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Review Article

Different Therapeutic Modalities for management of COVID-19

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ABSTRACT

There is a global health concern caused by the COVID-19 pandemic and a need for effective treatments to reduce morbidity and mortality associated with the disease. Various agents have been proposed as potential remedies against COVID-19. The review aims to highlight and compare between different therapeutic modalities for the management of COVID-19. We conducted a search strategy using medical subject headings (MeSH) and included literature reviews, systematic reviews, and relevant updated publications from 2019 up to October 2023. The transmission of the virus occurs through coming into direct contact with a person who is infected or respiratory droplets expelled during coughing and/or sneezing. Precautionary safeguards like isolation, handwashing, mask-wearing, and lockdowns have been implemented, but the need for effective treatment remains paramount. Antiviral, antimicrobial, and immunomodulatory agents have been proposed as potential remedies against COVID-19. Managing symptoms may involve administering antipyretics and/or anti-inflammatory medications to alleviate fever and mild pain, as well as providing oxygen therapy for respiratory distress. In extreme situations, the use of mechanical ventilation might become essential. In conclusion**,** Hydroxychloroquine and remdesivir have displayed promising outcomes in clinical settings. Tocilizumab, an immunomodulatory agent, has shown reduced mortality rates compared to controls. The pairing of bamlanivimab and etesevimab has shown a notable decrease in viral load. Fingolimod, a small molecule modulator, is being studied for its potential to regulate the immune response in severely infected COVID-19 patients. A small clinical trial found that taking pentoxifylline and vitamin C together resulted in the reduction of inflammatory markers levels. COVID-19 vaccination has shown promising protection against infection, reduced hospitalization rates, and lower mortality rates.

Keywords: *COVID-19; Therapeutic modalities; Antiviral agents; COVID-19 vaccination; Supplements.*

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1. Introduction

Since December 2019, an epidemic of a recent virus has disseminated across numerous nations and resulted in a multitude of instances and fatalities. The coronavirus 2019 (COVID-19) which originated in China, has spread to over 211 countries and territories across the globe **[1]**.

Severe acute respiratory syndrome coronavirus-2 (SARS COV-2) responsible for COVID-19, was declared a global pandemic by the World Health Organization on March 11th, 2020, and represents a noteworthy health apprehension. While the majority of those infected display mild respiratory symptoms that ultimately resolve spontaneously, a subset of individuals develop more severe afflictions, such as pneumonia **[2]**.

The transmission of the virus occurs through direct contact with an individual who is infected or employing respiratory droplets that are expelled through coughing or sneezing. Despite the implementation of precautionary measures worldwide, like isolation of confirmed and suspected cases, the dissemination of knowledge regarding proper handwashing techniques and the significance of using face masks, the prevention of large numbers of meetings, and the enforcement of lockdowns, the imperative need for an efficacious treatment remains paramount to halt the pandemic and lower the morbidity and mortality associated with coronavirus 2019 **[2]**.

Ever since the commencement of the outbreak, numerous agents have been proposed by researchers as potential remedies against COVID-19. The most recent guidelines issued by various countries have incorporated a range of antiviral, antimicrobial, and immunomodulatory agents. However, in accordance with the World Health Organization, there is currently no particular medication available for the prevention or treatment of coronavirus disease **[3, 4]**.

Symptom treatment may include the use of antipyretics or anti-inflammatory drugs to treat fever and moderate discomfort, as well as the use of oxygen therapy for patients experiencing respiratory distress. Depending on the patient's clinical condition, mechanical ventilation may be required in specific instances **[5]**. Nonetheless, there is ongoing research in various clinical trials worldwide to explore the potential use of a range of drugs approved for other conditions, as well as investigational agents, for the treatment of COVID-19 **[6, 7]**. Across different countries, the treatment protocols exhibit significant similarities, with many recommending the examination and utilization of drugs such as hydroxychloroquine, chloroquine, remdesivir, and lopinavir/ritonavir **[8, 9]**. Despite the fact that a growing number of research have been expeditiously published online and in educational publications, the existing evidence pertaining specifically to the therapeutic management of COVID-19 remains limited and insufficient.

The review aims to study and compare the different treatment modalities being employed for patients who have been infected with COVID-19.

2. Methods

The current review covered materials such as literature reviews, systematic reviews, and clinical trials. A search strategy was devised using medical subject headings (MeSH) to search the PubMed and MEDLINE scientific databases. The MeSH terms utilized included COVID-19, therapeutic modalities, anti-inflammatories, immunomodulators, antiviral agents, vitamins, and supplements. The inclusion criteria encompassed studies published in the English language from 2019 to October 2023, with a particular emphasis on the most recent literature pertaining to different therapeutic modalities for coronavirus disease 2019 **(Table 1 & Fig. 1)**.

Table. 1. Inclusion criteria for search strategy

Parameter	Criterion
Trials and studies	Clinical trials including covid-19 patients or *invitro*/animal studies
Intervention	Anti-inflammatories, antiviral agents, immunomodulators, vitamins, supplements, and vaccines.
Comparator	Other therapeutic interventions, or placebo group.
Outcome	Laboratory, Clinical, and radiological, symptoms of covid-19 Remission of covid-19 symptoms. Length of hospitalization. Mortality rates.
Setting	All settings

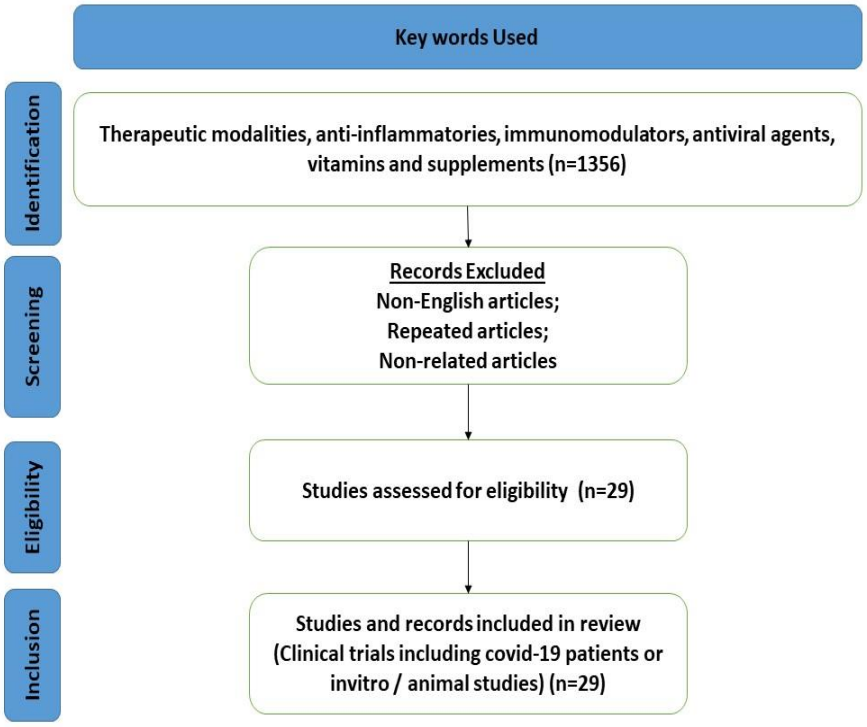

Fig.1. Study flow chart

3. Results and Discussion

3.1. COVID-19 Life Cycle and Pathophysiology

The viral life cycle in conjunction with its host is comprised of a series of five distinct stages. During the attachment stage, the viruses bind to specific receptors on the host cells. This binding allows the viruses to enter the host cells either via endocytosis or membrane fusion, which is known as the penetration stage. After entering the host cells, the viral components are liberated,

and the viral RNA infiltrates the nucleus to initiate the replication process. The process of biosynthesis then takes place, where viral mRNA is utilized to produce viral proteins. Following this, the maturation stage occurs, during which new viral particles are formed. Finally, the host cells release these recently formed viral particles. In the case of coronaviruses, they are composed of 4 structural proteins, namely Spike (S), membrane (M), envelop (E), and nucleocapsid (N). The Spike protein is particularly interesting as it consists of two subunits, the S1 and S2 subunits. The role of the S1 component is to bind to the receptor on the host cell, while the S2 component is in-charge of merging the viral and cellular membranes **[10] (Fig. 2)**.

