indexes of patients. There is a decreased level of Hb, neutrophil count, and an increase in serum ferritin, C-reactive protein, lactate dehydrogenase, erythrocyte sedimentation rate, and albumin in many patients [100]. A study conducted by Cao et al., including 31 articles and 46,959 patients showed that 28.8% of patients had ADRs, of which 75.5% showed double pneumonia and 20.4% shoed unilateral pneumonia. 69.9% of patients had ground-glass opacities as a major and frequently occurring abnormality. Irregular lesions, thickening of the bronchovesicular bundles, grid form shadow, hydrothorax, chest pain, chronic obstructive pulmonary disease (COPD) as symptoms in COVID-19 patients were also seen in the study [101]. Although the symptoms associated with lung are substantial, the long-term results are yet unknown.

## 7. IMPACT OF SARS COV-2 ON CANCER AND PREGNANCY

### 7.1. Cancer

As the affinity for binding between SARS CoV-2 and ACE-2 is 10-20 times higher than the affinity between SARS CoV and ACE-2 receptors [102]. The cells and tissues which express more ACE 2 receptors, potentially act as a SARS CoV-2 target.

*Jia et al.* studied three databases *i.e.* HCCDB, UALCAN, GEPIA2, and found that in 5 types of cancers, the tumor cells express more ACE-2 receptors than the adjacent tissues. These cancers include CESC (Cervical Squamous Cell Carcinoma and endocervical adenocarcinoma), KIRC (Kidney renal clear cell carcinoma), READ (Rectum adenocarcinoma), KIRP (Kidney renal papillary cell carcinoma), and PAAD (Pancreatic adenocarcinoma). In the case of CESC,the expression of

ACE-2 receptors in tumor cells was close to lung tissue while in the case of PAAD, the expression level ACE-2 receptors in tumor cells are higher than lung tissue. It might increase the risk level to those cancer patients, so there is a need to pay greater attention to cancer patients during this pandemic [103].

### 7.2. Pregnancy

According to some case reports from China and the USA (New York), pregnancy might not increase the severity of COVID-19 disease, and transmission vertically was not seen from mother to neonate [104,105].

A report from Wuhan stated that 13 pregnant patients of COVID-19 (10 patients with fever, 2 with dyspnea, and 1 asymptomatic) were admitted to a hospital. The 12 patients were discharged after delivery with no complications and 1 stillbirth was reported. No serological or clinical evidence which suggested transmission vertically of SARS CoV-2 was reported [106].

Another study from Wuhan University's Zhongnan Hospital shows that the characteristics of 9 pregnant COVID-19 patients appeared identical to non-pregnant patients, and there was no proof of vertical transmission of SARS-Cov-2 from mother to neonate [107]. These 9 patients were admitted in the 3rd pregnancy trimester, so the possibility of vertical transmission in the first and second trimester was not determined [107]. For example, infection with rubella in the first trimester will infect 50 percent of the fetus by intrauterine infection, which is reduced to half at the end of the second trimester [108].

A report from New York suggests that all the deliveries either vaginal or cesarean of COVID-19 positive cases should be done with N95 masks and PPE (personal protective equipment). Among 7 patients, 2 were asymptomatic when admitted, delivery of an asymptomatic patient can spread the virus among health care providers [108]. CDC (Centre for disease control and prevention) suggest that the patient with positive COVID-19 who choose to breastfeed their newborn should practice good hand hygiene and wear a mask to prevent transmission of the virus through respiratory droplets [109].Table 8 lists some studies of patients of SARS CoV-2 and its manifestations relating to different organs and systems.

