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Review

A Therapeutic Landscape of COVID-19: Where We Are?

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Abstract: COVID-19 has emerged worldwide last December'19. It is a highly contagious respiratory tract disease caused by novel Coronavirus (SARS-CoV-2). Initially, the etiology of the disease was unknown; therefore, healthcare practitioners were treating affected people based on their symptoms with drug repositioning; along with it, researchers worldwide started working on developing a vaccine to control the pandemic. In this article, we have discussed chiefly all the possible treatment options practicing for COVID-19 in Bangladesh and other countries of the world, including currently available and upcoming vaccines together with repurposed drugs, oxygen therapy, ventilation, plasma transfusion & antibody therapy, Interferon treatment, Immunosuppressants, herbal medicine such as Ayurveda, traditional medicines, nutritional and food supplements, Traditional Chinese Medicine (TCM), etc. This review paper could be an excellent guideline for frontline caregivers and researchers to assess the treatment options that will help them get a grip on the fatality of this disease also an inscription for any sudden viral emergence.

Keywords: COVID-19; SARS-CoV-2; Repurposed drugs; Complementary and Alternative medicine; Immunosuppressants; Immunostimulants; Vaccines; Ventillation and oxygen supply

1. Introduction

A new viral pneumonia-like disease broke out in China at the beginning of December 2019 [1]. It was declared as a Public Health Emergency by the World Health Organization (WHO) on January 30, 2020 [2], named COVID-19 on February 11, 2020 [3], and declared this outbreak as a global pandemic on March 11, 2020 [2]. As it was a new unknown virus, healthcare

practitioners treated affected people considering symptoms with repurposed drugs, and worldwide the urgency of developing vaccine started once the genetic sequence was revealed. As of March 2021, 179 vaccines are now in the preclinical stage, 63 vaccines are in the clinical development stage [4], and a few are now in emergency use in different countries.

Here in this article, we focus on available and promising therapeutic options of COVID-19, including repurposed drugs such as Chloroquine, Hydroxychloroquine, Lopinavir–ritonavir, Remdesivir, Ivermectin, Ribavirin, Favipiravir, Nelfinavir, Nitazoxanide, Tocilizumab, as well as Chinese therapeutic medicine, Ayurveda. A maximum of the people opted for home-based treatment from the beginning. We have tried to briefly review that some of these home-based practices are given national recognition to treat COVID-19 that will help in the cause either directly or as co-therapy.

2.0 Therapeutic approaches against COVID-19

COVID-19 was a new disease to people, so when it broke down, People were even scared of COVID-19 affected people, but within time, people tried to prevent and control it with their traditional therapeutic practices such as functional food, exercise even before exposing to repurposed drugs. Here we will be discussing the taken measures in almost every household from the beginning of the COVID-19 outbreak.

2.1 Traditional/ Conventional home-based practice

Initially, when people were unaware of the treatment of COVID-19, they used to try some orthodox treatment practices at home to treat the affected ones. From the beginning till now, some people are doing gurgle with warm water/saline water, inhaling vapor/ steam therapy in the belief that it will kill coronavirus. They inhale/ gurgle boiled water alone or sometimes mixing with other ingredients like lemon, orange, garlic, ginger, cayenne, tea tree, eucalyptus, neem, or essential oils (e.g., peppermint oil). It is advised to inhale the hot steam for 15 minutes or as much as one can stand with it.

A survey conducted by Al Hamdani found that 80% of the doctors suggest steam inhalation in respiratory tract infections caused by virus/ allergen [5]. During the lockdown, a similar practice went viral on social media that inhaling the steam of sea salt and orange peelings can prevent Covid-19; surprisingly, Tanzania believes inhaling steam can curb COVID-19. Their government initiates a nationwide campaign to promote steam inhalation calling out vaccines as "dangerous." However, this practice lacks scientific evidence; moreover, it is risky and reported scald injury. According to Brewster et al. [6], in the United Kingdom (UK), scalding has been increased 30 times more than usual due to this direct steam inhalation during lockdown due to Coronavirus.