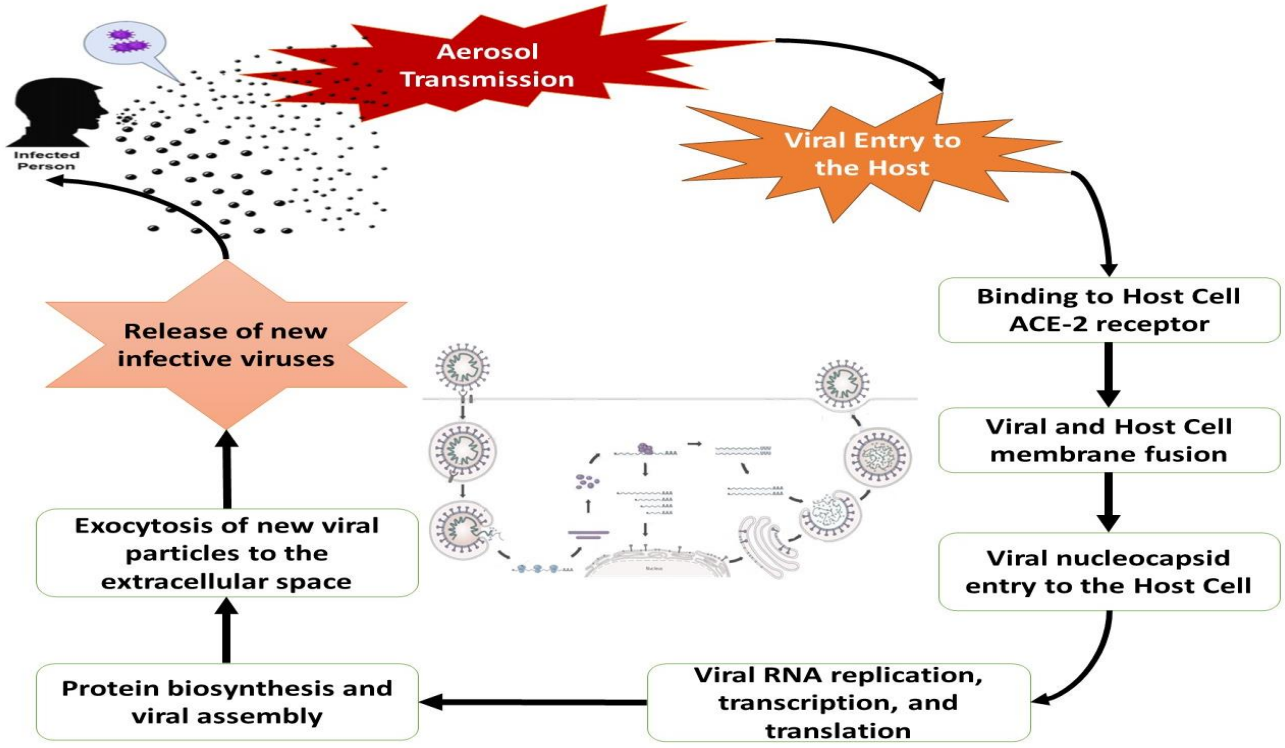

Fig. 2. COVID-19 Life Cycle

Researchers identified angiotensin-converting enzyme 2 (ACE2) as a functional receptor for SARS-CoV-2 **[11]**. The expression of ACE2 is high in important vital organs like the ileum, heart, kidney, lung, and bladder **[12]**. It is highly expressed in lung epithelial cells **[13]**. Due to its high expression on the apical side of lung epithelial cells in the alveolar space **[14]**, SARS-CoV-2 can probably invade and devastate them. This aligns with the observation that early lung injury frequently occurs in the distal airway, where alveolar macrophages, epithelial, and dendritic cells serve as the three primary components of innate immunity **[15]**. Dendritic cells are positioned beneath the epithelium, while macrophages are situated on the apical side of the epithelium. Both dendritic cells and macrophages function as innate immune cells to combat viruses until adaptive immunity is engaged **[10]**.

Antigen presentation through DCs and macrophages triggers the initiation of T-cell responses. DCs and macrophages can phagocytize apoptotic cells infected by the virus **[16]**, which results in the presentation of antigens to T cells **[10]**.

The majority of immunological studies focused on COVID-19 patients experiencing severe symptoms, where individuals with severe conditions showed lymphopenia, characterized by a specific decrease in peripheral blood T cells. Elevated levels of proinflammatory cytokines including IL-6, IL-10, G-CSF, MCP1, MIP1α, and TNF-α were observed in the plasma of patients with severe manifestations **[17, 18]**.

In patients with more severe conditions, elevated levels of IL-6 were observed alongside the activation of CD4+ and CD8+ T cells, as evidenced by increased expression of CD69, CD38, and CD44. Additionally, there was an increased presence of exhausted CD4+ and CD8+ T cell subsets, as indicated by a higher proportion of Tm3+PD-1+ checkpoint receptor expression **[19]**.

The depletion of T cells may have contributed to the progression of the illness. Another significant finding was the identification of abnormal pathogenic CD4+ T cells that expressed both interferon (IFN)-γ and granulocyte-macrophage colony-stimulating factor (GM-CSF) in patients with severe symptoms **[18, 20] (Fig. 3)**.

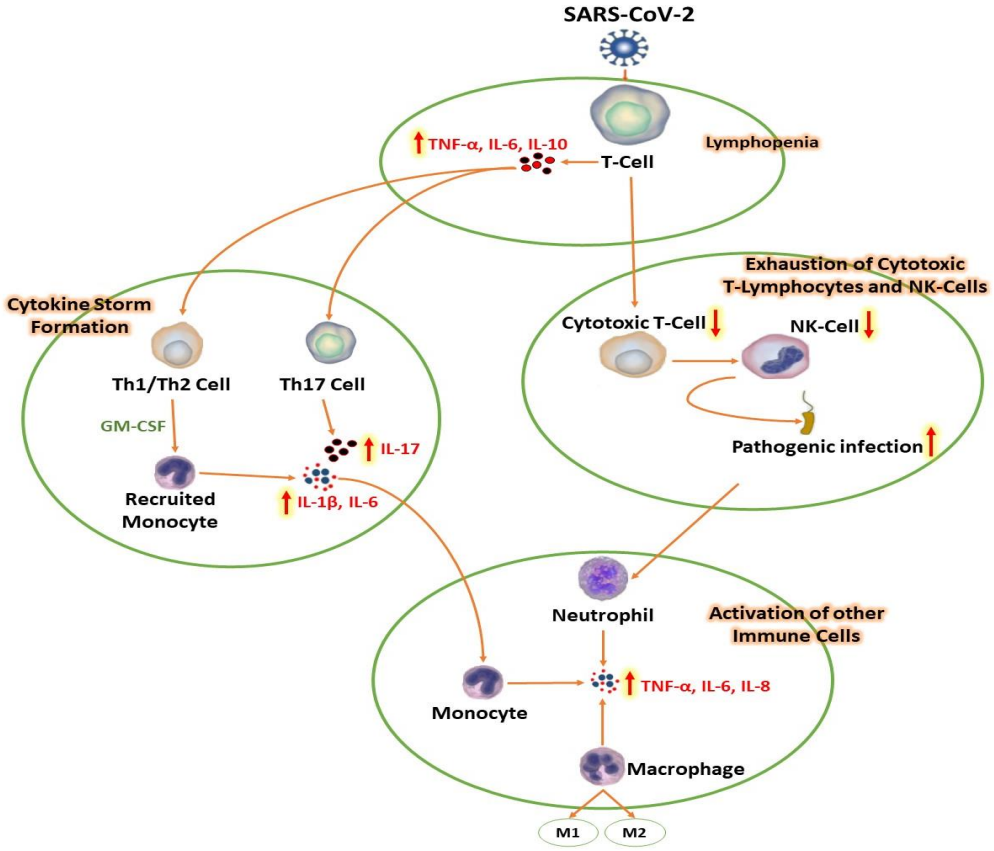

Fig. 3. Mechanisms of SARS-CoV-2 pathogenesis.

3.2. Therapies targeting inflammation and immunomodulators

Since the early phases of the COVID-19 pandemic, hyperinflammation has been suggested to play a significant role in the pathophysiology of severe cases **[21]**. Hospitalized patients exhibit higher levels of circulating acute phase reactants

(e.g., ferritin) **[22]**, pro-inflammatory cytokines (e.g., IL-6) **[23],** and markers of coagulation and fibrinolysis (e.g., D-dimer) compared to healthy individuals **[24]**. Furthermore, consistently elevated levels of these markers have been linked to a higher risk of mortality among infected patients **[23, 24]**. Despite later research indicating that the level of inflammation in COVID-19 could be comparable to that seen in patients with sepsis or ARDS unrelated to COVID-19 **[25]**, the correlation between inflammatory markers and the severity of outcomes led to a series of trials investigating interventions focused on inflammatory pathways.

