WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Covid-19: Different Approaches in Treatment

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ABSTRACT:

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the virus strain that caused coronavirus disease 2019 (COVID-19).SARS-CoV-2, an emerging zoonotic coronavirus, identified in December 2019 in Wuhan, Hubei province, China, has spread rapidly across the whole world, causing disproportionately high morbidity and mortality, along with unprecedented disruptions in the global economy and society functioning .The World Health Organization declared the outbreak of the novel coronavirus (COVID-19) as a global health emergency on January 30, 2020, and as a pandemic disease on March 11, 2020. Although exploration for a specific drug required for the COVID-19 treatment is under extensive research worldwide and some of them are in clinical trial now. Virtual drug library screening is one of the current techniques for repurposing accessible compounds .This review highlights the current and new therapeutical approaches, risk factors, and related protections to be taken as prerequisite measures and probable treatment options for the COVID-19-infected population in the current scenario.

Keywords- COVID-19, SARS-CoV-2, therapeutic Approaches, Pandemic, Respiratory, Airborne, Treatment of COVID-19

Introduction: -

Severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is the coronavirus strain responsible for the novel coronavirus 2019 (COVID-19) infection. COVID-19 emerged in the Wuhan city of China in late 2019 and swiftly occupied many of the individuals across the city with symptoms of atypical pneumonia, resulting in an outbreak of epidemic phase (Zhu et al. 2020a, b). Later, World Health Organization (WHO) declared the outbreak as a pandemic after assessing the situation around the world on March 11, 2020 (Cucinotta and Vanelli 2020). By the end of July 2021, more than 192 million cases had been recorded worldwide, resulting in the deaths of more than 4.1 million individuals worldwide from the beginning of the pandemic (WHO 2022a). Exceptional measures were taken to slow down the spread of this respiratory pathogen, including lockdowns, restrictions on travel and gatherings, mask mandates, and closures of businesses and schools, all actions with a high economic and psychological burden.

Airborne transmission is a major concern of SARS-CoV-2 as the expiratory activities (i.e., coughing, sneezing) of an infected person can generate respiratory droplets and infect individuals within a radius of 6ft (Ghinai et al. 2020). The front portion of the mouth is where atomization of droplets occurs; thus, covering the mouth by the use of a surgical facemask is essential.

The incubation period of a virus is the period between the exposure and the potential earliest date of symptoms, and current research showed that the incubation period for COVID-19 ranges from 2 to 7 days while the median estimate is 4 days (Guan et al. 2020). Fever, dry cough, dyspnea, myalgia, tiredness, regular or reduced leukocyte counts, and radiographic indications of pneumonia are all common signs of COVID-19 infection. Symptoms of lung abnormalities, lymphopenia, and thrombocytopenia have also been observed in certain COVID-19 individuals. The pathophysiological feature of COVID-19 is governed by proliferative and exudative stages of alveolar damage, necrosis of pneumocytes, inflammatory infiltrates, and microvascular damage (Carsana et al. 2020). To successfully combat current and possible future pandemics, detailed investigations of this new coronavirus, its mode of infection, and replication are required. This review focuses on the therapeutic approaches, discussion, description, clinical manifestation, precautions to be taken as a precautionary measure, and various treatment approaches for COVID-19.

History and Classification

Coronaviruses are a family of hundreds of viruses, and it was seen that the majority of these viruses showed their harmful effect on different animals like bats, chickens, camels, and cats.

In the 1960s, human coronaviruses 229E and OC43 were first discovered that were able to infect humans (Andersen et al. 2020). Among human

coronaviruses, four are endemic (229E, OC43, NL63, and HKU1) and are well known for causing mild diseases (Kahn and McIntosh 2005; Saxena et al. 2020).

In November 2002, the first SARS-CoV virus was identified, resulting in severe acute respiratory syndrome (SARS) (Lau et al. 2020). In 2003, the members of Canada's National Microbiology Laboratory identified this virus's genome and confirmed the reason for this outbreak (Pal et al. 2020). Since 2005, several novel coronaviruses have been recognized from bats, and the evidence showed that human respiratory coronaviruses, SARS coronavirus, and MERS coronavirus were initially derived from bat viruses ancestral (Paden et al. 2018; Burrell et al.2017). Another deadlier coronavirus MERS-CoV (Middle East respiratory syndrome) was discovered in 2012. In MERS, the first case was from Saudi Arabia. Later another two MERS outbreak was identified in 2015 and 2018 in South Korea and Saudi Arabia, respectively. Then the first SARS-CoV-2 or COVID-19 infection was reported in December 2019 in Wuhan city of China.

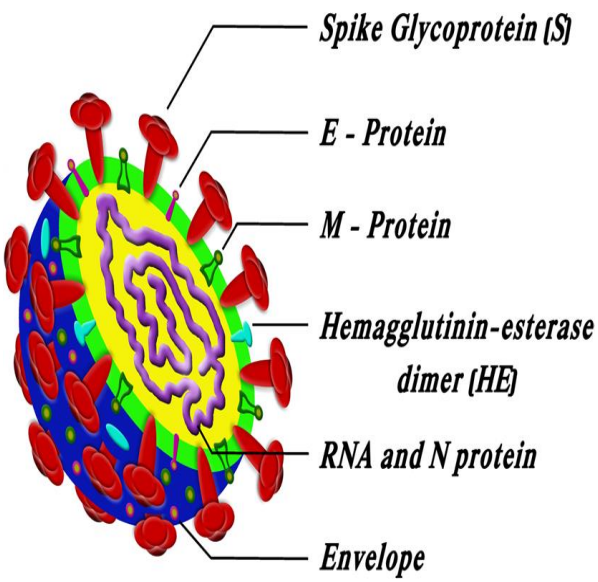
The virus was first discovered in bats and then pangolins (Panyod et al. 2020; Zhang et al. 2020). The genomic structure of virus SARS-CoV and SARS-CoV-2 bears many common characteristics and shows almost similar symptoms. This disease turns life-threatening if people are suffering from SARS. A total of 774 people was died from 2002 to 2014, according to the last reported case (Abdul-Fattah et al. 2021).

On account of their genus, there are four main subgroups of coronaviruses, known as alpha (α), beta (β), gamma (γ), and delta (δ) coronaviruses. Among them α and β coronaviruses are known to infect mammals, and other two γ and coronaviruses are known to create infection on birds (Wertheim et al. 2013; Guo et al. 2020).

Structure of Coronavirus

Coronaviruses are large, roughly spherical, and consisting of particles with bulbous surface projections . It is a single-stranded RNA-enveloped virus with the largest genomes (26.4–31.7 kb) among all known RNA viruses belonging to the *Coronaviridae* family. Its genome comprises around 30,000 nucleotides and contains four genes, which codify the surface protein characteristic of coronaviruses

1. Glycoprotein S, which exists as a homotrimer and forms the characteristic spikes found in the viral surface. Acting as a fusion protein, it allows entry of the virus into the host cell following recognition by its ACE2 membrane protein.
2. Envelope protein (E), E-protein is a tiny membrane protein with 76–109 amino acids that is a minor component of the viral particle. It is involved in virus assembly, host cell membrane permeability, and virus–host cell contact .
3. Membrane protein (M), which forms the matrix that connects the cover with the inner part of the virus.
4. Nucleocapsid (N) phosphoprotein, which holds the viral genome, a piece of positivestrand RNA N-protein coats the viral RNA genome which plays a vital role in its replication and transcription. It is responsible for encapsulating and protecting (+)-RNA, which contains the virus genome
5. HE protein ,The HE protein may have a role in viral entrance; it is not necessary for virus replication, but it appears to be important for natural host cell infection