During the pandemic, people also increased having warm water with ginger, clove & lemon; having warm water a few times a day clears the phlegm from the throat and reduces coughing. People were also consuming black cumin seeds, vitamin C-containing fruits, garlic, turmeric, ginger, cinnamon, black pepper, and honey. People are taking these as preventive measures, co-therapy, post-recovery treatment, even in many cases.

They take these only as a home-based treatment therapy against COVID-19 instead of admitting themselves into the hospital.

2.2 Intake of Functional foods as a prevention tool and/or treatment aid against COVID-19

In the beginning, people were dependent on their immunity as there were no treatments for COVID-19, so they tried their best being resilient against COVID-19 by taking functional food. The health fettle of an individual gets compromised by quite a lot of factors such as age, gender, lifestyle, disease condition, so during the pandemic; people have more plant-based green vegetables like Spinach, Kale, Artichoke, Broccoli, Arugula, Watercress, Okra, Green bean to boost up their health condition. Higher infection and mortality rates in COVID-19 affected people with weak immunity, corpulence, high pressure, cardiac diseases [7]. Especially in England, the mortality rate of COVID-19 patients with type-2 diabetes was 31.3% [8]; also, mechanical ventilation requirement increased twice among COVID-19 affected patients who were obese compared to the healthy weight individuals [9].

Functional food may not cure COVID-19, but it has excellent importance combating COVID-19 by controlling weight, blood pressure, sugar & cholesterol levels. Moreover, it helps us be healthy individuals to fight against any disease.

2.3 Intake of immune-boosting and anti-oxidant nutraceuticals

Optimal nutrition can improve the immunity of an individual and decrease the fatality rate of COVID-19. Individuals can boost their immune defense mechanism by having immune-boosting vitamins, micronutrients, and anti-oxidant nutraceuticals such as Vitamin C, E, D, B12, D, E, and Magnesium Copper, Selenium & Zinc, against different microorganisms along with SARS-CoV-2.

Vitamin C is an anti-oxidant that can induce a cascade of reactions, including phagocytosis, leading to eliminating microorganisms [10]. Studies found that having 1g of Vitamin C per day increased IL-10 secretion and reduced cold among 10708 participants [11]. In another study, Vitamin C is a vital key to combating COVID-19 as consuming 2 to 8 gm of vitamin C reduces the duration of respiratory infection and taking 6 to 24 g/day reduces mortality rate and hospital stays [12]. Among COVID-19 patients who received the high-dose vitamin C intake along with other drug treatments (such as hydroxychloroquine, azithromycin, colchicine, and zinc) showed faster recovery & lesser requirement of mechanical ventilation from the patients who didn't consume the vitamins[13]. The estimated average requirement (EAR) for fruits and vegetables is 100 mg/d or 200 mg/d [14].

The severity of COVID-19 is proportional to the unregulated increased production of cytokines, and Vitamin D helps modulate immune function by decreasing the production of pro-inflammatory cytokines [15, 16]. The dose for older people with diabetes and other disease conditions is 20-50µg/d of to enhance their resistance to Covid-19 [16].

Zinc is the crucial trace element for COVID-19 infection because of its double immunomodulatory and anti-viral effects. A high dose of zinc intake has increased the

efficacy of other medication for COVID-19 like hydroxychloroquine [17] and decrease COVID-19 symptoms as it has previously shown to have the ability to inhibit viral uncoating, binding, replication [18], and protect lung cells from damage caused by inflammation [19].

Another nutrient, Omega-3 fatty acid, has shown anti-viral effects by inhibiting influenza virus replication; we can assume that taking Omega-3 fatty acid-containing food will help control the SARS-CoV-2 virus though more research is necessary to establish the fact.

Anti-oxidants and nutraceuticals might not be the treatment for COVID-19. However, the immunomodulatory effect, stimulation for antibody production, cell-mediated immune response, adaptive immune response all accumulatively contribute to mitigating the fatality & progression of COVID-19, thus need to be investigated on a broader scale.