3.2.1. Dexamethasone

The largest Randomized Controlled Trial (RCT) to date on the use of glucocorticoids in COVID-19 patients was conducted **[26]**. The study randomly assigned 6,425 adult patients hospitalized to two groups: one receiving oral or intravenous dexamethasone at a daily dose of 6 mg for up to ten days, and the other receiving usual care. It was found that the group receiving dexamethasone had a lower mortality rate at 28 days (22.9% compared to 25.7%). When analyzing the primary outcome based on the level of oxygen support, a significant level of heterogeneity was observed (P-value less than 0.001) **[27]**.

In particular, the study revealed that the use of dexamethasone provided the highest mortality benefit for patients undergoing invasive mechanical ventilation (IMV) at the time of randomization (RR, 0.64). However, there was a potential trend toward negative effects in patients who were not receiving oxygen at the time of randomization (RR, 1.19). These findings were supported by a meta-analysis of seven RCTs involving 1,703 critically ill COVID-19 patients who were treated with glucocorticoids. The analysis found an odds ratio (OR) of 0.66 for 28-day mortality **[27]**.

3.2.2. Monoclonal Antibodies (mAbs)

There are currently around 24 ongoing clinical trials examining the effectiveness of various monoclonal antibodies in coronavirus disease treatment. The presence of heightened levels of cytokines IL-7, IL-10, IL-6, and IFN-α serve as indicators for the intense inflammatory response and cytokine storm observed in infected patients **[28]**. Among these, the primary cytokines accountable for the perturbed inflammatory reaction are IL-6 and granulocyte-macrophage colony-stimulating factor (GM-CSF). Consequently, monoclonal antibodies such as tocilizumab, sarilumab, and, (lenzilumab, an experimental medication) have been reassigned to manage COVID-19 patients **[29]**.

3.2.2.1. Tocilizumab

Tocilizumab is an IL-6 receptor monoclonal antibody that has been humanized. Early observational results revealed a survival advantage in hospitalized COVID-19 patients treated with tocilizumab **[30, 31]**, especially when given early in the illness course. These findings contradict the findings of the original RCTs **[32, 33]**, which mostly yielded negative results, although they were also underpowered to definitively exclude a significant therapeutic benefit. Subsequently, two large-scale RCTs discovered a survival advantage **[34]**.

A clinical trial was conducted to randomly allocate 755 critically ill adult patients with COVID-19 to either receive tocilizumab or standard treatment **[35]**. Tocilizumab was administered approximately 1.2 days after hospital admission. The incidence of death during the hospital stay was notably decreased in patients who received tocilizumab (28% compared to 36%), as well as the mortality rate at 90 days.

The RECOVERY group completed COVID-19's biggest RCT of tocilizumab till now. The

study included 4116 adult patients who were assigned to receive either tocilizumab or standard treatment at 131 UK hospitals. Tocilizumab was given a median of two days after being admitted to the hospital. Tocilizumab individuals had a decreased 28-day mortality (31% versus 35%) **[36]**.

Some researchers have expressed concerns about the lack of blinding in these large-scaled studies **[37]**, although the findings appear to be similar across investigations. Furthermore, the findings agreed with the findings of a meta-analysis that included 10930 adult COVID-19 patients from twenty-seven RCTs assessing the efficacy of IL-6 antagonists. Results showed that the OR for 28-day mortality was 0.86. Tocilizumab got FDA Emergency Use Authorization for COVID-19 on June 24, 2021, and is presently under assessment by the FDA for official use approval; the EMA authorized this medication on December 6, 2021 **[38]**.

The FDA has authorized bevacizumab, a VEGF inhibitor, for the management of malignancies such as colorectal cancer **[39]**. VEGF increases tumor development by inducing blood vessel growth and dilatation of bronchi and increasing blood vessel wall permeability **[40]**. While the significance of elevated levels of VEGF in lung damage or ARDS remains a topic of debate, a recent clinical trial discovered that these increased levels were responsible for lipid embolism-induced ARDS **[41]**. Bevacizumab's effectiveness in treating ARDS is being studied in two phase 2/3 clinical studies.

The complement protein C5 is targeted by eculizumab, which is authorized for the management of paroxysmal nocturnal hemoglobinuria **[42]**. Three clinical studies are now underway to evaluate eculizumab for COVID-19 therapy.

3.2.3. Interferons

Interferons of type I (IFN-α -β), commonly known as viral interferons, are cytokines that stimulate immune reaction to viral infections. IFNs are now licensed as a therapy for multiple sclerosis **[43]**. Interferon type I induces the expression of interferon-stimulated genes (ISG), which facilitate immune signaling and modulation [44]. IFN-1 therapy was examined in SARS-CoV patients and in-vitro, with or without antiviral medications **[45]**. Furthermore, IFN-β is more efficient than IFN-α against SARS-CoV **[46]** and MERS-CoV **[47]**.

A recent investigation suggests that IFN-1 pretreatment can effectively target SARS-CoV-2 due to its absence of ORF3b and the presence of a modified ORF6, which plays a crucial role in inhibiting IFN-1 **[48]**. IFNα2b has recently been shown to be effective in lowering SARS-CoV-2 virus load when given prophylactically by inhalation **[49]**. Interferon type I treatment is recommended only in the initial stage of infection because exaggerated IFN-1 activation may lead to a cytokine storm **[50]**. Retrospective research found that IFNα2b therapy of COVID-19 patients with or without arbidol lowered viral burden and IL-6 levels **[51]**. A late phase 2 randomized clinical study revealed that the combination of IFNβ1b with lopinavir/ritonavir/ribavirin led to quicker improvement in patients experiencing early symptoms compared to treatment with lopinavir/ritonavir/ribavirin alone **[52]**.

Interferon-λ (IFN-λ) constitutes an additional cytokine that demonstrates antiviral properties when present at epithelial surfaces, effectively restraining an exacerbated inflammatory reaction within the organism **[53]**.

3.2.4. Janus Kinase (JAK) Inhibitors

The JAK molecule serves as a signal transducer for the Janus kinase signaling pathway, which in turn regulates gene expression and various cellular processes. This pathway,

known as the JAK-STAT signaling pathway, is responsible for controlling the transcription process **[54]**. The JAK/STAT pathway triggers the production of inflammatory cytokines that are associated with cancer, autoimmune disease, as well as bacterial and viral diseases **[55]**.

3.2.4.1. Baricitinib

Baricitinib, an orally administered inhibitor of JAK1 and 2, exhibits anti-inflammatory properties. An RCT involving 1033 hospitalized people revealed that the administration of baricitinib (at a daily dosage of 4 mg for a maximum duration of fourteen days), combined with remdesivir, was superior to the use of remdesivir alone in terms of reducing the time required for recovery **[56]**. In a later phase III randomized controlled trial, 1525 adult patients who were admitted to 101 different medical facilities across 12 countries were subjected to a random allocation process. This process aimed to determine whether the patients would receive a daily dosage of baricitinib at 4 mg or a placebo for a maximum duration of fourteen days. Whilst the primary composite outcome demonstrated similarity between the respective groups, 28-day mortality was significantly lower in the baricitinib group (8%) compared to placebo (13%). Patients getting intermittent mandatory ventilation were specifically excluded from this research **[57]**.

However, a second smaller RCT in 101 severely ill COVID-19 patients who were undergoing intermittent mandatory ventilation or extracorporeal membrane oxygenation, revealed a notable discrepancy in 28-day mortality rates. Baricitinib exhibited a mortality advantage of 39%, whereas the placebo group recorded a mortality rate of 58% **[58]**.

In the largest randomized controlled trial of baricitinib conducted thus far, a total of 8156 patients who were hospitalized were randomly assigned to receive either a daily dosage of baricitinib at 4 mg until either 10 days or their discharge from the hospital or to receive standard therapy. Baricitinib patients reported decreased mortality at 28 days than those who received standard therapy (age-adjusted RR 0.87) **[59]**.

Ruxolitinib was the first medicine licensed in the USA for the treatment of myelofibrosis **[60]**. Ruxolitinib has been used for the management of COVID-19 patients who are admitted to hospitals to increase survival by reducing lung harm caused by the cytokine storm **[61]**.

3.2.5. Fingolimod

Fingolimod, an FDA-approved therapeutic compound, functions as a small molecule modulator targeting subtype 1 of the sphingosine-1-phosphate receptor. This particular treatment has been authorized for the management of multiple sclerosis **[62]**. Fingolimod causes lymphocytes to be released from organs of the lymphatic system and lowers the inflammatory reaction **[63]**. This compound is now undergoing a phase 2 clinical study to modulate the immune action in patients who are badly affected by coronavirus disease **[29]**.