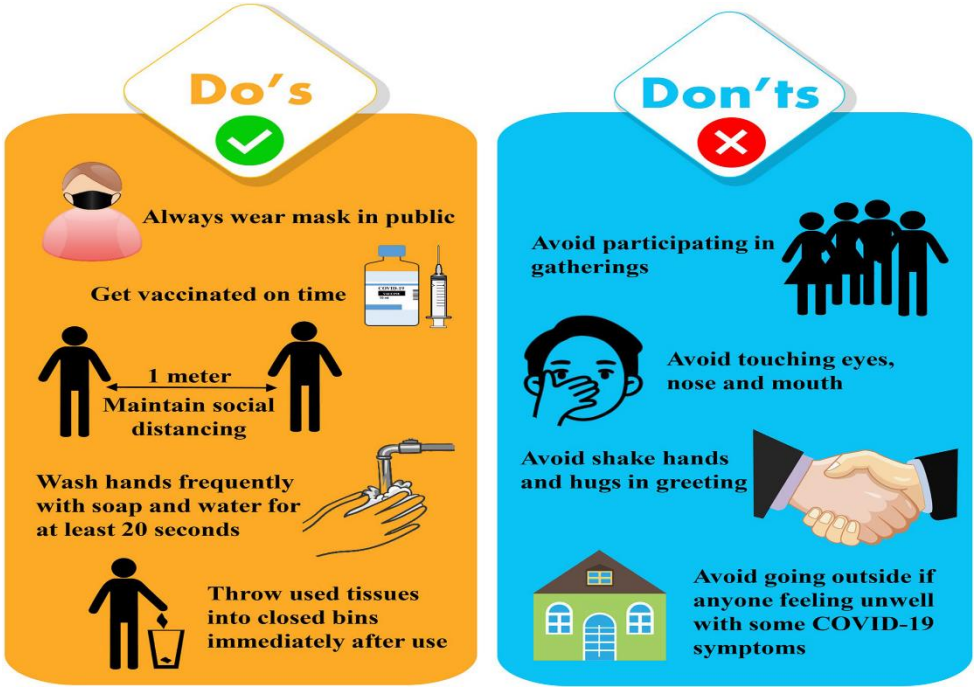
Preventions:

Prevention is better than cure; hence, the spread of this disease can be controlled by paying constant attention to some basic preventative measures given below.

- Get vaccine on time, and follow the local vaccination guideline.
- Maintain social distancing of at least 1-m space between yourself and others to reduce your threat of infection when others cough, sneeze,

or talk

- Use a face mask when being around other people .
- Frequently, in a proper manner, clean and rub your hands (at least 20 s.) with an alcohol-based hand wash or usage soap, followed by rinsing with water. If hand wash or soap is not available, use alcohol-based hand sanitizer (minimum 60% alcohol).
- Avoid going to crowded, congested, and/or involving close touch areas.
- Surfaces that are often handled, such as doorknobs, faucets, and phone displays, should be cleaned and disinfected regularly.
- Cover the nose and the mouth with the bent elbow or tissue during coughing or sneezing. After that, throw away the used tissue in a closed container and wash hands to maintain good respiratory hygiene.
- If anyone is feeling unwell with some COVID-19 mild symptoms, they should stay home and self-isolate until they recover
- If the person develops fever, cough, or difficulty breathing, get medical treatment, call the doctor ahead of time if possible, and follow your local health authority's instructions (WHO 2022c).



Feasible Therapeutic Approaches: -

Since the beginning of the COVID-19 pandemic, different measures have been taken to treat COVID-19infection. Still, there is no clinically validated and specific antiviral medication available to treat COVID-19 infection at this time Patients are usually provided medical treatment or supportive therapy, such as oxygen supplementation and mechanical ventilation, toalleviate symptoms For the treatment of COVID-19 infection, many strategies have been explored, and repurposing drugs is one of them. Some of the antivirals that have been repurposed include remdisivir, lopivir, lopinavir–ritonavir, ribavirin, baloxavirmarboxil, favipiravir, and arbidol/umifenovir. Other drugs that show potential action against COVID-19 but are not antivirals include chloroquine ,hydroxychloroquine, corticosteroids, losartan,statins, interferons, nitric oxide, and epoprostenol, which are instances for the repurposing strategy. Some medications have been suggested for treatment in critically sick patients. Tocilizumab, siltuximab, sarilumab, anakinra, and ruxolitinib were used to treat COVID-19 individuals who developed cytokine release syndrome (CRS). Antibiotics like azithromycin are frequently used to treat secondary infections (Ginsburg and Klugman 2020). The vaccine is another better approach for the prevention of COVID-19 infection. Though various vaccines against the SARS-CoV-2 virus have recently been approved, availability remains a major barrier, and public acceptance has become a contentious issue. But day by day, SARS-CoV-2 virus becomes more contagious and harmful due to their new mutants called variants. Recently the omicron variant's capacity to evade vaccine-elicited immunity is a major concern. So, there is a requirement for potential therapeutic molecules to treat the infection. Several antiviral drugs might be potentially repurposed or developed into viable treatments for this novel coronavirus. However, several clinical trials exploring possible therapies are now underway

Remdesivir-

Remdesivir is a nucleotide analog that competes with intracellular nucleosides for incorporation in the viral RNA and induces premature chain termination. Remdesivir is administered as a prodrug, metabolized intracellularly to an active metabolite, an analog of ATP. Its half-life of about 35 h

allows a single dose administration daily. Treatment is recommended for 5–10 days, with a higher initial loading dose (200 mg on the first day), followed by a maintenance daily dose of 100 mg to reach a stable plasma concentration .

Timing is essential for remdesivir efficacy. Initially recommended for hospitalized patients, remdesivir was proven to be more efficacious during the first 7 days of SARS-CoV-2infection. In high-risk outpatients (age > 60 years, diabetes, obesity, hypertension), an early,short, 3 days course of remdesivir significantly decreases the rates of hospitalization .Conversely, patients who are already symptomatic for more than 7 days and require oxygen support have no clinical benefit after remdesivir administration.

Remdesivir is EMA and FDA approved for the treatment of both hospitalized patients hospitalized ones (with mild to moderate forms of COVID-19, but at high risk for severe disease), aged _ 12 years and weighing _ 40 kg. The initial data on remdesivir efficacy came from the WHO SOLIDARITY study, that combined data from four clinical trials, showing a decrease in symptoms' severity in patients treated with remdesivir, and a significant increase in life expectancy in critically ill patients Among the side effects of remdesivir observed during clinical trials, and further reported during clinical use on the FDA or EMA websites, are gastrointestinal reactions (constipation, nausea, vomiting, diarrhea), increased prothrombin time, hypersensitivity reactions, hepato-, and renal toxicity .Therefore, monitoring of liver and kidney functions is recommended before and during remdesivir administration. Remdesivir is not administered if the glomerular filtration rate is less than 30 mL per minute, due to the presence of an excipient (sulfobutyl ether beta-cyclodextrin sodium) that accumulates in the kidney, causing renal toxicity . Remdesivir is not approved for the treatment of COVID-19 in pregnant women, but it was used off-label on a small number of patients, with good efficacy and minimal side effects. A large study on the safety of remdesivir administration in pregnant and breastfeeding women, conducted by the National Institute of Allergy and Infectious Diseases, US, is expected to be completed in 2022 . Treatment with remdesivir was available through an emergency authorization for patients younger than 12 years, due to insufficient data on the pharmacokinetics and safety of the drug in these patients. The evidence for remdesivir use in children is limited. A study done in early 2021 on 77 children (under 18 years old, with an average age of 14 years) with severe forms of COVID-19, showed improvement in the symptomatology, with good tolerance and few side effects [. In April 2022 FDA has approved remdesivir use in pediatric patients 28 days of age and older weighing at least 3 kg, based on the efficacy results in adults and on the data from a phase 2/3, single-arm, open-label clinical study of 53 pediatric patients

Favipiravir

Favipiravir is a broad-spectrum antiviral and antiinfluenza drug that restricts viral RNA replication by inhibition of RNA polymerase (Fang et al. 2020). Several studies have revealed that favipiravir can effectively treat COVID-19, particularly in patients with mild-to moderate disease. Favipiravir has been demonstrated in certain investigations to lower viral load in the upper respiratory tract and the lungs (Shirali and Daikoku 2020)
Favipiravir initially acts as a prodrug entering cells through endocytosis, and then after phosphoribosylation and phosphorylation, it is converted into an active favipiravir ribofuranosyl phosphates (Furuta et al. 2013). The antiviral activity is exhibited through selectively targeting the conservative catalytic domain of RNAdependent RNA polymerase (RdRp), interrupting the nucleotide incorporation process during viral RNA replication (Furuta et al. 2017). Favipiravir demonstrated 100% effectiveness in protecting mice against the Ebola virus, although its EC50 value in Vero E6 cells was high (Oestereich et al. 2014). Favipiravir has been used in the treatment of infectious diseases caused by RNA viruses such as influenza, Ebola, and norovirus (DeClercq 2019).