3. Treatment of patients with the repurposing of existing anti-viral drugs

Chloroquine

Chloroquine is a broad-spectrum drug used to treat malaria [20] and autoimmune diseases [21]. It inhibits virus cell entry by increasing the endosome's pH level, lysosome and interrupting glycosylation of cellular receptors [21,22]. Gangliosides and ganglioproteins attaching to Sialic acids act as receptors for virus-cell entry [23] binding with viral spike proteins [24,25] such as influenza virus [26] and Coronavirus [27,28]. Fantini et al. [29] illustrated that chloroquine interrupts the interaction of the Spike glycoprotein of SARS-CoV-2 with the gangliosides, thus blocking the first phase of viral replication.

Initially, chloroquine phosphate was prescribed to the COVID-19 patients in Wuhan twice a day, a dose of 500 mg [30] and later in the US and other countries stock them for the treatment of COVID-19 but soon after finding out its side effects such as gastrointestinal, ocular, and cardiovascular toxicity the use of this drug was revoked by FDA in June 2020 [31, 32].

Hydroxychloroquine

Hydroxychloroquine is a synthetic derivative of chloroquine [33] used to treat autoimmune diseases for many years [34, 35], and comparing with safety, dose requirement hydroxychloroquine is found better than chloroquine [35,36].

In a non-randomized open-label clinical trial, COVID-19 patients were treated the first seven days with hydroxychloroquine sulfate only with a 200 mg dose three times a day. Next, eight days patients were given hydroxychloroquine sulfate and azithromycin in combination showed a significant change in viral clearance than in patients treated only with hydroxychloroquine [37]. In another six studies where hydroxychloroquine didn't show any significance to the patients, hydroxychloroquine couldn't decrease the viral load, need mechanical ventilation, and hospitalization duration [38]. Added that the

effect of hydroxychloroquine is not consistent with clinical trials done on humans [39], and it shows a wide range of drug-drug interactions such as Tramadol, rifampicin, Amitriptyline, amiodarone, Duloxetine [38,40] hence we can not conclude hydroxychloroquine as a repurposed anti-viral drug for COVID-19, and its use against COVID-19 has been revoked as well [38,41]

Lopinavir-ritonavir

Lopinavir/ritonavir is an anti-viral drug that decreases viral load in SARS-infected patients in a clinical study [42]. In a randomized clinical trial,199 patients were given 400 mg and 100 mg oral doses twice a day for 14 days, and at the end of the trial, lopinavir-ritonavir failed to reduce viral load was no noteworthy improvement in COVID-19 patients. With great disappointments, 40.7% SARS-CoV-2 RNA was retained on the 28th day of the trial[43].

On the contrary, a 54 years old patient was treated with 200 mg of lopinavir and 50 mg of ritonavir twice a day for eight days, and from the second day of drug administration, viral stock reduced and almost cleared out the viral load at the end of the trial [44].

The reduction of viral load may also happen due to other biological natural mechanisms because the treatment by lopinavir-ritonavir failed to show earlier clinical improvement, so more clinical research is needed to establish it as a potent therapy for COVID-19.

Remdesivir

Remdesivir is an anti-viral agent formulated for the Ebola virus [45]. In the case of in vitro assays, remdesivir and interferon-beta showed more efficacy than lopinavir-ritonavir, and it was also highly potent against RNA virus due to its ability to delay RNA virus synthesis [46]. The first COVID-19 patient in the United States was treated with remdesivir, and their health condition got better within the first few doses [47]. In a randomized placebo-controlled, double-blind clinical trial, remdesivir was injected intravenously 200 mg on the first day and 100 mg from the second day to the tenth day of the trial; and intravenous remdesivir was well tolerated in the patients there weren't any concerning adverse effects, but it wasn't significantly effective to the seriously ill patients [48].

The FDA approved remdesivir under the brand name Veklury only for hospitalized COVID-19 patients, and it is found effective in three separate randomized clinical trials [49] with very little drug-drug interaction.

Ivermectin

Ivermectin is an FDA-approved broad-spectrum drug [50] with anti-viral effect [51, 52]. It was invented in 1975 and first introduced to veterinary usage in 1981 and for human use in 1988 [53, 54]. It has effectively inhibited integrase protein (IN) nuclear import of host cells [55, 56].