3.2.6. Aviptadil

Aviptadil is a combination of vasoactive intestinal polypeptide of 28 amino acids and phentolamine approved for the treatment of erectile dysfunction in Europe [64]. The vasoactive intestinal polypeptide is predominantly present in the nasal tissue and lungs. Aviptadil causes significant widening of airways, dilation of blood vessels, and anti-inflammatory effects, making it beneficial in the treatment of respiratory illnesses such as cystic fibrosis, breathing difficulties, sarcoidosis, and primary pulmonary hypertension **[65]**.

3.2.7. Thalidomide

A patient in China infected with coronavirus

disease 2019 was effectively treated with thalidomide and glucocorticoids **[66]**. Since its discontinuation from the market owing to embryotoxic consequences, thalidomide has been reutilized as an anti-cancer and anti-inflammatory agent **[67]**. The administration of thalidomide resulted in an extension of the average duration of life in BALB/c mice that had been subjected to H1N1 virus infection through the reduction of cytokine levels, specifically interleukin-6 and tumor necrosis factor-alpha. Similarly, individuals who experienced resolution from coronavirus disease following the administration of thalidomide and glucocorticoid therapy exhibited reduced levels of cytokines. These promising results encouraged the launch of phase II clinical trials to evaluate the efficacy of thalidomide in the management of coronavirus disease 2019 **[68]**.

3.3. Antiviral therapies

At the start of the pandemic, no antiviral medicines were approved for coronavirus disease therapy. As a result, several repurposed medicines proven to have an in-vitro antiviral efficacy have been incorporated into clinical practice and subjected to clinical investigations. In properly conducted randomized controlled trials, many commonly used drugs, such as lopinavir, ritonavir, ivermectin, and hydroxychloroquine have been demonstrated to be inefficient in treating coronavirus disease 2019 **[69-71]**; but more effective antivirals are now widely available.

3.3.1. Remdesivir

Remdesivir is an inactive precursor nucleoside analog with antiviral efficacy against numerous RNA viruses in laboratory conditions, involving SARS-CoV-2. Its active form lowers gene replication by blocking viral RNA polymerase **[72, 73]**.

Investigations of Remdesivir have been conducted on COVID-19 patients in both outpatient and inpatient settings. In clinical research, a three-day treatment of intravenous remdesivir in non-immunized outpatients who were at significant likelihood of disease advancement decreased 28-day hospitalization or mortality by 87% when compared with placebo (0.7 against 5.3 percent) **[74]**. In contrast, the extent of benefit from remdesivir was limited in patients receiving hospital treatment. A study, which involved 1062 patients, found that remdesivir reduced the recovery period (10 days) compared to placebo (15 days). Furthermore, the results showed that there was a trend towards reduced mortality within 29 days (11.4% in the remdesivir group versus 15.2% in placebo) **[75]**.

In the WHO Solidarity experiment, the biggest remdesivir randomized controlled trial up to now, 8275 patients receiving hospital treatment were assigned randomly to remdesivir or no study medication. Generally, remdesivir did not affect hospital mortality when compared to the control group (14.5% versus 15.6%), though it did reduce hospital death rate modestly among patients who did not require ventilator support at the beginning of treatment (11.9% versus 13.5%); Patients who were already on ventilator support at the commencement of treatment did not experience any advantages. Remdesivir received FDA approval on October 22, 2020, and EMA approval on July 3, 2020 **[76]**.

3.3.2. Nirmatrelvir–ritonavir

Nirmatrelvir-ritonavir is a treatment combination comprising of nirmatrelvir, an oral inhibitor of the 3C-like protease that targets the primary viral protease responsible for cleaving SARS-CoV-2 polyproteins during viral replication. It is accompanied by ritonavir, a potent CYP3A4 inhibitor and agent that enhances pharmacokinetics **[77]**. In a clinical study, that involved 2246 non-immunized adult outpatients with COVID-19 at an elevated risk of disease

progression, the combination therapy of Nirmatrelvir-ritonavir reduced the likelihood of hospitalization or death within 28 days by 89% compared to the placebo (0.7% against 6.5%). Nirmatrelvir-ritonavir got FDA clearance on December 22, 2021, and EMA approval on January 28, 2022 **[78]**.

3.3.3. Molnupiravir

Molnupiravir serves as an oral inactive precursor of -D-N4-hydroxycytidine (NHC), which is a cytidine analog displaying extensive antiviral activity against SARS-CoV-2 in laboratory conditions **[79]**. As novel RNA strands of the SARS-CoV-2 genetic material are produced, NHC is integrated, resulting in an accumulation of harmful mutations known as fatal mutagenesis. A clinical study involving 1433 adult outpatients who presented with mild-to-moderate infection observed a reduction in twenty-nine-day hospitalization or mortality by approximately 33% when utilizing molnupiravir, compared to a placebo. It is worth noting, however, that the efficacy of molnupiravir in achieving this outcome was found to be comparatively lesser than that of alternative antiviral treatments **[80]**.

3.3.4. Oseltamivir

Since 1999, the FDA has authorized oseltamivir, a nucleoside analog and neuraminidase inhibitor, for the prevention and treatment of influenza **[81, 82]**. Oseltamivir is also being studied as a COVID-19 therapy. In vitro investigations have so far revealed little effectiveness against SARS-CoV-2. Furthermore, Oseltamivir was evaluated on a small number of coronavirus disease patients in China and no advantages were found **[83]**.

3.3.5. Triazavirin

Since 2015, the new antiviral agent, Triazavirin (TZV), has been accessible in Russia. TZV's principal mode of action is to block the production of viral RNA and the replication of viral genomic fragments via its synthetic counterpart to purine nucleoside bases **[84]**.

It was found to considerably reduce the length of the primary clinical symptoms of influenza (intoxication, fever, and respiratory symptoms) as well as the incidence of influenza-related complications and the usage of symptomatic medicines in a phase II clinical study **[85]**.

Due to its antiviral properties, triazavirin has demonstrated potential in a pilot trial for the management of COVID-19 by generally lowering inflammatory responses and so minimizing damage to important organs and the need for therapeutic assistance **[86]**.

3.4. Repurposed Drugs

It is also known as drug re-tasking, reprofiling, or repositioning which is a method of discovering new therapeutic applications for authorized medications. The study and approval of new pharmaceutical treatments for SARS-CoV-2, along with their clinical effectiveness, will require extensive research efforts and a prolonged administrative review period. Due to the elevated transmissibility and fatality rate linked to the infection caused by the SARS-CoV-2 virus, scientists are actively seeking an authorized medicine that could potentially be repurposed to target SARS-CoV-2 **[87]**.

Scientific researchers used affinity mass spectroscopy to discover numerous targets involved in different phases of viral replication and disease to assess possible candidates for repurposing [88]. From the SARS-CoV-2-human interactome, chemoinformatic analysis revealed 66 human target proteins. At various phases of clinical or pre-clinical development of SARS-CoV-2 treatment, these proteins have the potential to function as a prospective molecular

target through the utilization of drugs that have been repurposed **[29]**.

3.4.1. Chloroquine/Hydroxychloroquine

In 1949, the FDA granted authorization to chloroquine (CQ), a medication used for treating malaria and amoebicidal infections. Hydroxychloroquine (HCQ), which is derived from chloroquine (CQ), is approved for the treatment of rheumatoid arthritis, malaria, and systemic lupus erythematosus, and is known for having a more favorable safety profile. CQ and HCQ function by inhibiting the heme polymerase enzyme in trophozoites, leading to the accumulation of toxic heme and the demise of the parasites **[29]**.

In vitro studies have reported the antiviral effects of CQ against various strains of coronaviruses, such as HCoV-229E **[89]**, SARS-CoV [90], and MERS-CoV **[91]** indicating its potential as a repurposed drug. In a study involving pregnant mice infected with HCoV-O43, administration of CQ (at a dosage of 5 mg/kg) resulted in a survival rate of 88% among newborn mice, compared to only 20% in untreated mice six days after infection **[92]**. Similarly, recent studies have confirmed the in vitro half maximal effective concentration (EC50) of CQ against SARS-CoV-2 to be 1.13 μM, while the EC90 was found to be 6.9 μM **[93]**. Moreover, it has been demonstrated that CQ exhibits greater efficacy at lower doses, with an EC50 of 2.71 μM, compared to HCQ which has an EC50 of 4.51 μM **[94]**.

Chloroquine's (CQ) antiviral effect is attributed to its ability to acidify endosomes/ lysosomes, thereby disrupting the fusion, replication, and release of the SARS-CoV virus from the host cells. Furthermore, CQ has been observed to inhibit the glycosylation process of the ACE2 enzyme, preventing viral entrance into host cells. In light of these encouraging findings, the effectiveness of HCQ and CQ is being investigated in 117 clinical trials for the treatment of COVID-19. The initial findings of a trial involving 100 patients revealed that CQ outperformed the control group in terms of effectiveness **[29]**.