Lopinavir, Ritonavir

The antiretroviral drug, Lopinavir is widely used for treating HIV and is a potential candidate for the treatment of COVID-19.19 Ritonavir helps to stabilize Lopinavir and together they inhibit the replication of coronavirus *in vitro*.20 Cao *et al*. carried out an open-label trial for Lopinavir–Ritonavir in 199 hospitalized patients with severe COVID-19 and administered Lopinavir–Ritonavir (400 mg and 100 mg, orally every 12 h for 14 days). The authors found no benefit with Lopinavir–Ritonavir therapy in terms of time to clinical improvement beyond the standard of care.21 However, the analyses of secondary outcomes revealed that Lopinavir–Ritonavir may be associated with substantial lowering of overall mortality (19% in patients in Lopinavir–Ritonavir group vs. 25% in the standard-care group), reduced risk of severe adverse events (20% vs. 32%), and decreased risk of respiratory failure or acute respiratory distress syndrome(13% vs. 27%).22 Though this therapy has not shown meaningful clinical improvement, Lopinavir– Ritonavir may not be abandone d by clinicians in the current scenario of shortages of alternative drugs.

Arbidol

Arbidol is also known as umifenovir, a Russian antiviral drug that seems to be effective against many viruses, including influenza, respiratory syncytial virus (RSV), poliovirus, rhinovirus, Zika virus, hepatitis and SARSCoV, and MERS-CoV coronaviruses (Gao et al. 2020). The clinical evidence for using Arbidol in the treatment of COVID-19 is scarce.
A retrospective cohort study, case reports and case series revealed that Arbidol alone or combined with antiviral drugs produced certain benefits in the treatment of COVID-19.26 The dosing followed for Arbidol is 200mg every 8 h orally for 7-14 days. 4 The trimerization of SARS-CoV-2 spike glycoprotein, which is important for cell adhesion and penetration, may be effectively blocked or hampered by arbidol. When the trimerization of the SARS-CoV-2 spike glycoprotein is blocked, a bare or immature virus is formed, which is less infectious (Vankadari 2020). As a host-targeting drug, Arbidol also disrupts many steps of viral cycle replication, including entrance, attachment, internalization, and membrane fusion. Arbidol substantially improved the clinical state of hospitalized COVID-19 patients, including peripheral oxygen saturation, the need for ICU admissions, the length of hospitalization, chest computed tomography involvements, white blood cells, and erythrocyte sedimentation rate, according to a randomized controlled trial (Nojomi et al. 2020).

Ivermectin

Another natural product that has shown antiviral activity related to the blockade of a host cell target is ivermectin, which, together with the closely related avermectins, has an interesting history. The avermectins were discovered by Ōmura in *Streptomyces avermitilis* (currently *avermectinius*) isolated from soil samples and were studied as antiparasitic agents by Campbell in Merck. It was soon found that compounds lacking the double bond at the spirocyclic fragment of the molecule (ivermectins) were less toxic and had a broader antiparasitic spectrum. Commercially available ivermectin is an 8:2 mixture of ivermectins B1a and B1b (Figure 25). It has low toxicity and is widely employed as an antiparasitic medication for veterinary use; it has also been approved for a number of human parasitic diseases, most notably onchocerciasis (river blindness), and also filariasis, and pediculosis. Ōmura and Campbell shared half the 2015 Nobel Prize in Physiology/Medicine for their discovery.Regarding its use against COVID-19, in 2020, ivermectin was discovered to be antiviral in vitro. Its potency was moderate, with an IC50 = 2 _M, which is 15–30 times higher than the concentration that can be reached with a dose of 200_g/kg. Nevertheless, it seemed promising in early clinical testing [54] and it was later found to act on multiple targets, including the viral S protein and the host importins, which act as transporters of several viral proteins (ORF-3a, ORF-6, NSP-1) to the nucleus, where they block the production of the natural antiviral interferon. Moreover, ivermectin was found to act by other mechanisms not based on its viral action, since it is anti-inflammatory and antithrombotic. The clinical efficacy of ivermectin has become highly controversial; one meta-study showed a reduction of the risk of death in COVID-19 patients, especially for avoiding the progression of the disease towards the more severe stages but several problems with the data and the methodology have been pointed out by other authors and another meta-study concluded that the evidence available that can be considered reliable does not support the use of ivermectin for the treatment or prevention of COVID-19 outside of randomized trials . This is also the recommendation of the World Health Organization and of regulatory agencies such as FDA and EMA

Corticosteroids

Corticosteroids decrease the COVID-19-induced systemic inflammatory response, leading to an improvement in the clinical outcomes and a reduction in the 28-day mortality (8.7% in the critically ill and 6.7% in patients with severe COVID-19 who were not critically ill). Dexamethasone is the first-choice corticosteroid, widely used throughout the pandemic, with similar oral and intravenous bioavailability. Corticosteroids are highly effective in hospitalized patients in severe or critical conditions, requiring mechanical ventilation, while in those with mild forms of the diseases, their use is not recommended. Low-dose dexamethasone used in pregnant women requiring mechanical ventilation resulted in a decrease in COVID-19-induced complications, with a low risk of fatal adverse reactions. The international treatment guidelines do not recommend the use of corticosteroids in pediatric patients, as there are insufficient data to confirm extrapolation of corticosteroid doses used in adults for patients younger than 18 years .Inhaled administration of corticosteroids might be recommended in COVID-19 patients, due to an anti-inflammatory effect in the respiratory tract, that can decrease the innate immune inflammatory responses and the macrophages' infiltration in the lung tissue. In addition, inhaled corticosteroids can interfere with the replication of SARS-CoV-2, by downregulating ACE2 receptor expression, especially in patients with chronic obstructive pulmonary disease. Nevertheless, the COVID-19 EMA pandemic Task Force is advising that there is insufficient evidence on the benefits of inhaled corticosteroids for people with COVID-19 with normal levels of oxygen . The general safety profile of corticosteroids is well known, and the main side effects (including hyperglycemia, fluid retention, increased risk of opportunistic infections, and reactivations of latent infections) are manageable.