Caly et al. [57] conducted an experiment where ivermectin was given the concentration of 5μM to the SARS-CoV-2 virus-infected Vero cells to find out its anti-viral activity. After RT-PCR analysis of the supernatant cell pellets, 93% viral load was reduced in 24 hours, and 99.8% was reduced in cell pallets. Compared to the control group, viral load reduced around 5000 fold in the ivermectin-treated group, and there wasn't any presence of toxicity[57]. In Bangladesh, a study was performed where COVID-19 positive patients were treated with Ivermectin and Doxycycline with the dose of 0.2 mg/kg and 100 mg, respectively. Patients fully recovered within 72 hrs with no visible side effects [58]. In a review by Vora et al. [59], Ivermectin is suggested possible repurposed drug for the treatment of COVID-19. The proposed dose is 12 mg for 5 to 7 days [59]. In another study, Ivermectin .2/kg and Doxycycline 100 mg/kg were given to 60 COVID-19 patients simultaneously for ten days, and a new 56 COVID-19 patients were treated with Hydroxychloroquine and azithromycin with 400 and 500 mg dose respectively for five days. Both of the drug combinations were well tolerated, but the efficacy of Ivermectin and Doxycycline came out better than the drug duo Azithromycin and Hydroxychloroquine in terms of safety adverse effect and recovery time [60]. Ivermectin has convincing efficacy; thus, further rigorous researches are required to establish it as COVId-19 drug therapy.

Ribavirin

Ribavirin, a broad spectrum guanosine analog, and an anti-viral agent were found effective against MERS-CoV [61]. Ribavirin reduces viral load by frustrating RNA & DNA virus replication. It was one of the first five drugs that got approval for emergency use for the COVID-19 treatment, and the revised intravenous dose was 500 mg twice or thrice a day [62]. Though Ribavirin can reduce viral load, it has shown teratogenic effect in an animal model, so pregnant COVID-19 patients should avoid it; it also increases anemia, gastrointestinal adverse effects making it less eligible repurposed drug for the treatment of COVID-19 [63].

Favipiravir

Favipiravir is another guanine analog that impedes RNA virus replication by inhibiting RNA-dependent RNA polymerase enzyme reaction and using against the Influenza virus since 2014 [64,65]. The current dosage regimen is 1800 mg BID on the first day and 800 mg BID from the 2nd day to a maximum of the 14th day [66]. Favipiravir reduced the SARS-CoV-2 virus in Vero E6 cells [67] and reduced the viral load in COVID-19 patients in an open-label, non-randomized trial compared to the lopinavir/ritonavir [68]. Furthermore, Favipiravir performed better than arbidol with a 71.43% recovery rate, where arbidol had 55.86% [69].

Though favipiravir has a good safety profile from 4000+ patients [70], it increases blood sugar level, gastrointestinal adverse effects, and found contraindicated to pregnant and lactating women.

Arbidol

Umifenovir, branded as arbidol, is a derivative of indole used in China and Russia for influenza, showing the potential to inhibit SARS-CoV-2 virus entry and replication [71]. In a randomized clinical trial in Iran, arbidol is found effective and better than KALETRA (Lopinavir/ritonavir) to treat COVID-19 patients. Arbidol was given 200 mg TDS for 7 to 14 days considering the condition of patients [72]. In another study conducted on the frontline health workers in China, Arbidol inhibited viral replication and didn't significantly change in severe cases; mainly, it works well as a prophylactic drug [73]. In another retrospective study, Umifenovir aka arbidol neither could improve the prognosis of mild or severe COVID-19 patient's condition nor have any severe adverse effects [74]. Due to the different outcomes of clinical trials, it's confounding to conclude. Hence we suggest carrying out more randomized clinical trials to determine the role of arbidol against SARS-CoV-2.