Similarly, in a clinical study involving 62 patients, HCQ was shown to be moderately successful, as 80.6% of individuals displayed amelioration in pneumonia **[95]**. On March 28, 2020, the FDA issued an emergency use authorization (EUA) for hydroxychloroquine sulfate and chloroquine phosphate, allowing their use in the treatment of hospitalized patients with COVID-19. Subsequent clinical research involving a cohort of 368 individuals within the confines of US veterans' medical facilities found that using HCQ either in isolation or in conjunction with azithromycin did not yield a diminished likelihood of mechanical ventilation, but instead exhibited an escalation in overall mortality **[96]**.

3.4.2. Antithrombotic therapies

It has been observed that COVID-19 patients who are hospitalized frequently have a significant infection-related coagulation disorder as well as an elevated likelihood of microvascular blood clot formation. Anticoagulants may have a good impact here, lowering the burden of thrombotic illness and coagulation hyperactivity, and they may also have direct anti-inflammatory benefits against sepsis and the development of ARDS. Heparins, especially unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH) are known to have numerous non-anticoagulant characteristics and to have anti-inflammatory effects **[97] (Table 2)**.

Table 2. Showing the effect of use of antithrombotic agents on COVID-19 clinical outcomes

Reference	Setting	Number of subjects	Duration	Demographics and disease conditions	Antithrombotic agents used and clinical outcomes
[98]	Prospective uncontrolled observational study	*n* = 16	Follow-up period is not specified, at least seven to fourteen days.	• The median age was 61 years. • 94% of the participants were male. • The baseline intubation time was 7 days. • The percentage of participants with specific comorbidities were as follows: BMI > 30 (5%), diabetes (20%), cardiovascular disease (16%), tobacco use (24%), and prior DVT (4%).	• Administration of a comprehensive thromboprophylaxis regimen involving LMWH, antithrombin, and clopidogrel • There were no major thromboembolic events observed, with a rate of 0 out of 16 cases (0%). • During the observation period, 7 out of 16 cases (43.7%) resulted in mortality. • Six out of 16 cases (37.5%) were discharged from intensive care. • All 16 cases (100%) exhibited a pro-coagulation profile at baseline, characterized by elevated levels of fibrinogen and D-dimer. • After receiving increased thromboprophylaxis at day 14, 9 out of 16 cases (56.3%) showed a progression towards a normal coagulation profile, evidenced by decreased clot stiffness, platelet contribution to clot stiffness, and fibrinogen contribution to overall clot stiffness.
[99]	Retrospective cohort	*n* = 449	January 1–February 13, 2020	• The mean age was 65 years. • 60% of the participants were male. • The percentage of participants with specific comorbidities were as follows: hypertension (40%), diabetes (21%), and cardiovascular disease (9.1%).	• The administration of thromboprophylaxis using either UFH or LMWH. • Out of 449 cases, the 28-day mortality rate was 29.8% (134 cases).
[100]	Case series	*n* = 3	NR	• Case 1: A 75-year-old man diagnosed with hypertension, hyperlipidemia, type 2 diabetes mellitus, and coronary artery disease. • Case 2: A 59-year-old female with a history of hypertension. • Case 3: A 49-year-old male with no reported medical history.	• The administration of tPA with or without heparin. • Case 1: Showed a temporary improvement in the PaO2/FiO2 (P/F) ratio, but unfortunately passed away three days later. • Case 2: Demonstrated a minor improvement in the P/F ratio, increasing from 90 to 135 after three days. • Case 3: Experienced a temporary improvement in the P/F ratio, necessitating the use of proning.

3.5. Therapies for Acute Respiratory Failure

The most essential treatment objective is to maintain respiratory function by supporting appropriate gas exchange and, most importantly, sufficient blood oxygenation. Because of its availability, convenience of use, and capacity to monitor this essential parameter continuously, transcutaneous pulse oximetry should be employed in the evaluation of blood oxygenation. Assessment of the partial pressure of oxygen (PaO2) should be utilized only if there are concerns about the accuracy of the SpO2 measurement or if hypercapnia is suspected **[101]**. Currently, the WHO advises maintaining SpO2>94% in recommendations for the management of COVID-19 respiratory failure **[102]**.

Conventional (passive) oxygen therapy: Passive oxygen treatment refers to spontaneously inhaling air with a higher oxygen content,

defined as a FiO2 of 0.22 to 1.0 (22% to 100%). This therapy can be carried out using a nasal cannula, a simple oxygen mask, a venturi mask, and a non-rebreather mask **[103]**.

High-flow nasal oxygen therapy: High-flow nasal oxygen treatment (HFNOT) is the administration of high-flow air (10-60 L/min.) enhanced with oxygen at concentrations ranging from 22% to 100% using nasal prongs. Furthermore, the gas combination is moistened and heated to 31-37 °C, which closely mimics the natural conditions in the nasal cavity. As a result, the patient tolerates high airflow well. This would be impossible to do with dry, chilly gas **[104]**.

Active oxygen therapy: It refers to the intake of positive pressure (greater than atmospheric pressure) inspiratory gases. Positive airway pressure can be administered invasively by intubating the patient and initiating mechanical breathing, or it can be administered non-invasively by various types of interfaces (masks) attached to the patient's face. Positive airway pressure serves several functions, including recruiting alveoli and increasing gas exchange area, as well as preventing atelectasis in the lung parenchyma **[101]**.

3.6. Neutralizing antibody therapies

Convalescent plasma exhibited potential in the initial stages of treating patients with COVID-19. However, the overall findings from phase 3 clinical trials have been underwhelming due to inconsistencies in the levels of neutralizing antibodies (nAbs) and the lack of standardized dosing among patients. Pharmaceutical-grade monoclonal neutralizing antibodies (nAbs) have overcome these limitations and have emerged as the primary therapies specifically designed for SARS-CoV-2 [104].

Only a limited quantity of neutralizing antibodies (nAbs) has previously undergone the necessary approval process and have been utilized in the clinical management of viral ailments. Examples include palivizumab, which is employed as a prophylactic measure against Respiratory Syncytial Virus, as well as the more recent developments in Ebolavirus disease treatments, such as the employment of a solitary nAb (ansuvimab-zykl) as a form of monotherapy and the utilization of a triple monoclonal nAb cocktail (REGN-EB3). Many nAbs are currently under investigation for their potential in treating ambulatory COVID-19 patients. However, comprehensive data regarding their efficacy is only available for the solitary nAb known as bamlanivimab and the combination of bamlanivimab/etesevimab, as well as the nAb combination of casirivimab and imdevimab **[104] (Table 3)**.

In the BLAZE-1 (NCT04427501) trial, which focused on the ambulatory phase 2/3 of bamlanivimab, it was discovered that the virological impact varied among the 452 randomized patients. A noteworthy decrease in average viral load was observed solely in the cohort that received a dosage of 2800 mg (p= 0.02), while the group that received the lower dosage of 700 mg (p= 0.38) and the group that received the highest dosage of 7000 mg (p= 0.70) did not exhibit this reduction. It is worth noting that the doses administered were fixed, rather than weight-based. The underlying causes for these disparities remain unclear, although one possibility is the manifestation of the "prozone effect," whereby the abundance of antibodies may impede the development of immune complexes. Moreover, the administration of bamlanivimab led to a decrease in the number of patients necessitating hospital care or emergency department visits. Only 1.0% of patients who received doses of 700 mg, 1.9% who received doses of 2800 mg, and 2.0% who received doses of 7000 mg required such measures, as opposed

to the considerably higher rate of 6.3% observed in patients who were administered a placebo **[105]**.