Chloroquine and Hydroxychloroquine

Chloroquine and hydroxychloroquine have a long history of use in the inhibition and treatment of malaria and the treatment of chronic inflammatory disorders such as rheumatoid arthritis. Hydroxychloroquine is derived from chloroquine, and initially, they have been proposed as an antiviral treatment for COVID-19 (Gasmi et al. 2021; Horby et al. 2020). Later on, a randomized controlled trial reported that hydroxychloroquine was administered as a postexposure prophylactic within 4 days of a high-risk or moderate-risk COVID-19 exposure, and hydroxychloroquine did not protect against COVID-19-related illness or infection (Boulware et al. 2020; Mitja et al. 2021). Another open-label randomized controlled trial reported that chloroquine/hydroxychloroquine treatment in patients brought to the hospital with severe COVID-19 resulted in clinical deterioration and increased rates of invasive mechanical ventilation and renal failure (Rea-Neto et al. 2021). The Food and Drug Administration (FDA) granted emergency use authorization (EUA) to chloroquine and hydroxychloroquine in May 2020 to treat severe cases of COVID-19 in hospital settings. Although additional mechanisms are involved, including clathrin interaction, their antiviral activity seems to be mainly due to their ability to alter endosomal pH . These compounds have two basic centers, namely the heterocyclic nitrogen belonging to the 4-aminoquinoline moiety, and the tertiary amine at the end of the side chain. As a consequence, at acidic pH values they can generate a monoprotonated species (CQH+) and even small amounts of a diprotonated one (CQH2+), which, due to their low lipophilicity, become trapped in the acidic organelles, raising vesicle pH and hampering the membrane fusion process. . This property of CQ and HCQ renders them potentially useful for suppressing the immune system response characteristic of the severe forms of COVID19. Both chloroquine and its hydroxy derivative were broadly used in the clinic in many countries during the first wave of COVID-19. However, subsequent clinical studies have not shown evidence of clinical benefit and safety in their use for treating the SARS-CoV2 patients

Anakinra

Anakinra is a 17-kD recombinant human IL-1 receptor antagonist (blocking both IL-1α and IL-1β), with a short half-life of around 3–4 h and a favorable safety profile, authorized for the treatment of rheumatoid arthritis, gouty arthritis, and other uncommon auto-inflammatory disorders. Anakinra is a safe and effective treatment strategy for delaying mechanical ventilation, reducing the need for supplemental oxygen, and regulating SARSCoV- 2-triggered inflammation in patients with severe COVID-19 pneumonia and a high oxygen need (Balkhair et al. 2021). Later on, Tharaux et al. reported that the

patients with COVID-19 and mild-to-moderate pneumonia, a randomized clinical study found that anakinra was ineffective in lowering the requirement for noninvasive or mechanical ventilation or mortality. No major safety concerns were raised during anakinra use for the treatment of COVID-19. Reported side effects included neutropenia (particularly when given concomitantly with other drugs that decrease the number of leukocytes), headache, diarrhea, and flu-like symptoms . Data on pregnancy and breastfeeding are limited, and the efficacy in children under 18 years of age is not yet established .

Tocilizumab

Tocilizumab, a monoclonal anti-interleukin-6 (IL-6) antibody, has been identified as a possible therapeutic option for COVID-19 patients at risk of cytokine storms. IL-6 is an essential cytokine in inflammatory reaction and immune response and is one of the most significant cytokines involved in COVID-19-induced cytokine storms (Luo et al. 2020). However, a different study report showed that it is an effective treatment preference for critically ill COVID-19 patients, as it substantially reduces their oxygen requirements and their ICU stay, median hospital stay, and death. COVID-19-induced cytokine storms are effectively treated with this drug by decreasing the level of IL-6 (Chachar et al. 2021; Luoet al. 2020 Nevertheless, not enough data are presented yet to propose tocilizumab or sarilumab use as the standard treatment plan of COVID-19 patients (43)

Sotrovimab

Sotrovimab, a monoclonal antibody, has been developed to treat various types of coronaviruses, including COVID-19. It is primarily used to treat mild and moderate COVID-19 infection and prevent the progression of the disease condition from critical to severe. A retrospective study reported that the use of sotrovimab significantly improved symptom resolution, outcome, laboratory marker, and decreased hospitalization rate in individuals with mild and moderate COVID-19. This study suggests the use of sotrovimab in the early stages of COVID-19 treatment (Elesdoudy 2021). Later on, Guta and his group reported that the sotrovimab lowered the probability of disease progression in high-risk patients with mild-to-moderate COVID-19. And there were no threatening signs found during the study (Gupta et al.2021). The use of sotrovimab for treating mild or moderate COVID-19 in patients at high risk of hospitalization has also been conditionally recommended by the WHO (Kmietowicz 2022).

Janus Kinase Inhibitors;

Janus kinase (JAK) inhibitors interfere with one of the critical cellular pathways involved in the inflammatory response: the JAK/STAT signaling pathway, blocking phosphorylation of STAT proteins (signal transducer and activator of transcription) and preventing inflammation and immune activation . JAK inhibitors can be used as supplemental therapy in hospitalized patients receiving remdesivir and/or dexamethasone, who have signs of systemic inflammation and require rapid oxygen supplementation.

Baricitinib

Baricitinib , a clinically approved drug for rheumatoid arthritis, is a selective JAK1/JAK2 inhibitor with potent anti-inflammatory activity and a potential direct antiviral effect, by inhibition of the pivotal regulators of the ACE2 receptor that mediate the clathrin-dependent viral endocytosis . Three clinical trials (ACTT-2, COV-BARRIER, STOP-COVID) evaluated the efficacy of baricitinib for COVID-19 treatment, with positive results, demonstrating a decrease in hospitalization lengths, duration of mechanical ventilation, and mortality . Baricitinib was administered in monotherapy or in combination with other immunomodulatory and antiviral drugs. Co-administration of baricitinib and remdesivir improved the clinical outcome, compared to remdesivir alone, with a lower frequency of adverse effects . Coadministration of baricitinib and corticosteroids was associated with a significant decrease in the short and medium-term all-cause mortality, with a safety profile similar to the standard of care . No serious adverse reactions were reported and the drug can also be administered to children over 2 years of age .

Ruxolitinib

a selective JAK1/JAK2 inhibitor, and Tofacitinib (Xeljanz® Pfizer, Brooklyn, NY, USA),a JAK1/JAK3 inhibitor, are recommended in combination with corticosteroids, only if baricitinib or IL-6 inhibitors cannot be used. Currently, a beneficial effect on the clinical outcomes was not fully demonstrated, therefore their use in COVID-19 treatment remains limited

Convalescent plasma therapy

Convalescent plasma treatment is a type of adoptive immunotherapy that can treat a wide range of illnesses.Passive immunity can be created by using antiviral antibodies from recovered individuals to treat additional patients with a specific infectious illness. Other respiratory viral diseases, including SARS-CoV-1, H1N1 influenza, MERS-CoV, West Nile virus, and Ebola virus, have recently been treated with this technique (Marano et al. 2016). Hyperimmune immunoglobulin showed a statistically significant reduction in the risk of death among those treated with convalescent plasma or serum in all of the investigations (Al-Tawfiq and Arabi 2020). This treatment has played an essential role in treating COVID-19 patients when no effective antiviral drugs are available. In an initial uncontrolled case series, five critically sick patients with COVID-19 and acute respiratory distress syndrome underwent convalescent plasma treatment, and the result showed improvement in their clinical status (Shen et al. 2020). Later on, Duan et al. (2020) reported that a single dosage of CP (200 mL) was well tolerated and could considerably raise or sustain neutralizing antibodies at a high level, resulting in viremia disappearing in 7 days. However, clinical symptoms improved quickly over 3 days. This suggests that CP might be a viable rescue strategy for

severe COVID-19 and that a randomized study is necessary. Due to sample and experimental design constraints, a definitive conclusion on the potential efficacy of this form of treatment cannot be made, and further clinical observations will be required

Antibiotic

Azithromycin

Azithromycin is an antibiotic applied for the treatment of several different types of infections caused by susceptible bacteria (Perter et al. 1992). Azithromycin binds to the 50S subunit of the bacterial ribosome, inhibiting mRNA translation (Bulkley et al. 2010, Tu et al. 2005).
The use of Azithromycin together with other drugs has been successfully applied in the clinic for the treatment of viruses and to prevent severe respiratory tract infections for patients suffering from viral infection (Madrid et al. 2015, Retallack et al. 2016). As discussed before, the positive data for the use of its azithromycin along with hydroxychloroquine, in a COVID-19 clinical trial have been proposed (Gautret et al. 2020). In an open-label non-randomized study in France hydroxychloroquine + azithromycin presented with the highest virologic cure rate following 6-day treatment (Gautret et al. 2020). However, other studies affirm the data presented to date are insufficient to evaluate possible clinical benefits of azithromycin in patients with COVID-19 and repeated the experiments found patients had significant comorbidities (Molina et al. 2020).