**Table 8: Studies relating to the manifestation of various organs by SARS CoV-2 [83, 110-114]**

| System/organ | Study | Features/Findings observed |
|---|---|---|
| Pulmonary | A retrospective study on confirmed forty-one cases. | Haemoptysis, Sputum, dyspnoea, dry cough, fever, an abnormal chest was observed in the CT scan. |
| | A retrospective study on confirmed one thousand ninety-nine cases. | In 56% of patients ground-glass opacity, abnormal chest in 86% of patients, the fatality rate was 1.5%, ARDS, hemoptysis, nasal congestion, sore throat, sputum formation, cough, and fever. |
| Cardiovascular | A retrospective study on confirmed forty-one cases. | 12% of patients showed cardiac injury in 31% of patients in ICU. An increase in 12% of troponin levels was observed. ICU patients showed increased blood pressure. |
| | A case report on confirmed four cases. | Cardiogenic shock, heart failure, myopericarditis, increased cardiac enzymes. |
| Gastrointestinal | A clinicopathologic study on confirmed one hundred thirty-eight cases. | Abdominal pain in 2% of patients, vomiting, nausea, diarrhea, anorexia in 39% of patients. |
| | A retrospective study on confirmed two hundred four cases. | Decreased monocyte count, prothrombin time increased, abdominal pain, vomiting, diarrhea, loss of appetite. |
| Renal | A retrospective study on confirmed one hundred thirty-eight cases. | An increase in creatinine levels, 3.6% of patients showed acute kidney injury, as the disease progressed urea along with creatinine increased. |
| | A retrospective study on confirmed seven hundred one cases. | 26% showed haematuria, 43% showed proteinuria, Increased urea and creatinine levels, cytokine-induced renal failures. |
| Neurological | A retrospective study on confirmed two hundred fourteen cases. | 36% showed symptoms of neurological systems, 16% dizziness, 13% showed headache, 5% showed hyposmia and hypogeusia. |
| | A retrospective study on confirmed fifty-eight cases. | Dysexecutive syndrome, confusion, agitation, 57% showed low albumin content, 14% showed high protein and IgG levels. |

## 8. COVID-19 AND PHARMACEUTICAL INDUSTRY

As sectors of the economy are struggling with Covid-19's effects, companies are undergoing loss, employees are jobless and so many faces the prospect of a complete lifestyle upheaval. Throughout these unpredictable days, drug manufacturers are reacting to the quick obstacles raised by distribution network disruptions and the need to adjust workflows. The pharma industry is continually subject to transition. If the present COVID-19 pandemic persists for a prolonged period, it might just affect the availability of active products and ingredients (mainly from China), as well as pharmaceutical imports and exports. In the last few years, in particular, the processing of active substances and raw materials has been gradually moved to countries where manufacturing can be more cost-effectively carried out. "Contract Manufacturing Organizations" (CMO) outsourcing has become extremely common. Though, the globalization of supply chains and increasing dependency on third parties have indeed contributed to severe slowdowns in the supply of drugs in individual situations particularly for life-saving drugs which are important. The world's current COVID-19 outbreak could also contribute to higher restrictions or perhaps even supply drug bottlenecks. However, this move of CMOs outsourcing may be reversed to maintain the availability of essential drugs. COVID-19 has impacted the pharma in various aspects such as: [115-117].

### 8.1. Price of Drugs and Excipients

The effect Covid-19 and the lockdown in different nations expanded the odds of shoot up at the expense of crude materials and medications. 13% of the brand and conventional makers are from China and as per the FDA, 24% of meds and 31% of clinical medications were imported from India which is now impacted.

The price of Paracetamol in India has risen to 400-450 as per kilogram from Rupees 250-300 as per kilogram. Also, the cost of nutrients and penicillin have risen by 40-50 % in India. If the current circumstance keeps on delaying, the expense of fundamental medications may also rise in the US and different nations too [115].

### 8.2. Supply Chain

The Pharma supply chain is delicate, and the effect made by Covid-19 has carried it to the spotlight. There are two sorts of medications *i.e.* Brand medications: these are items secured with a dependable gracefully chain and beneficial to the producers and Generic medications: the benefit for these sorts of medications is extremely peripheral and the chain is weak. The API might be fabricated in a solitary plant and each step results in lesser invention techniques. The issue at any stage can cause medicate deficiency with the normal medication lack going on for 14 months and there are situations where it has gone on for a long time even. As indicated by an ongoing crisis, vital drugs are the medications that are getting influenced because of unavailability. The current circumstance may cause a lack and increment in requests of specific meds, for example, Chloroquine, and remdesivir which are most discussed during these pandemic occasions. It is accepted that the lack probably won't happen for the time being as organizations have stocks at any rate for the following 5 months [116, 117].

### 8.3. FDA Policies

The pandemic and the lockdown in different nations may drive the FDA to permit unwinding in a couple of zones. The audit procedure of Generic medication is protracted; the interest of lack may drive small changes. The Federal based law requires the makers to inform the FDA about deficiencies when the condition emerges. The principles don't have any significant effect on the clinical devices as it is produced at numerous plants. The deficiency of medical devices during the pandemic may compel the FDA to re-evaluate the guidelines of medical devices [115-117].