Table 3. Clinical efficacy and Safety Data Comparison for Neutralizing Antibodies in the Treatment of Ambulatory COVID-19 Patients

Drug	Dosing regimen	Patient population	Virological efficacy	Clinical efficacy	Safety profile
			Viral load change at 11 days from baseline	Hospital care needs or emergency visits	Incidence of serious adverse events
Bamlanivimab	(700 mg, 2800 mg, or Single dose of 7000 mg)	Treatment N= 309	Treatment -3.70	Treatment 1.6%	Treatment 0.0%
		Placebo N= 143	Placebo -3.47	Placebo 6.3%	Placebo 0.7%
			Viral load change at 11 days from baseline	Hospital care need or mortality	Incidence of serious adverse events
Bamlanivimab & etesevimab	Single dose (2800 mg per nAb)	Treatment N= 109	Treatment -4.37	Treatment 2.1%	Treatment 0.9%
		Placebo N= 152	Placebo -3.80	Placebo 7.0%	Placebo 0.6%
			Viral load change at 7 days from baseline	Hospital care need or mortality	Incidence of serious adverse events
Casirivimab & imdevimab	Single dose (1200 mg per combination)	Treatment N= 736	Treatment Not yet available	Treatment 1.0%	Treatment 1.1%
		Placebo N = 748	Placebo Not yet available	Placebo 3.2%	Placebo 4.0%
			Viral load change at 7 days from baseline	Hospital care need or mortality	Incidence of serious adverse events
Casirivimab & imdevimab	Single dose (2400 mg per combination)	Treatment N= 1355	Treatment Not yet available	Treatment 1.3%	Treatment 1.3%
		Placebo N= 1341	Placebo Not yet available	Placebo 4.6%	Placebo 4.0%

Predominantly founded on the decrease in the necessity for subsequent employment of healthcare resources, the FDA in the United States has officially granted Emergency Use Authorization for bamlanivimab 700 mg dose. This authorization specifically pertains to the management of patients who can walk around and possess a high probability of advancing toward a critical state of COVID-19, which may include hospitalization **[106]**.

The current investigation known as the BLAZE-1 study is presently engaged in evaluating the amalgamation of bamlanivimab and etesevimab in ambulatory coronavirus disease 2019 patients. The scientific data derived from 577 patients revealed an added efficacy stemming from the bamlanivimab/etesevimab cocktail, which was correlated with a noteworthy decrease in log10 viral load (- 0.57) compared to the placebo ($p = 0.01$). However, the utilization

of bamlanivimab as a sole therapeutic agent did not produce remarkable reductions **[107]**.

Compared to the administration of a placebo, it was also demonstrated that bamlanivimab/etesevimab exhibited a decrease in the occurrence of hospital care (2.1 versus 7 percent; resulting in a risk mitigation of 70%, p= 0.0004) as well as fatalities (0 versus 10) amongst a total of 1035 patients. Consequently, the FDA extended an Emergency Use Authorization for bamlanivimab/etesevimab utilization in the management of mild to moderate cases of coronavirus disease 2019 in patients aged 12 years old or above who are afflicted with coronavirus disease 2019 and possess a heightened susceptibility to transitioning into a more severe illness **[108]**.

The cocktail of nAbs casirivimab and imdevimab is currently under investigation in an outpatient setting in a clinical trial being conducted across multiple countries. The study (N = 4567) has reported its findings, which evaluated the effectiveness of 1200 mg or 2400 mg casirivimab/imdevimab in comparison to a placebo among patients with at least one risk factor for severe COVID-19. The study successfully achieved its primary objective and demonstrated that the casirivimab/imdevimab combination remarkably reduced the likelihood of need for hospital care or death by 70% in patients who received doses of 1200 mg (p = 0.0024) and 71% in patients who received doses of 2400 mg (p<0.0001) when compared to placebo **[109]**.

3.7. Vitamins and supplements

The sales of dietary supplements that are marketed for the enhancement of the immune system experienced a surge following the emergence of the COVID-19 pandemic. This occurred due to the widespread hope among individuals that these particular products could potentially offer some level of protection against the SARS-CoV-2 infection. Furthermore, it was believed that these supplements could also aid in reducing the severity of the disease for those who contracted COVID-19 **[110-113]**.

It is widely recognized that individuals require various vitamins and minerals, such as vitamin C, vitamin D, and zinc, to maintain proper immune function. In instances where there is a clinical deficiency of these essential nutrients, one's susceptibility to infections can be significantly heightened **[114, 115]**. On the other hand, certain ingredients found in nutritional supplements, such as herbals and probiotics, are not deemed vital to bodily functions but are believed to potentially impact immune system activity.

Evaluating the influence on the immune system of vitamins, minerals, and other constituents of nutritional supplements poses a formidable challenge due to the intricate interconnections of organs, tissues, and cells within the immune system. The absence of a single, unambiguous metric for immune system functionality and resistance to diseases is evident. Alternatively, an individual's vulnerability to infectious diseases and the gravity of associated symptoms may serve as indirect indicators of immune function **[116]**.

Ginseng is the general appellation assigned to many varieties within the Panax genus, most notably *Panax ginseng* (also referred to as Asian ginseng or Korean ginseng) and *Panax quinquefolius* (commonly known as American ginseng) **[117]**. Triterpene glycosides, which are alternatively referred to as ginsenosides, are regarded as the primary purported active components of ginseng **[118]**.

Several clinical trials have investigated the potential of ginseng in preventing upper respiratory tract infections, including the

common cold and influenza. However, the findings from these studies have yielded inconsistent results, and none of them specifically addressed the role of ginseng in the context of COVID-19 **[119]**. Given the limited evidence available on the effects of ginseng on immune function and its therapeutic potential for upper respiratory tract infections, certain researchers suggest further exploration of ginseng as an adjunctive treatment for COVID-19 **[120]**.

Quercetin is a polyphenolic compound known as a flavonol and can be found in a variety of spices, fruits, vegetables, and beverages. These include dill, tea, citrus fruits, apples, onions, berries, broccoli, cilantro, and red wine **[121, 122]**. Research studies indicate that quercetin may possess antiviral, anti-inflammatory, antioxidative, and immunomodulatory properties **[123]**. It might also inhibit platelet aggregation **[123]**. Quercetin exhibits a notably low oral bioavailability, estimated to range between 3-17 percent **[122]**, however, when sunflower lecithin is combined with quercetin, its bioavailability experiences a remarkable enhancement, potentially reaching up to 20-fold **[123]**.

In a clinical trial conducted in Pakistan, a total of 152 adults ranging from 18 to 80 years old, who were diagnosed with coronavirus disease 2019 and exhibited minor to moderate symptoms but were not required to be admitted to the hospital, were categorized into two distinct groups. The initial group was administered Quevir, a supplementary treatment comprising 200 mg of quercetin in conjunction with sunflower lecithin, twice per day along with the standard medical regimen (including fever-reducing drugs, oral steroids, analgesics, and antibiotics), while the second group solely received the standard medical care for a period of 30 days. The individuals who were provided with quercetin supplements demonstrated a significantly lower likelihood of requiring hospitalization compared to those who were not given such supplements. Moreover, it was observed that the duration of hospital stays for patients who necessitated hospitalization was comparatively shorter in cases where they had been administered quercetin supplements **[124]**.

The addition of Quercetin as a supplement resulted in a decrease in the need for oxygen therapy. In a subsequent study conducted, an open-label investigation was carried out to compare the effects of quercetin supplementation with the standard of care. The study involved 42 adults diagnosed with mild to moderate COVID-19 who were not hospitalized. Quercetin supplementation was administered three times a day, with a total dose of 600 mg per day of quercetin for seven days, followed by 400 mg per day for an additional seven days. After one week of treatment, 16 out of 21 individuals who received quercetin alongside the standard of care showed negative SARS-CoV-2 test results, whereas only 2 out of 21 patients in the standard-of-care group displayed negative results. Following two weeks of treatment, all patients who received quercetin and the standard of care exhibited negative SARS-CoV-2 test results, along with 19 out of 21 patients in the standard-of-care group **[125]**.

Probiotics are viable microorganisms that provide a positive impact on the host's health when administered in sufficient quantities. Examples of bacteria are (*Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacterium longum*) and yeasts (e.g., *Saccharomyces boulardii*). Probiotics occur naturally in certain fermented foods, are incorporated into select food items, and can also be obtained as dietary supplements **[126]**.

Probiotics primarily affect the gastrointestinal system. They may promote immune function in a variety of ways, including improving gut barrier role, elevating

immunoglobulin synthesis, blocking virus replication, besides, increasing white blood cell phagocytic activity. However, the mechanisms behind their possible impacts on immunological function remain unknown **[127, 128]**.

A meta-analysis of 42 randomized clinical trials involving 2,258 participants found that probiotic supplementation, specifically with lactobacillus, bifidobacteria, saccharomyces, or combinations of strains, for durations ranging from 1 to 52 weeks, significantly decreased serum levels of certain proinflammatory cytokines, including C-reactive protein, tumor necrosis factor-alpha, interleukin-2, and interleukin-6. However, the treatment did not have an impact on the levels of other proinflammatory cytokines, such as interleukin-8 and interleukin-17. This suggests that probiotics may have a beneficial effect in reducing inflammation **[129]**.