Nitazoxanide

Nitazoxanide , an antiprotozoal, is an orally active nitrothiazolysalicylamide and antiviral prodrug that is converted rapidly to the active metabolites tizoxanide and nitazoxanide conjugates and unlike metronidazole (Rang et al. 2007, Rossignol 2016). Similarly, nitazoxanide is also known to potentiate interferon-alfa and interferon-beta production and it has been previously shown to exhibit an in vitro activity against MERS-CoV and other coronaviruses (Rossignol 2016). Nitazoxanide is hypothesized as a likely therapeutic approach and could have antiviral potential against Sars-CoV-2, as it works by interfering with host-regulated pathways in viral replication, amplifying the detection of cytoplasmic RNA and Interferon type 1. Some author suggests that nitazoxanide/azithromycin combination could have a potential that should be properly tested in clinical trials including randomized controlled trials

Serine Protease Inhibitor

Nafamostat

Nafamostat, a serine protease inhibitor that works as an anticoagulant, has demonstrated satisfactory results in inhibiting the action of MERS-CoV and has been shown to be effective against SARS-CoV-2 infection, preventing membrane fusion (Wang et al. 2020). Nafamostat mesylate inhibits TMPRSS2-dependent host cell entry of MERS-CoV (Yamamoto et al. 2016), and TMPRSS2 is responsible for cleaving and activate Sars-Cov-2 S protein.
However, the use of this anticoagulant in the treatment for COVID-19 is in a clinical trial, and the exact concentration of the compound to inhibit viral replication is not yet clear. In the deficiency of this information, other serial protease inhibitors were tested to inhibit the entry of Sars-Cov-2 into the cell, such as Naphthostat mesylate, which is already used for human use in Japan and the fact that this drug inhibits the action of TMPRSS2 in the host cell for infections caused by MERS-CoV (Hoffmann et al. 2020b). Nafamostat has FDA approval (unrelated to infections caused by coronavirus), and has been shown to inhibit the entry of Sars-Cov-2 mediated by protein S into the host cell with greater efficiency than Naphthostat mesylate, thus being considered the best option for the treatment of COVID-19.

New Therapeutical Approaches for COVID-19

- ***Broadly Neutralizing Antibodies***

Broadly neutralizing antibodies, active against different variants of SARS-CoV-2, including Omicron, were isolated from convalescent plasma donors or vaccinated individuals .Cryo-EM studies showed antibodies that were cross-reactive between sarbeco-,merbeco- and embecoviruses, and have flexible binding modes, targeting both the “up” and “down” conformations of the RBD. The development of such ultrapotent antibodiesvdirected towards conserved viral epitopes, with broad-spectrum activity against bothvwild-type and mutant virus strains, is an important strategy for COVID treatment and a step forward towards a pan-coronavirus vaccine. In addition, innovative antibody delivery techniques, such as inhaled antibodies, might offer a convenient, highly accessible method for COVID-19 prevention. Nanobodies (Nbs) are single-domain antibodies, similar to the heavy-chain-only antibodies initially isolated from camelids and cartilaginous fish . Nbs have a truncated structure, without any light chains and with a single variable domain in the two heavy chains (VHH), representing the antigen-binding region. Nbs exhibit ideal attributes for large-scale manufacture and have numerous advantages over classical human antibodies: ultra-high antigen-binding affinity, due to a very long CDR3, that can access otherwise inaccessible epitopes; recognition of a higher diversity of paratopes; good physicochemical qualities with increased solubility; good tissue penetration; and high stability, allowing for oral or inhalation administration. Bi- or multi-specific heavy chain antibodies and nanobody-drug conjugates are tested as antitumoral therapeutic strategies and can be used to prevent or treat inflammatory and infectious diseases .

Caplacizumab, a bivalent single-domain antibody, is the first nanobody-based medicine approved by the EMA and FDA in adults with thrombotic thrombocytopenic purpura and thrombosis in November 2018, and February 2019, respectively. Due to their high antigen affinity and stability, nanobodies can be administered in oral or inhaled versions and might be beneficial for COVID-19 non-hospitalized patients, during the early stages of the disease, acquiring high pulmonary concentrations with minimal systemic adverse effects. Nanobodies able to recognize the RBD of different variants of SARS-

CoV-2 were identified using phage display libraries derived from camels and llamas immunized with SARSCoV- 2 spike protein or receptor-binding domain . Engineered multivalent nanobodies constructs with superior neutralizing activity can block SARS-CoV-2 entry, either by inhibition of receptor binding or by inducing conformational modifications that prevent viral–cell fusion . In experimental mice models, prophylactically administered combinations of bivalent nanobody-Fc fusions, recognizing different epitopes in SARS-CoV-2 RBD, were able to decrease viral replication .Nanobodies that target chemokines or cytokines, can be customized to modify inflammatory responses in COVID-19 disease . Previously, several studies using the phage display method to elicit nanobodies directed towards cytokines were published, proving higher efficacy compared to the traditional cytokine blocking antibodies

- ***Novel Viral Entry Inhibitors***

Bemcentinib is a selective inhibitor of the AXL receptor tyrosine kinase, that mediates uptake of the apoptotic bodies, used by SARS-CoV-2 in a process of apoptotic mimicry, to adhere to and internalize into the host cells. Bemcentinib is currently tested in two phase 2b clinical trials in hospitalized COVID-19 patients. The first study recently reported the short-term efficacy results, with minor benefits in the primary trial endpoints (time to improvement by two points on the WHO ordinal scale or time to discharge), but with potentially significant clinical benefits in a key secondary endpoint (avoidance of clinical deterioration) .

Inhibitors of Host Transmembrane Surface Protease TMPRSS2

Camostat mesylate, an oral serine protease inhibitor, primarily used for symptomatic treatment in gastrointestinal tract disorders, is a potent inhibitor of the TMPRSS2 protease used by SARS-CoV-2 to prime and activate the spike protein. Randomized, double-blinded studies, with clinical endpoints including viral load, number of hospitalization days, and mortality, show that camostat mesylate might be a promising repurposed drug, with a very good safety profile in humans. N-0385 is a small peptidomimetic molecule, an inhibitor of TMPRSS2, that shows high efficacy in vitro on several SARS-CoV-2 variants (Alpha, Beta, Gamma, Delta) at low, nanomolar concentrations. The drug demonstrated a potential prophylactic and therapeutic effect during experimental intranasal infection in a transgenic mouse model, that expresses the human ACE2 receptor driven by a keratin promoter. Further studies are necessary to evaluate the efficacy of this compound on the Omicron variant, which was shown to have a decreased use of TMPRSS2 and a preference for endocytosis dependent cell entry, with altered spike processing and reduced fusogenicity

Interferons

A limited and delayed interferon (IFN) response might stimulate an uncontrolled viral replication and an aberrant immune response, leading to severe forms of SARS-CoV 2 infection. Patients with errors in the type I IFN activating pathways and those with auto antibodies neutralizing type I IFN are prone to a severe course of COVID-19. Systemic and inhaled IFN alpha and beta were administered in hospitalized patients, either alone or in combinations with antivirals, such as remdesivir or ribavirin, without major clinical benefits Interferon lambda has a limited inflammatory activity, due to a more restricted distribution of its IFNLR1/IL10R2 receptors, on epithelial and immune cells. Smallrandomized clinical trials with peginterferon lambda did not show significant clinical benefits for non-hospitalized patients , although an accelerated suppression of viral replication was demonstrated . Interferons can inhibit cell division, as such, treatment is associated with flu-like symptoms,nausea, fatigue, weight loss, hematological toxicities, alopecia, elevated transaminases, and psychiatric problems (e.g., depression, suicidal ideation) can most often occur. Concomitant treatment with immunomodulatory drugs or chemotherapeutic agents is not recommended, due to an increased risk of toxicity. Administration in pregnancy is not safe, as congenital anomalies in the fetus or spontaneous abortion may occur. There are insufficient data for interferons' administration in children

Immunonutrition

A healthy and 'well-fed' immune system is one of the most important weapons against COVID-19. Though an array of micronutrients is required, a large body of evidence is seen for Vitamin C and Zinc.