Nelfinavir

Nelfinavir is an FDA-approved HIV protease inhibiting agent that markedly inhibits SARS-CoV-2 replication, whereas arbidol works at the entry site of the virus; nelfinavir exerts its effects in the post-viral infection [76]. On the contrary, in research conducted on the hamster, nelfinavir didn't show any anti-viral impact, but it could reduce viral pathology significantly [77]. Another study performed in Vero cells found nelfinavir effective in inhibiting SARS-CoV-2 cell infusion and cytopathic effects of the virus [78]. Nelfinavir effectively reduced mild to severe condition patients who have cough, fever, myalgia, and shortness of breath, 1250 mg of nelfinavir was given two times a day [79].

Nelfinavir has the potential to be a protective drug that can reduce SARS-CoV-2 fatality, but the current data aren't consistent; hence more exploration is required to clear out its role ta battle COVID-19.

Nitazoxanide

Nitazoxanide is an FDA-approved anti-parasitic and anti-viral agent that can inhibit SARS-CoV-2 replication when given a dose of 500 mg BIS for five days [80]. While other drugs, including hydroxychloroquine, arbidol, remdesivir, act on the mild to moderate stage of COVID-19, nitazoxanide performs on the severe stage as it can reduce the cytokine storm [81]. In Mexico, a study was conducted on COVID-19 affected frontline healthcare workers to determine the efficacy of nitazoxanide; they were orally administered 500 mg every six hours for two days and 500mg BIS for the next four days. In this study, nitazoxanide reduced viral load and the requirement for hospitalization [82].

More than ten clinical trials are registered only with nitazoxanide and other drugs, and these clinical trials mostly use 500 mg to 600 mg BIS a day [83]. Nitazoxanide has a significant potential to reduce the cytokine storm; hence it can attenuate the disease's fatality. To establish it as a prophylactic drug for COVID-19 more randomized clinical trial should be performed.

Tocilizumab

Tocilizumab, a monoclonal antibody, is an IL-6 receptor antagonist used to treat rheumatoid arthritis [84] is one of the potential drug targets for COVID-19. China and Italy approved the use of tocilizumab for the cure of COVID-19 [85]. The SARS-CoV-2 virus induces the overproduction of cytokines such as interleukin-6 (IL-6) that binds with the host cell and causes cytokine storms leading to severe inflammation in the lungs and other organs [86]. Tocilizumab binds with these IL-6 receptors, blocking IL-6 from binding with the target cell, stalling the disease prognosis [87]. In a study, tocilizumab reduces cytokine storm that was performed on 15 patients [88]. In another clinical trial, tocilizumab showed rapid relief of hypoxemia and lung opacity after the administration of tocilizumab [86].

Another significant effect of tocilizumab was recorded when a man with the symptoms of COVID-19 was admitted into the Infectious Disease Department of Landspitali, ICELAND. He was treated with intravenous ceftriaxone and oral azithromycin, and hydroxychloroquine, but his condition worsened with increased blood inflammation. He was taken into ICU and treated with tocilizumab with a dose of 400 mg intravenously. Within few hours, he was feverless and was discharged from the hospital with an improved vital sign and remained asymptomatic 34 days after the onset of illness [89].

On the contrary, a 40 years old COVID-19 patient was administered hydroxychloroquine and azithromycin initially, but after two days, his condition continued to deteriorate with hypoxemia, bilateral chest infiltrates. On the fourth day, he developed septic shock and increased inflammatory markers; then, 4000 mg of tocilizumab was given intravenously but with a high fever of 109 degrees, decreased C-reactive protein (CRP), and septic shock he passed away the very next day [90].

Another case study of 69 years older woman was administered 560 mg tocilizumab intravenously when she had acute hypoxemic respiratory failure and septic shock, but her condition deteriorated. Inflammatory biomarkers kept increasing even though the intravenous dose increased to 700 mg, and she succumbed to death [90]. In some cases, tocilizumab showed a very rapid cure, and in some other cases, it failed to do so, and it's not even clear that the worsened condition is due to tocilizumab; it's still not clear if tocilizumab might have worsened the clinical situation of those. So more clinical trials in a wide range should be conducted to explore its efficacy and reverse effects.