Due to these observations, numerous scholars posit that probiotics may serve as valuable supplementary treatments for the management of COVID-19 **[130]**. In Italy, a clinical trial was conducted involving 70 hospitalized patients (with a median age of 59 years) who had coronavirus disease 2019. All patients received a combination of hydroxychloroquine, antibiotics, and tocilizumab (a monoclonal antibody), either individually or in various combinations. Additionally, 28 of the 70 patients were given a probiotic supplement containing a mixture of Streptococcus, Lactobacillus, and Bifidobacterium strains. These patients took the probiotic three times a day, resulting in a total daily dose of 2,400 billion bacteria, for a duration of 14 days. Notably, within 7 days, patients who took the probiotic experienced significantly reduced manifestations and symptoms, such as diarrhea, fever, weakness, headaches, muscle pain, and difficulty breathing, compared to those individuals on standard treatment only. Moreover, the use of probiotics also decreases the likelihood of death, the need for an Intensive Care Unit (ICU), and respiratory failure **[131]**.

Another clinical trial was carried out to determine the impact of a combination of an enzyme and probiotic on a group of 200 adults (with a mean age of 41 years) suffering from fatigue and muscle weakness that occur after recovering from a COVID-19 infection. All participants had previously tested negative for coronavirus three weeks before the trial. The treatment included the administration of capsules containing 500 mg of ImmunoSEB and 5 billion CFU of ProbioSEB CSC3. The subjects were advised to take 2 doses in the morning and the evening before meals, and an additional 2 doses with lunch. The researchers assessed the level of fatigue by asking questions related to fatigue, difficulty initiating a piece of work, shortage of energy or muscle power, trouble concentrating, and memory problems. After 14 days of treatment, it was observed that fatigue alleviated in 91% of subjects who received the ImmunoSEB and ProbioSEB capsule, while only 15% of those who were given a placebo reported a comparable alleviation of fatigue **[132]**.

Zinc plays a role in various aspects of cellular metabolism. Zinc is important for the catalytic activity of approximately 100 enzymes and plays a role in multiple bodily functions, including the functioning of the innate and adaptive immune systems **[133]**.

Zinc contains antiviral and anti-inflammatory qualities. Moreover, it aids in tissue barrier maintenance like epithelial cells of the respiratory system. Furthermore, zinc is required for the proper functioning of the taste and smell senses **[134]**.

Zinc deficiency impairs immune function by affecting lymphocyte production, activation, and maturation. Furthermore, zinc deficiency reduces

the ratios of helper and suppressor T cells, as well as the synthesis of IL-2 and the activity of NK-cells and cytotoxic T cells **[135]**. Furthermore, insufficient zinc levels have been associated with elevated levels of proinflammatory mediators **[134]**. These immune-related consequences most likely enhance susceptibility to infections **[136]** and inflammatory illnesses, particularly those affecting the lungs **[134]**.

Certain scholars propose that the consumption of adequate amounts of zinc may lessen the occurrence and intensity of COVID-19. This is attributed to zinc's role in bolstering the immune system and preserving the integrity of epithelial cells, as well as its antiviral, and anti-inflammatory properties **[137, 138]**.

A study was conducted wherein 249 patients (with a median age of 65 years) suffering from COVID-19 were observed during their hospitalization in Spain. The study discovered that patients who had serum zinc concentrations below the threshold of 50 mcg/dL upon admission exhibited more pronounced symptoms, experienced a longer duration of recovery (with a median of 25 days as opposed to 8 days), and exhibited a greater fatality rate (21% compared to 5%) when contrasted with their counterparts possessing higher zinc levels **[139]**.

A comparable investigation conducted in India elucidated that 47 patients who required hospital care due to coronavirus disease, with a median age of 34 years, exhibited a diminished level of zinc in their blood serum upon admission (74.5 mcg/dL) in comparison to a control cohort of 45 randomly selected healthy subjects who did not admitted to the hospital. The control group had a median age of 32 years and a median serum zinc concentration of 105.8 mcg/dL. It is worth noting that despite these values falling within the normal range, the disparity in median values between the two groups was apparent **[140]**.

Furthermore, COVID-19 patients exhibiting zinc levels below 80 mcg/dL were found to be at a heightened risk of complications compared to those with higher levels. In Germany, a study involving 35 hospitalized patients (with a median age of 77 years) revealed a notable decrease in mean blood zinc concentrations (measuring at 71.7 mcg/dL), particularly among the six patients who succumbed to the disease. This decline in zinc levels was in stark contrast to a control group consisting of randomly selected healthy individuals, whose blood zinc concentrations measured at 97.6 mcg/dL **[141]**.

Hypozincemia, on the other hand, is a constituent of the acute-phase response in the context of infection, and the levels of zinc can similarly decrease considerably due to acute physiological stress **[142]**.

Vitamin C is crucial in both innate and adaptive immunity, most likely due to its antioxidant properties, antibacterial and antiviral properties, and effects on immune system modulators **[143]**. Vitamin C aids in the maintenance of the structural integrity of epithelial cells, the differentiation and proliferation of B and T cells, the enhancement of the process of phagocytosis, the normalization of cytokine production, and the release of histamine **[144]**. It may also prevent viral replication **[145]**.

Vitamin C insufficiency weakens immune function and makes you more susceptible to illnesses **[144]**. Some evidence shows that taking vitamin C supplements improves immune function **[146]**, however, the results may differ based on an individual's vitamin C status **[147]**.

In a modest clinical study in Mexico, 22 individuals who were admitted to the hospital due to pneumonia caused by COVID-19, and with an average age of 57.9 years, were administered a dosage of 1,000 mg of vitamin C every 12 h for a duration of 5 days. Additionally, these patients

were also given the pentoxifylline medication **[148]**. It was observed that those patients who received both vitamin C and pentoxifylline exhibited notably lower levels of the inflammatory markers interleukin-6 and procalcitonin compared to those who solely received pentoxifylline. The combination of vitamin C and pentoxifylline significantly enhanced the overall antioxidant capacity, whereas the administration of pentoxifylline alone did not yield similar effects **[149]**.

Notably, both treatments resulted in a substantial increase in nitrite levels (indicating higher oxygen levels) when compared to baseline values, as well as a decrease in levels of the inflammatory marker C-reactive protein. However, neither treatment led to an improvement in the lipid peroxidation index. Moreover, the COVID A to Z study aimed to evaluate the potential benefits of daily supplementation with 8,000 mg of ascorbic acid, 50 mg of zinc (in the form of zinc gluconate), or a combination of both for a duration of 10 days, alongside standard care, in 214 individuals with coronavirus who were not admitted to the hospital. Regrettably, none of the aforementioned supplements were found to reduce the duration of symptoms **[149]**.

3.8. Vaccines

Mass immunization against the SARS-CoV-2 pathogen has played a pivotal role in curtailing the ramifications of the coronavirus disease 2019 outbreak **[150]**. However, the levels of antibodies generated by the vaccine decline six months after the initial COVID-19 vaccination regimen, which consists of either two doses of a two-dose vaccine or one dose of a single-dose vaccine **[151]**. Additionally, the efficacy of the vaccines in preventing infections and hospitalizations when compared to unvaccinated individuals **[152]** might also decrease between two to seven months following the completion of the primary vaccination regimen. The potential decrease in the efficacy of vaccines could be amplified by the appearance of novel variants that are of particular concern. Nevertheless, there exists a range of research studies that examine the durability of COVID-19 vaccines over an extended period, which differ in terms of their design, approach, and caliber, and have produced a wide array of results. Consequently, policy makers face considerable difficulty in formulating evidence-based decisions, such as determining the optimal timing for administering booster doses of the COVID-19 vaccine **[153]**.

It has been observed that the efficacy of the initial vaccine regimen in preventing SARS-CoV-2 infections starts at a satisfactory level, as defined by the World Health Organization, at 83% between 14 to 42 days after completing the regimen. Nevertheless, the effectiveness of the vaccine notably declined by 112 days post-vaccination, reaching 47% by 280 days after vaccination, which is considerably below the acceptable threshold **[153]**.

For COVID-19 hospitalizations and mortality, the efficacy of the vaccine was deemed satisfactory at the outset, surpassing the 90% threshold. However, this effectiveness declined after 112 days following vaccination. Nevertheless, the vaccine's efficacy remained commendably high over time, exceeding 75%. Upon analyzing exclusive omicron data, we observed similar patterns of waning efficacy, with the exception being that the initial levels of vaccine effectiveness did not attain the required standard for preventing infections or hospitalizations. It remains unclear as to what factors are driving these omicron-related patterns, such as a potential degradation in immunogenicity, alterations in public health measures, fluctuations in case numbers and general transmission, or a combination of these aforementioned factors **[153]**.