Vitamin C (Ascorbic Acid):

Vitamin C, a potent antioxidant agent is an effective anti-viral agent against influenza viruses. It helps to develop and mature T lymphocytes and NK (natural killer) cells. In 50 moderate to severe COVID-19 patients, intravenous vitamin C (between 10 g and 20 g per day given over a period of 8–10 h) improved oxygenation index. All patients were cured and discharged. 11 Though high dose vitamin C is safe, large clinical studies are needed for bedside use.

Zinc:

Zinc is a potential supportive therapy of COVID-19 owing to its immunomodulatory and antiviral effects. Zinc inhibits SARS-CoV RNA polymerase and decreases angiotensin-converting enzyme 2 (ACE2) (SARS-CoV-2 receptor). It also upregulates interferon α to improve antiviral immunity. In elderly individuals, 45 mg/day of oral zinc supplementation for a year has shown to lower the incidence of infections. It is hypothesized that Zinc

supplementation in HCQ-treated patients may lead to improved outcomes in COVID-19 patients. HCQ has Zinc ionophore characteristics, leading to increased intracellular levels of Zinc specifically in lysosomes. This elevated intracellular

Herbal Drugs used in COVID-19

For several years, medicinal plants have been used in different indigenous health schemes and traditional medicines for treating diseases. 21 Naturally occurring herbal medicine provides a wide variety of natural products, which can be used as an ancillary guide to unlocking many mysteries behind human illnesses. 22,23 According to a report by the WHO, 80% of people in developing countries rely on conventional plants for health needs. 23–25 With the enhanced resistance of microorganisms (bacteria, viruses, and parasites) to traditional anti-microbial therapy, alternative therapies are being re-explored at a growing rate, particularly from herbal sources. 25 Assessing the possible antiviral activity of various natural resources has gained remarkable attention with the emergence and re-emergence of new viruses, concerning the availability of advancing technological resources. 21,23,26 A variety of herbs have been investigated, and their effects against viral infections have been identified. 21 Amidst the mounting global concerns about the COVID19 outbreak, understanding the natural products with antiviral properties is essential for providing an alternative management option for COVID-19. The use of natural products and phytomedicine continues to grow fast around the world, with many people nowadays reverting to such remedies in different national healthcare settings for the treatment of various health challenges. 23 Herbal phytoconstituents effectively reduced infectious conditions, where they were the only treatments available before antibiotics were introduced. In particular, herbal medicinal products provide a rich tool for the production of novel antivirals. The use of these plants dates back to the beginning of civilization. 27,28 Traditional Chinese medicine includes treatments of herbal and acupuncture, where those aim to prevent and treat diseases by enhancing the immunity of the body. 29,30 Chinese medicine needs experience and knowledge; here, no adverse reactions could be identified if Chinese herbs are properly used, 30,31 Seven coronaviruses have been detected with an ability to spread among humans; three of them are harmful, namely, SARS (severe acute respiratory syndrome, China, 2002), MERS (Middle East respiratory syndrome, Saudi Arabia, 2012), and SARS-CoV-2 (COVID-19, 2019). These viruses are belonging to the coronaviridae family of the coronavirus genus. The genome sequence analysis concluded that SARS-CoV-2 belongs to the beta type genus, where this type also contains the Bat SARS-like coronavirus, SARS, and MERS. Furthermore, based on the nucleic acid structure similarity, COVID-19 is a betacoronavirus

Andrographolide

The andrographolide is a labdane diterpenoid that is mainly isolated from the Andrographis paniculate (green chiretta) herbaceous plant extract. This component was utilized in different medical functions due to its remarkable biological activity, such as immunity regulation, anti-hyperglycemia, anti-bacteria, anti-virus, anti-parasite, and anti-tumor. 32–34 Previous reports showed that andrographolide could treat multiple viruses such as influenza A virus (IAV), 35 human immunodeficiency virus (HIV), 36 Enterovirus D68 (EV-D68), 37 dengue virus (DENV), 38,39 and Chikungunya virus (CHIKV) 40 due to its wide range of antiviral properties. Recently, Enmozhi et al. found that andrographolide could be a good inhibitor for SARS-CoV-2 through in silico studies by influencing the viral 3-chymotrypsinlike cysteine protease (3CLpro). 41 In general, andrographolide is highly abundant and has low cost and cytotoxicity; though, its strong antiviral activity against different types of viruses needs to be further studied

Quercetin

It is a flavonoid compound that could commonly found in fruits and vegetables. In addition to its dietary property, quercetin owns multiple biological activities, including its anti-functions against inflammations, oxidants, viruses, allergies, cancer, and mood deterioration, similar to vasoprotective medication. 42–44 Previous studies showed that quercetin has antiviral activity against a group of viruses, including IAV, 44 Hepatitis C Virus (HCV), 45 Enterovirus 71 (EV-71), 46 SARS-CoV, etc. 47,48 Regarding the SARS viruses, quercetin showed a relatively high inhibition rate and half-maximal inhibitory concentration (IC50) values of 82% and 73 µM, respectively, against SARS-CoV 3CLpro in Pichia pastoris fungus.

Baicalin

It is another medicinal component found in Scutellaria baicalensis Georgi (Chinese name: Huang Qin) and has a wide window of curative applications as sensitizer and antiapoptosis. 49,50 Chen et al. reported the antiviral activity of baicalin versus SARS type viruses, with an effective concentration to reduce the virus forming unit by 50% (EC50) value of 12.5 µg/ml within two days. The activity was reduced as the incubation time continued more than two days. 51 The similarity between the current COVID-19 virus (SARSCoV-2) and SARS-CoV is anticipated to obtain an analogous antiviral effect from baicalin on the recent virus. Furthermore, Deng et al. utilized UV spectrophotometry to identify angiotensin-converting enzyme inhibition, where baicalin was found to be a good in vitro inhibitor angiotensin-converting enzyme (ACE), with an IC50 value of 2.24 mM. 52 Considering the low toxicity of baicalin, its usage as a drug or treatment agent could be promising against COVID-19

Curcumin

Its International Union of Pure and Applied Chemistry (IUPAC) name is (1,7-bis(4- hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione). It is an anti-cancer, antioxidant, anti-inflammatory, and amphipathic molecule that contains a polar center and a lipophilic methine segment surrounding it. 53 The β-dicarbonyl group in curcumin structure promoted the H-bond donating and accepting, where this group functions as a phenylic hydroxyl moiety and methoxy group. Also, curcumin can be used as a Michael reaction acceptor due to its affinity to multivalent metals and non-metals, which leads to a high polymerization around CC. 54 Here, two polyphenols, Catechin and Curcumin, were reported through computational approaches, which have a dual

binding affinity. Catechin binds to viral S-protein and ACE2 with a binding energy of -10.5 Kcal/mol and -8.9 Kcal/mol, respectively. As a result, it binds with a greater affinity than that of curcumin, which are -7.9 Kcal/mol and - 7.8 Kcal/mol for S-protein and ACE2, respectively. While curcumin gets bound directly to the receptorbinding domain (RBD) of viral S-protein, catechin binds to the proximity of S-protein's RBD sequence. A molecular simulation study demonstrated that curcumin directly binds with the RBD site of S-protein during 40-100ns. In contrast, catechin binds with S-protein near the RBD site and causes fluctuation in amino acid present in the RBD and its proximity. In conclusion, this computational study predicted the possible use of the above two polyphenols for therapeutic/preventive intervention.