Corticosteroid therapy

Corticosteroid therapy was used to treat MERS (Middle East respiratory syndrome), mostly hydrocortisone, dexamethasone, and methylprednisolone were found to associate with reducing viral load in the clinical trials [91] and as SARS-CoV-2 is similar to MERS hence corticosteroid therapy is also being suggested for the treatment of COVID-19. The doses for COVID-19 are suggested as follows, Dexamethasone 6 mg intravenously daily until recovery or methylprednisolone and prednisone 32 mg and 40 mg, respectively [92]. Between them, methylprednisolone performed better [93] due to its ability to

335 penetrate the lungs deeper [94]. The mortality rate was lesser than the
336 dexamethasone-treated group demonstrated from a triple-blinded randomized trial [93].
337 The duration for therapy should not exceed more than 14 days after the onset of acute
338 respiratory distress syndrome (ARDS) because the prolonged use of corticosteroid
339 increases the risk of mortality even though it improves the disease condition [95]. In a
340 randomized open-label clinical trial, 6 mg dexamethasone was given intravenously for
341 ten days. Dexamethasone suppressed the over inflammation and reduced mortality in
342 critically ill COVID-19 patients [96,97], but there wasn't any effect on respiratory support
343 [96].

344 According to another randomized double-blinded clinical trial, corticosteroid does
345 not have a significant therapeutic effect and suggested not to use due to their delayed
346 viral clearance, the immunosuppressing impact [97], the inability to halt disease
347 progression the possibility of inducing psychoses [98].

348 On the whole, there is no substantial proof available that corticosteroids are
349 beneficial to treat SARS-CoV-2. It is suggested not to conclude corticosteroid treatment
350 further for the treatment of COVID-19 except for clinical trials [99, 100].

351

352 **4. Treatment of patients with antibiotics to prevent secondary infection**

353 Antibiotic does not work against the virus; they mainly act against bacteria;
354 therefore, antibiotics cannot be used for prevention or cure of SARS-CoV-2 infection, but
355 during the pandemic, health care practitioners weren't much aware of the prognosis of
356 the disease COVID-19 hence they used antibiotics to treat the infected ones.

357 Clarithromycin, Teicoplanin, Ciprofloxacin, Metronidazole, Moxifloxacin,
358 Piperacillin, Tazobactam, Benzylpenicillin, Amoxicillin, Meropenem are some antibiotic
359 drugs that were used to treat suspected as well as confirmed COVID-19 patients for
360 associated pneumonia or flu-like symptoms [101]. It was also reported that among
361 COVID-19 patients, 8% of people experienced both fungal and bacterial co-infection;
362 however, 72% received antibacterial therapy [102].

363 Teicoplanin, a glycopeptides antibiotic [103, 104] used to treat the influenza virus,
364 MERS-CoV is a potential repurposed drug for SARS-CoV-2 as well [104,105].
365 Furthermore, Zhang et al. [103], teicoplanin ceases viral replication by acting on the early
366 stage by preventing the release of virions with a dose of 400 mg per day [103], thus
367 makes it a potential candidate as a COVID-19 repurposed drug.

368 Azithromycin is one of the most used antibiotics; azithromycin can reduce viral
369 load when combined with hydroxychloroquine [106]. In a Bangladeshi real-life
370 observational study, we found, out of 33 patients, 30 patients recovered after 14 days of
371 treatment with azithromycin in combination with hydroxychloroquine[107]; in contrast,
372 nineteen hospitalized patients in France treated with some antibiotics such as amoxicillin,
373 cephalosporins, and macrolides [108] didn't receive any change [108]. Supporting this
374 conflict, Touret et al. [109] said azithromycin alone could inhibit viral replication, where
375 Andreania discarded this, explaining that azithromycin is effective only when given in
376 combination with antiviral drugs such as hydroxychloroquine [110].

However, antibiotic is suggested only in mild cases of COVID-19 and in some severe cases where the secondary infection is present also, overuse of antibiotics can lead to multidrug resistance.