### 8.4. Data Analysis

The Pharmaceutical industry has a huge measure of information, which additionally is associated with difficulties like Infer bits of knowledge, a framework to use the intensity of larger data, utilizing unstructured information, advance bits of knowledge from the clinical path, and information protection. The expense of medication advancement is soaring, and the time required for medication to be formulated is additionally high. The business has been utilizing information for quite a long time, yet the test lies in utilizing its maximum capacity. A lot of clinical and atomic information accessible throughout the years can help in the prescient investigation, which can be utilized to hurry the procedure of clinical preliminaries and medication advancement. Organizations are utilizing information and examination; however, the current circumstance may need them to utilize information considerably more effectively for clinical preliminaries, estimating, and advertising [115-117].

### 8.5. Real-World Data (RWD)

New medication advancement is assessed to cost about $2.6 billion which increases from 1 billion every year from 2013. On the head of the cost in question, the time taken for development & clinical preliminaries may get more concentration towards the RWD. Practically 95% of the organizations are utilizing RWD or will utilize it by 2021. Information availability and security issues are a couple of the difficulties in utilizing RWD, however, it tends to be sifted through and will acquire ubiquity as organizations and the administrative bodies from here on might hope to get creative measures in clinical preliminaries. Clinical preliminaries are gold residue for pharma. The primary issue with clinical preliminary is it takes a gander at a homogeneous populace. To address this, the FDA may have to loosen up the guidelines on RWD.

### 8.6. Digital Health

Computerized wellbeing may be the enormous thing as telemedicine or video conferences, wellbeing related recordings, and applications are picking up notoriety. Interest in online entrances that help specialist persistent cooperation is increasing. The case of increasing computerized prevalence is as follows: Well-mind (gives online courses to care based subjective treatment) has seen an ongoing upswing, Headspace, and Meditation apps 'Calm' have started free computerized contributions to assist individuals dealing with panic and nervousness [115-117].

## 9. EMERGING THERAPIES AND TECHNOLOGY

The world is observing the worst scenario of a pandemic. While the research for finding a suitable drug and vaccine is still going on. There is a need for alternative approaches and technology development to tackle down this virus. Thus, ayurvedic medicines should also be focussed on the management of COVID-19 as it shows minimum/no adverse effects and also provides immunity to the body. Also, the world is seeing many innovations developed by various countries that are providing extreme support in this situation.

### 9.1. Role of Ayurveda to combat COVID-19

This COVID-19 pandemic focusses our senses towards maintaining immunity which is the body`s defense mechanism towards viruses, bacteria, and other pathogens. Various psychological factors also increase susceptibility towards different viral respiratory tract infections [118, 119]. Ayurveda, a traditional system of medicine that was developed 3000 years ago in India can also show promising results like Traditional Chinese medicine to treat COVID-19 patients. Some proposed interventions of Ayurveda against COVID-19 are shown in table 9 [120].

Fumigation of places can be done by using different ayurvedic herbs such as Allium sativum, Curcuma longa and it may be beneficial for disinfectant purposes [119]. Various approaches by modern medicine and traditional medicine will help us to cope up with this pandemic.

**Table 9: Ayurvedic treatment in COVID-19**

| Category | Proposed intervention |
|---|---|
| Unexposed healthy individuals | Physical activity, Practice of Yoga and meditation (for mental health), and intake of *Swarna prashan, SanjeevaniVati, Amrit Bhallataka, Brahma Rasayana, Chyavanprasha.* |
| Exposed Asymptomatic individuals | Trikatu, Triphala, Moringa oleifera, Swertia chirata, Andrographis paniculata, Adhatodavasica, Glycyrrhiza glabra, Ocimum sanctum, Curcuma longa, Zingiber officinale, Tinospora cordifolia, Brahma Rasayana, Chyavanprasha, ChitrakatdiVati and SanjeevaniVati. |
| Patients with mild symptoms | *Yashtimadhu, Talishadi, Sitopaladi, Dashamulkwath, Vyaghriharitaki, ChitrakadiVati, KantakariAvaleha, Go JihvadiQuath, Pippali Rasayana.* |
| Patients with severe symptoms of COVID-19 | *Siddha Makardhvaja, Mrityunjaya rasa, BrihataVataChintamni rasa, Tribhuvan Keerti rasa, Sanjeevanivati, Laghu Vasant Malati, Pippali rasayan* etc. |

### 9.2. Role of Innovation and Technology against COVID-19

COVID 19 pandemic has brought a lot of difficulties and challenges along with the infection. People across the world have innovated and used technology in a way to fight against the coronavirus pandemic and to effectively control the situation. Different countries innovated distinguishing solutions and also used different technologies for the same.