LUTEOLIN

Luteolin (3′ ,4′ ,5′ ,7′ -tetrahydroxyflavone) is one of the flavonoids group that naturally exists in a massive number of plants and has multiple pharmaceutical functions, such as anti-diabetic, anti-inflammatory, anti-bacterial, anti-cancerogenic, antiviral, antioxidant, anti-proliferative, and heart protective. 65 This component is obtained from Chinese medicine herbs available almost everywhere and at a low price. 66 Hence, Luteolin is suggested as a potential therapy to treat COVID-19 pandemic

MYRICETIN

Myricetin is a common plant-derived flavonoid and has many types of nutrition. Moreover, it commonly enters the ingredients of different foods and beverages. Likewise, Myricetin's previous plants and herbs show a wide window of potentials and roles as anti-inflammatory, anti-cancer, anti-diabetic, and antioxidant. This component has a long history that dates back to more than a century. The first isolation was from Myrica nagi Thumb (Myricaceae) in the late 1800s in India and was finally obtained as pale-colored crystals. 67 Yu. et al. reported that myricetin in vitro inhibited SARS-CoV's helicase protein by influencing the ATPase action, but not the unwinding activity of nonstructural protein 13 (nsP13). Furthermore, it was observed that myricetin and scutellarein had no cytotoxicity versus normal breast epithelial MCF10A cells. It can be suggested that the naturally-existing flavonoids, including myricetin, might serve as a SARS-CoV 2 inhibitor. 68

Azadirachta Indica (Neem)

The main clinical symptom of COVID-19 is fever and to reduce it these plants have valuable outcomes. The leaves of neem are traditionally boiled and consumed for the management of fever-related with COVID-19, with reported anti-inflammatory effects in animal studies . The animal study and in-silico docking research confirmed that neem leaves extracts and their metabolic constituents such as flavonoids and polysaccharides have direct antiviral effects against different viruses including Hepatitis C Virus . Specific to SARS-CoV-2, molecular docking research has demonstrated that neem-derived compounds such as nimbolin, nimocin, and cycloartenol can bind to the SARS-CoV-2 envelope (E), membrane (M), glycoproteins, and also inhibitory role . Its leaves have positive effects on immunoregulatory effects to boost immune response in animals models . In mice vaccinated with Brucella Rev-1 vaccine, neem seed extract given subcutaneously boosted the production of IFN-γ post-vaccination neem seed extracts must be avoided in pregnant women as animal research its shown abortifacient effects . while clinical studies have reported its anti-human chorionic gonadotropin effects . Studies reported that the traditional purpose of neem for medicinal purposes mainly depends on leaves consumption, boiled the leaves in the water, and drank . One of the main concerns is about safety, a clinical trial should be done to establishing safe doses of neem leaves specific to the formulation intended for use are required before further investigations on efficacy. Although neem leaves have been used traditionally for a long time, the toxicity profile is not well-documented. clinical cases of acidosis and renal injury in the body system have also been reported on neem seed oil users [32]. The main challenges of ethnopharmacological study for therapeutic claims are quality control, identification, and standardization of biomolecules on herbal products.

Mentha Piperita

Peppermint (*M. Piperita*) is the oldest herbal remedy for different diseases condition in the world. Dry peppermint has been composed since 1000 BCE, and its importance has been described in ancient Egypt, Greece, and traditional Chinese medicine. Peppermint has essential oil and significant antibacterial and antifungal activity against Gram-negative and Gram-positive bacteria, yeast, and fungi, mainly as a result of the presence of the abundant phytochemicals menthol and menthone . However, to the best of our knowledge, a study done of Saudi Arabia stated that about 78% of non-hospitalized patients used peppermint, compared with only 22% of hospitalized patients without using peppermint supplement, due to COVID-pandemic so that use of peppermint during infection with COVID-19 was associated with lower odds of hospitalization

Glycyrrhiza Glabra

Glycyrrhizin, also called glycyrrhizic acid (GLR), is a triterpenoid saponin mainly isolated from the roots (Glycyrrhizae Radix) of the plant Glycyrrhiza . GLR effectively inhibited the replication of two clinical isolates of SARS-associated coronavirus (FFM-1 and FFM-2). The drug was found to inhibit the cytopathic effect of the virus with an EC50 of 300 mg/ml while being non-cytotoxic to the host cells. GLR inhibited virus replication but also the penetration and adsorption of the virus into cells . The mechanism of action at the origin of this activity was not known at that time but a drug-induced production of nitrous oxide synthase was mentioned, signifying that nitrous oxide could be accountable for the inhibition of virus replication . GLR also showed active when it was tested against 10 clinical isolates of SARS coronavirus in infected Vero-E6 cells but the activity was limited in time. The rapid metabolism of the drug limits the drug exposure, not permitting it to reach an effective concentration . The modification of the GLR structures, particularly to make amino-acid conjugates and amide derivatives can rise significantly the activity against SARS-CoV-2 but it can be at the expense of elevated cytotoxicity

Psoralea Corylifolia

Psoralea corylifolia L is used in Chinese medicine and traditional Ayurveda against different types of skin diseases, such as leukoderma, psoriasis, and leprosy . This plant is also known for its antimicrobial and anti-inflammatory activities . In a while, 6 aromatic constituents were isolated from seeds of Psoralea corylifolia ; the isolated phytoconstituents inhibited the enzyme in a dose-dependent manner with IC50 ranging from 4.2 to 38.4 μM. Likewise, numerous natural products have revealed antiviral effects at nanomolar concentration against SARS-CoV (e.g., homoharringtonine, ouabain, lycorine, tylophorine, 7 methoxycryptopleurine, and Silvestro) . Clinical trials of a few herbal compounds against SARS-CoV-2-3CLPro aroused hope for plant-derived *anti*-SARS-CoV-2 drugs. Very recently, 3CL protease inhibitor NLC-001, a plant product administered orally as a dietary supplement, got US FDA approval

Coronil : An Ayurvedic Attempt

On 23rd June, Patanjali launched Coronil and Swasari as an Ayruvedic cure for treating coronavirus infections. The launch of Coronil kit was based on the company's claim that the results were based on placebo controlled clinical trials. The drug was given to 95 COVID 19 infected patients and the company claims that 69 % patients were cured in 3 days and 100 % recovered in 7 days. The company further claims that high sensitive C-reactive protein and IL-6 levels were reduced in patients who were given Coronil. The reduction in IL-6 level reduces the chances of cytokine storm which has created a disturbing impact on patients. The company claimed that Coronil can cure Covid 19 patients in 3-14 days and it has no side effects. Coronil is made of the extracts of pure Giloy, Tulsi and Ashwagandha. Giloy has its own benefits. It improves platelet count, removes toxins from body, purifies the blood and fights bacteria. It is said to make immune system stronger and makes respiratory system stronger. Tulsi has proved to be highly effective in fighting against infection. It also acts as a natural immune booster, reduces fever, pain, reduces stress, cold, cough and other respiratory disorders and considered to be good for heart. Ashwagandha is said to be very beneficial herb for health of human beings. It is a rich source of antibiotics and very helpful in reducing body stress. The other ingredients were Kakda Singi,, Rudanti and Powerful Minerals. Patanjali launches this Coronil kit at Rs 545. They have planned to launch e-commerce application for delivery of coronil medicine within 2 hours of order placement using its own network. The entire Coronil kit included the medicine for 30 days and was expected to available on Patanjali stores in a week's time of its launch. The company also claimed that Coronil can also be used not only to cure corona but can be used also to prevent a person from getting infected

Covid-19 Vaccines

The world has taken different significant actions to control the COVID-19 pandemic from its beginning. However, the disease spreads unabated, wreaking havoc on people's health, social lives, and economies. Therefore, the prevention and control of the COVID-19 pandemic were immediately needed. Several vaccines have been studied, produced, tested, and assessed at a breakneck speed, and in 2021 many vaccines have been approved.
According to the WHO, more than 9.8 billion vaccination doses had been delivered as of January 27, 2022 (WHO 2022a). The immune system is triggered by vaccination, resulting in the generation of neutralizing antibodies against SARS-CoV-2. But the variants of the virus are always a major cause of concern. Vaccines have longbeen known to lose their potency over time. As a result, various countries have authorized the administration of an additional dose of vaccine (known as a booster) to people 3–5 months after their vaccination cycle is completed. This method appears to be efficient in preserving SARS-CoV-2 immunity