5. Usage of NSAIDs/ anti-inflammatory drugs to prevent inflammation and cytokine storm

Non-steroidal anti-inflammatory drugs (NSAIDs) are broadly used in cases of ibuprofen, diclofenac, aspirin. NSAIDs were suggested to use as an adjunct treatment for patients with severe COVID-19 infection [111]. Relying on some unpublished small-scale study on March 14, France asked to stop using NSAIDs (eg. Ibuprofen) and it got attention worldwide [112].

One of the most common drugs is ibuprofen which is available as an OTC drug also and was being used as co-treatment for COVID-19; later on, its usage was withdrawn, suspecting that ibuprofen is associated with the increased adverse reaction and worsen disease condition among COVID-19 patients [113, 114]. However, according to Wong et al. [112], they declared that there is no such evidence that routinely used NSAIDs such as ibuprofen [115] using for the treatment of COVID-19 can deteriorate the condition or can cause death [112].

NSAIDs neither reduce viral load nor induce adaptive or innate immunity, but there is an indirect association of NSAIDs with COVID-19 as these drugs reduce cytokine production, which is a pathological condition. However, its efficacy is also not cleared as it neutralizes the antibody production of the host [116]. Hence, the use of NSAIDs in the treatment of COVID-19 is still a pressing topic for researchers; therefore, more clinical trials should be conducted in the future.

6.0 Immunotherapy

6.1 Convalescent plasma transfusion

Convalescent plasma therapy is the passive immunization method that is in use since the 1890s, and this is one of the emergency methods to combat any endemic/pandemic disease; utilizing the previous experience from MERS and Ebola virus, convalescent plasma therapy is being used to treat SARS-CoV-2 patients [117]. We can see the real-life efficacy of the plasma therapy for COVID-19 when it was given to the health workers in a Taiwan hospital during the SARS epidemic. The virus was cleared within one day, along with reducing fever and respiratory infiltrates [118]. Recently, in a lab test, serum collected from the bronchoalveolar lavage of a critical patient neutralized SARS-CoV-2 [119]. High neutralizing antibody titer convalescent plasma should be collected not more than two weeks after recovery [120].

The difficulty in obtaining plasma during the period of recovery puts a limitation on its clinical application. Therefore, well-designed clinical trials are needed to evaluate further the efficacy, safety, and availability of convalescent plasma therapy.

417 *6.2 Antibody neutralizing therapy*

418 Antibodies can reduce viral production by inhibiting the attachment and
419 penetration on the host cell and ceasing viral uncoating into the cell [121]. In SARS-CoV-2,
420 spike glycoprotein is the main target of neutralizing antibodies (NAbs) [121].

421 Monoclonal antibodies MAbs casirivimab and imdevimab under the brand name
422 REGN-COV to treat mild to moderate COVID-19 patients produced by Regeneron
423 Pharmaceuticals are approved by FDA for emergency use. The cocktail of the antibodies
424 is laboratory-made and specific to SARS-CoV-2; they act by inhibiting the attachment
425 and entry of the virus and are found to improve disease conditions for less severe cases
426 of COVID-19, the dose for both antibodies is 1200 mg each in a single intravenous
427 infusion [122, 123]. In a randomized study, 7000 mg of Monoclonal antibody LY-CoV555
428 was co-administered with remdesivir, but there were no significant outcomes in severe
429 cases and found a slight decrease in viral load in outpatients [124].

430 Between two immunotherapy mAbs are more efficient, precise, and safe than
431 convalescent plasma therapy [122]. The drawbacks are titer antibody, the requirement of
432 vast range production along with its high cost [121]; however, a more clinical trial should
433 be performed for prophylaxis and treatment of COVID-19 because vaccines are still
434 uncertain and the vaccine requires few more weeks to activate whereas neutralizing
435 monoclonal antibodies acts right after administration.

436

437 *6.3 Interferon treatment*

438 Interferons are signaling proteins that are produced and released by host cells in
439 response to viral pathogens. Currently, they are in use to treat sclerosis, hepatitis B, and
440 C [125]. Interferons are classified as type I including subtype g α, β, ω, ε and κ, type II
441 and type III.