Although there may be promising prospects for boosters in terms of reinstating certain levels of protection, our findings indicate that the initial effectiveness of boosters (within 7-28 days of administration) still falls slightly below the recommended thresholds set by the World Health Organization. Furthermore, over time, these figures experience a further decline. The estimates presented here primarily pertain to mRNA vaccines targeting the omicron variant, thereby reflecting the prevailing conditions in numerous countries. Cumulatively, these data imply that vaccines continue to offer reasonably consistent safeguards against hospitalization and mortality in the long run, albeit with a more modest level of protection against infections **[153] (Table 4)**.

Table 4. Comparing different treatment modalities in COVID-19

Therapy	Number of subjects	Disease conditions	Clinical outcomes	Ref
Dexamethasone at a daily dosage of 6 mg for a maximum duration of ten days.	6425	Adult patients with covid-19	The dexamethasone group had a lower mortality outcome at 28 days, with a rate of 22.9 compared to 25.7 percent in the comparison group	**[26]**
Tocilizumab	755	Critically ill adult patients with COVID-19	Patients who were given tocilizumab had significantly lower in-hospital mortality (28 versus 36 percent), as well as lower 90-day mortality	**[35]**
Tocilizumab	4116	Adult patients with covid-19	Patients who were assigned to receive tocilizumab had a lower mortality rate at 28 days (31 versus 35 percent)	**[36]**
Interferon IFNα2b	-------	Adult patients with covid-19	Viral load and levels of the inflammatory cytokine IL-6 were decreased with or without arbidol	**[51]**
Baricitinib at a daily dosage of 4 mg, for a maximum duration of fourteen days, along with Remdesivir	1033	Adult patients with covid-19	The combination of baricitinib and remdesivir was more effective than remdesivir alone in reducing the time to recovery	**[56]**
Baricitinib at a daily dosage of 4 mg for a maximum of fourteen days	1525	Adult patients with covid-19	The baricitinib group had significantly lower 28-day mortality compared to the placebo group (8 versus 13 percent)	**[57]**
Remdesivir Intravenous (i.v.) administration for three days	-------	Unimmunized outpatients with covid-19 at a high risk of disease progression	The reduction in 28-day needs for hospital care or death compared to placebo was 87 percent	**[74]**
Remdesivir	1062	Adult patients with covid-19	Remdesivir resulted in a shorter time to recovery compared to the placebo group (10 days versus 15 days), and also lower 29-day mortality (11.4 versus 15.2 percent)	**[75]**
Nirmatrelvir–ritonavir	2246	Unvaccinated adult outpatients with covid-19 at a high risk of disease progression	The risk of 28-day hospitalization or death was reduced by 89% compared to the placebo group (0.7 versus 6.5 percent)	**[78]**
Molnupiravir	1433	Adult outpatients with mild-to-moderate covid-19	The treatment reduced the incidence of 29-day hospitalization or death by approximately one-third compared to placebo (6.8 versus 9.7 percent)	**[80]**

Hydroxychloroquine	62	Adult patients with covid-19	80.6% exhibited improvement in their pneumonia condition	**[95]**
Bamlanivimab	452	Adult patients with covid-19	Only the dose group receiving 2800 mg showed a significant reduction in mean viral load. Additionally, there were fewer patients requiring hospital care or emergency department visits.	**[105]**
Bamlanivimab / etesevimab	577	ambulatory COVID-19 patients	There was a significant reduction in the log10 viral load (−0.57) compared to placebo ($p = 0.01$)	**[107]**
Bamlanivimab / etesevimab	1035	Adult patients with covid-19	The treatment resulted in a reduced number of hospitalizations (2.1 versus 7 percent) and deaths (0 versus 10 percent)	**[108]**
Casirivimab/imdevimab	4567	Adult patients with covid-19	A notable decrease in the likelihood of being hospitalized or experiencing mortality by a substantial 70% when taking the 1200 mg dosage, and a slightly higher 71% reduction when taking the 2400 mg dosage, as compared to the administration of a placebo.	**[109]**
Quercetin at a dosage of 200 mg administered twice per day, with the standard of care for a period of 30 days	152	Adult patients with mild to moderate symptoms of COVID-19 who did not require hospitalization	Significantly less likely to require hospitalization. Shorter hospital stays if required.	**[124]**
Quercetin 600 mg per day for a duration of seven days, followed by a reduced dosage of 400 mg per day for an additional seven days	42	Adult patients with mild to moderate symptoms of COVID-19 who did not require hospitalization	It was observed that all individuals who were administered quercetin in conjunction with the standard of care protocol exhibited unfavorable SARS-CoV-2 test outcomes.	**[125]**
Streptococcus, Lactobacillus, and Bifidobacterium strains three times daily, totaling 2400 billion bacteria per day, for a duration of fourteen days, in addition to standard of care	70	Adult patients with covid-19	individuals using the probiotic experienced considerably less diarrhea, fever, asthenia, headaches, myalgia, and dyspnea than those who did not. Reduced the chance of death, ICU transfer, and respiratory failure.	**[131]**
ImmunoSEB 500mg and ProbioSEB CSC3 5 billion CFU (The dose: two capsules in the morning and two in the evening on an empty stomach, plus two capsules with lunch) for 14 days	200	post-COVID tiredness and muscular weakness in patients who had a negative test result three weeks before	Fatigue was alleviated in 91% of those who took the enzyme and probiotic supplement, but just 15% of those who took the placebo.	**[132]**
Zinc	249	Adult patients with covid-19	Patients with blood zinc levels less than 50 mcg/dL had more severe illness upon admission, took longer to recover (median of 25 versus 8 days), and died at a greater rate (21 versus 5 percent).	**[139]**
1000mg of Vitamin C every 12 hours for a span of 5 days, in addition to pentoxifylline	22	Adult patients with covid-19	Interleukin-6 and procalcitonin levels were lower than at baseline in individuals who got pentoxifylline alone, but not in those who did not	**[148]**
Ivermectin	-----	Cell culture (Vero/hSLAM cells)	Ivermectin treatment resulted in a 93% and 99.8% reduction in supernatant and cell-associated viral RNA, respectively, at 24 hours compared to controls. This effect amplified to a 5000-fold decrease in viral RNA by 48 hours.	**[154]**
Favipiravir	240	COVID-19 patients	A clinical trial compared favipiravir and arbidol	**[155]**

			in COVID-19 patients. While recovery time remained similar, favipiravir significantly reduced fever duration and cough with mild adverse effects.	
Combination of Azithromycin and hydroxy-chloroquine (AZT + HCQ)	36	COVID-19 patients	Clinical follow-up revealed improved vital signs, shorter hospital stays, and reduced mortality in patients treated with azithromycin and hydroxychloroquine, who also achieved negative COVID-19 tests after 10 days.	**[156]**
Azithromycin (AZT)	-----	Infected cell-based assay	AZ exhibits antiviral activity by inhibiting viral entry and increasing host cell pH. In vitro, AZ displayed an EC50 of 2.12 mM against SARS-CoV-2 after 72 hours at a low multiplicity of infection (0.002).	**[157]**
Antiviral/herbal (Chinese traditional medicine) Shuang Huang Lian (SHL)	3 Family Case reports	COVID-19 patients	SHL treatment achieved rapid resolution of all symptoms in COVID-19 patients unresponsive to standard therapies, with no observed adverse effects.	**[158]**

Conclusion

The review discusses different therapeutic modalities for COVID-19 management, including the use of bamlanivimab with etesevimab, fingolimod, vitamin C, and pentoxifylline, and other treatment options. The findings of this review imply that hydroxychloroquine and remdesivir have displayed promising outcomes in clinical settings. Reduced mortality rates in the tocilizumab group compared to controls were noticeable. The use of bamlanivimab with etesevimab together showed a remarkable decrease in viral load, while bamlanivimab monotherapy did not. Fingolimod, a small molecule modulator, is being studied for its potential to regulate the immune response in severely infected coronavirus disease patients. A small clinical study in Mexico found that the combination of pentoxifylline and vitamin C resulted in lower levels of inflammatory markers. Finally, covid-19 vaccination showed promising protection against covid-19 infection, reduced hospitalization rates, and lower mortality rates.

Declarations

Consent to publish

All authors have read and agreed to the published version of the manuscript

Ethics approval and consent to participate

Not applicable.

Availability of data and material

All data generated or analyzed during this study are included in this published article in the main manuscript.

Conflict of Interest

The authors assert that there are no conflicts of interest.

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Authors Contribution

All authors contributed to the study's conception and design. Material preparation, data

collection, and analysis were performed by Sara Samir Mohamed Elmenshawy, Mohamed Farouk Ahmed Abdelsalam, and Tarek Refaat El Nagdy. The first draft of the manuscript was written by Sara Samir Mohamed Elmenshawy and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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