Vaccines authorized in India:

Globally, many vaccines are available some of them are Covishield® (Oxford-AstraZeneca), mRNA-1273 (Moderna), Janssen (Johnson & Johnson), AZD1222 (Pfizer BioNTech), Sputnik V® (Gamaleya), Covaxin® (Bharat Biotech), CoronaVac (Sinovac), NVX-Cov2373 (Novavax), BBIBP-CorV (Sinopharm) etc. In India, DCGI has approved three vaccines for restricted use in emergency situation in the India: the Covishield®, Covaxin®, and SputnikV®.15,16 As on 25th April, around 140.91 million vaccine has been inoculated24 which is around 10% of total population

Covishield:

The ChAdOx1 nCoV-19 vaccine (AZD1222) is made up of the replication-deficient simian (Chimpanzee) adenovirus vector ChAdOx1, which carries the full-length structural surface glycoprotein of SARS-CoV-2 along with a tissue plasminogen activator leader sequence. ChAdOx1 nCoV-19 expression optimizes the coding sequences for the codon of the spike protein. Two doses are required to administer at a dose of 0.5ml, contain 3.5-6.5×1010 viral particles as a single intramuscular injection (IM) into the deltoid up to 12 weeks apart (target 4 weeks) which induced maximum humoral and cellular immune responses against SARS-CoV-2.25,26,27 It can be kept in the refrigerator at temperatures ranging from +2˚C to +8˚C. When opened, multi-portion vials should be used as soon as practically possible and within 6 hours if held between 2˚C to 25˚C.28 It has shown the general efficacy of 70.42% in primary analysis population (Licensing regimen + Exploratory analysis) in the trials carried out in the UK and Brazil.26,28 Same vaccine shows only 22% efficacy according to preliminary South African data. It might be the reason of new variant 501Y.V2 (B.1.351), which is resistant to both natural and vaccine-induced immunity.29 Due to the South Africa variant (B.1.351), Shabir AM *et al.* found just 10.4 percent vaccine effectiveness and vaccine did not provide defense against mild-moderate Covid-19. However, the vaccine's effectiveness against the UK strain (B.1.1.7) of SARS-CoV-2 is comparable to that of other lineages.30 So it may not be effective in new variants. It is available at rate Rs. 600/- (8.04$) for private hospital per dose.31 Injection site tenderness (>60%); injection site discomfort, headache, exhaustion (>50%); myalgia, malaise (>40%); pyrexia, chills (>30 %); and arthralgia, nausea (>20 %) were the most commonly recorded unfavorable reactions. The majority of adverse reactions were mild to moderate in intensity

and apparently went away after a few day. By day 7 the incidence of subjects with at least one local or systemic reaction was 4% and 13%, respectively. As compared to the first dose, the second dose's adverse reactions were milder and were recorded less frequently.25,27,28 In the case report reported by Marie S *et al.*, anti-PF4 antibodies were observed 6 to 24 days after receiving the first dose of Covishield, unrelated to the use of heparin therapy, in a case report of 23 mostly young, usually healthy patients who presented with atypical thrombosis, mainly involving cerebral veins, and thrombocytopenia..32 With the exception of one patient who presented with fatal intracranial haemorrhage, Andreas G *et al.* confirmed that 11 original patients starting 5 to 16 days after vaccination presented with one or more thrombotic events; nine had cerebral venous thrombosis, three had splanchnic-vein thrombosis, three had pulmonary embolism, and four had other thromboses; six of these patients died.33 Chatterjee S *et al*. has reported a case of myocardial infraction post vaccination after 2 days.34 National Adverse event following immunization (AEFI) has documented which include myocardial infraction, cardiac death, trigger pro-thrombotic state, cardiovascular event, hypertensive emergency and anaphylaxis as adverse events in 11 patients and among them 10 had loss their lives.35 Although a causal link has yet to be established, viral vector, a vaccine additive, or a flaw in the manufacturing process may all play a role.32,36

Covaxin

The virus strain (NIV-2020-770) with the Asp614Gly mutation, which was isolated and sequenced from a Covid-19 patient, was used to produce BBV152. It is an entire virion β-propiolactone-inactivated SARS-CoV-2 vaccine with a toll-like receptor (TLR) 7/8 agonist molecule absorbed to alum (Algel-IMDG). To induce full cell mediate response, it injects intramuscularly in to deltoid muscle at a volume of 0.5ml/dose in two-dose regimen 28 days apart. It can be stored in the refrigerator at temperatures ranging from +2˚C to +8˚C, which is ideal for immunization cold chains. A Phase 3 clinical trial with 25,800 participants is ongoing, with interim analysis results indicating vaccine efficacy of 81 percent..37,38,39Sapkal GN *et al.* study shown that this vaccine is effective against B1.1.7 variant.40 It is available at the rate Rs. 1200/- (16.08$) for private hospital.41 Pain and swelling at the injection site were listed as local adverse effects, while fever, weakness or malaise, myalgia, body aches, headache, nausea or vomiting, anorexia, chills, generalised rash and diarrhoea were listed as systemic adverse events.37,38,39 AEFI had document 2 adverse event associated with vaccination which include sweeting, dizziness, anxiety, cold extremities, hypotension and anaphylaxis.35 Detail phase 3 clinical trial report will be revealed imminently, which will give more data with respect to the immunization efficacy and undesirable impact of it.

Sputnik:

Recombinant adenovirus type 26 (rAd26) and recombinant adenovirus type 5 (rAd5), both of which bear the gene for SARS-CoV-2 full-length glycoprotein S, are included in the vaccine (rAd26-s and rAd5-s).42,43 For both recombinant adenoviruses, a complete dose of the vaccine contain 1010 or 1011 viral particles44 and given intramuscularly one followed by another with 21 days apart. The antigen transmitted by adenoviral vectors is known to induce both cellular and humoral immunity after a single immunization, making it useful as an emergency pandemic prevention method. A long-lasting immune response can be achieved by combining two immunizations. It is available in two formulation, frozen and lyophilized dry powder vaccine. For injection per dose, frozen vaccine inoculated at a volume of 0.5 mL and lyophilized dry powder vaccine must be reconstituted in 1 mL of sterile water. Frozen vaccine required -18˚C and lyophilized dry powder vaccine can storage at +2 ˚C to +8˚C. It has shown 91.6% vaccine efficacy.42,43,44 It is equally effective in case of B1.1.7 variant and in case of B1.351 variant it has shown only minimal efficacy but better than other available vaccines.45,46,47 It is expected to be accessible in India by end of May 2021 at the rate less than 10$ per dose.48,49 Immunization with this vaccine is linked to mild adverse events such as discomfort at the injection site (58%), hyperthermia (50%), headache (42%), asthenia (28%), muscle and joint pain (28%). There were no severe adverse events identified

Conclusion

Extensive research has been being carried out on SARSCoV-2 and its different variants to combat them with the new treatment strategies. With the continued enormously hard efforts to prevent the spread of SARSCoV-2 globally, Some strategies like vaccination, social distancing, self-quarantine, stay home, stay safe, night curfew, partial or complete lockdown, maintaining hygiene, wearing masks, and using hand sanitizer frequently have been imposed to control the transmission of COVID-19. Presently, multiple vaccines have been approved, which are significantly efficacious toward prevention of COVID-19. Some of them In the current review, we presented the latest advancements in the treatment of COVID-19 patients. Along with supportive therapies, no specific treatment has been introduced for COVID-19. The efficacy of some antivirals, convalescent plasma transfusion, and many similar cases need to bestudied in more clinical trials

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