#### *9.2.1. Artificial intelligence: a way to track*

In India, the government has launched the "AarogyaSetu" application on smartphones to track infected people and to give information about the

proximity of people from infected people. It uses Bluetooth technology to give information about the vicinity. In Australia, a similar app "COVID Safe" is launched to help health professionals to get the information in case the person has come in contact with a confirmed case. It also uses Bluetooth wireless technology and stores the mobile number if a person is in a 1.5 m range of the confirmed case for more than 15 minutes. China developed an application to prevent the second wave of the coronavirus infection. The applications compel the user to scan the QR code before using any public transport and share their health information. The different colors indicate different health statuses and if found red, he/she has to undergo 14 days of quarantine. Similar applications have been developed in Italy, South Korea, and Germany [121-123].

#### *9.2.2. Equipment's aiding in breathing*

Respiratory issues are a common and major symptom of COVID-19. It has become a major cause of death in COVID infection. Breathing equipment plays a major role and is important for patients suffering from COVID-19. Reports from Italy have shown that there is a decline in the need for invasive mechanical ventilation if oxygen is given by the aid of continuous positive airway pressure (CPAP). Similar machines have been designed and developed in the United Kingdom which requires 70% less oxygen as compared to earlier models. Three prototypes of a low-cost ventilator were developed by the design innovation center (DIC) of the Islamic university of science and technology in collaboration with IIT Bombay students before finalizing Ruhdaar. Ruhdaar is a low coat ventilator that would cost around rupees 15000. It has shown successful working in laboratories. Jeeva Setu is a small, oven sized ventilator that is portable and cheap. It is developed by REVA University, Bengaluru to aid the medical infrastructure of India. Its delivery is estimated to be around 15-18 breaths per minute and 500-600 ml of air per breath which is required by a COVID-19 patient [121-123].

#### *9.2.3. Mask: More safety, less cost*

Automatic mask machines are being produced by engineers to overcome the shortage of N 95 masks and also to decline the import of parts and automatic machines from China. Different start-ups and firms are trying to bring new alternatives to N95 masks and some had already succeeded [121-123].

#### *9.2.4. Patient and medical care staff safety*

Increasing cases of COVID-19 has been challenging the healthcare system. It has led to problems relating to the safety and care of patients and healthcare staff. The increasing cases are stressful for medical staff worldwide. Robots are being used in China to assist the medical staff. These robots help in taking swabs of patients, using a stethoscope for listening to different organs, and to perform ultrasound scans. Similar robots are being used in Italy to aid in delivering food and to monitor routine health symptoms A patent is acquired by a doctor in the Indian navy in collaboration with the national research development corporation (NRDC) for developing a low-cost PPE that is made up of fabric with high breathability. The PPE is suitable for the climatic conditions of India that is hot and humid [121-123].

## 10. CONCLUSION

As of today, COVID 19 has been spread across almost to all countries, some having little cases whereas some struggling to manage the crisis of the pandemic. Various scientists across the world are studying the characteristics of the SARS CoV-2 and extensively trying to find out the best possible vaccines and therapies for its treatment. Firstly, studies are showing that the disease emerged from bats but there can other intermediate hosts which need to be searched. Secondly, extra care and attention are required on elderly patients and those with a compromised immune system, as they are highly susceptible to the disease with a greater death rate. Thirdly, the clinical trials undergoing various drugs such as ritonavir, chloroquine, and remdesivir need to be scaled at a large scale. Also, the accurate mechanism of transmission and replication of the virus needs to be explored.

## 11. FUTURE PROSPECTS

Organizations are looking for safe and appropriate candidates for vaccinations and therapies to manage the deadly COVID-19. There are still no vaccines or medicines available. Therefore, we must rely solely on implementing strict prevention and control strategies measures that reduce the risk of the potential spread of disease. Although work is underway to improve COVID-19 mitigation, diagnosis, and regulation, the recorded clinical evidence on various therapeutic strategies for CoVs is limited. Further work should be geared towards the analysis of SARS-CoV-2 in suitable experimental animals for replication, transmitting, and pathogenic analysis. Pharmaceutical industries need to

scale the pace of trials in humans by increasing the number of studies at each stage of trials.

***Conflict of interest***

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