442 Interferon α (IFN-α) has reduced viral count and shortened disease duration [126].
443 A clinical trial was conducted on 446 COVID-19 patients in Hubei, China, where IFN-α2b
444 was given in the early stage of treatment and found less mortality than patients treated
445 the same. However, administering IFN-α2b at the last stage increased mortality among
446 critical patients of COVID-19 [127]. From previous, in vitro studies of severe acute
447 respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome
448 coronavirus (MERS-CoV), we get to know about the antiviral effects of Interferon β
449 (IFN-β) [128]. Furthermore, IFN-β-1a, named SNG001, has also been found to improve
450 lung function, recovery rate, shortness of breath, and mortality rate when administered
451 as a nebulizer in a phase-II trial conducted on July 20, 2020 [129].

452 IFN-γ is an immune regulatory protein that exerts its antiviral activity by
453 restricting viral replication and production, inducing regulatory T cells and
454 antigen-specific regulatory B cells, and found effective in the last stage of COVID-19
455 treatment by inhibiting replication of SARS-CoV-2 virus [129].

456 Pegylated Interferon lambda 1 (IFNλ-1) is the only therapeutically used Interferon
457 lambda. The key mechanism is to induce an antiviral effect within epithelial cells and
458 halt viral replication [128,130]. Several clinical studies have been conducted, but those are

either for a short period or with some other antiviral drug, so further investigation should be done.

Interferon therapies have great potential to treat COVID-19. However, some crucial factors need to be determined, such as route of administration (for bioavailability), time of the therapy (early or critical stage of the treatment), combination with other drugs, existing proven side effects.

7.0 Treatment of COVID-19 patients with herbal medicines/phytomedicines

7.1 Traditional Chinese Medicine (TCM) against COVID-19

Whether herbal medicines can kill viruses is still not a fact, but Therapeutic Chinese Medicine (TCM) is believed to alleviate symptoms [131], reduce the severity of the virus, improve recovery rates and reduce the mortality rate. Generally, Therapeutic Chinese Medicine (TCM) is formulated and suggested considering the patient's clinical symptoms mainly.

The most common symptoms of COVID-19 disease are fever, myalgia, and dry cough, then it deteriorates to pneumonia and finally death. Based on these, different herb formulas are introduced to treat COVID-19 patients [131]. To treat the mild condition of COVID-19 Lianhuaqingwen capsules and Jinhuaqinggan granules and for severe infections, injectable Xuebijing is declared as a treatment option in China on April 14, 2020; they claim to alleviate COVID-19 fever, fatigue, cough and doesn't let the condition get deteriorated [132].

In the case of Therapeutic Chinese medicine (TCM), Qi is considered as the significant substance which is divided into the healthy Qi and the pathogenic Qi. Properties that help to maintain the human body's regular operation are known as healthy Qi, where else The pathogenic Qi can harm the health of our body [133]. In the article, Xu [133] mentioned, Yupingfeng San, an ancient herb, can be potent preventive medicine for COVID-19 as it was practiced in TCM used to protect lung Qi and to heal the pathogenic Qi; herbs Astragalus, Fangfeng, and Atractylodes is suggested to use for their ability to reduce dampness in the lungs [133].

There are another two prescriptions used in TCM to treat viral lung infections. They are called Sangju yin (Mulberry leaf, Chrysanthemum, Forsythia, Almond, Mint, Chinese bellflower, Reed root, Licorice) and Yinqiao san (Forsythia, Chinese bellflower, Honeysuckle, Mint, Bamboo leaves, Licorice, Nepeta, Light tempeh, Burdock). The primary function of these two prescriptions is to restore normal lung function reducing lung heat, cough & expelling phlegm. Clinically, Yinqiao san is suggested for patients with a high fever and Sangju yin for patients with severe cough [133]. The mixture of these plants is boiled with 1000 ml pure water for 15 minutes, and a 600 ml tincture is obtained from it and orally administered 200 ml dose three times a day [133].

Glycyrrhizin, a principal active constituent of licorice root, is the most commonly used in TCM has been found to inhibit the replication of coronavirus significantly in Vero cells [134, 135]. The early stages of the replicative cycle inhibit the virus from attachment and penetration to the host cell. Though the mechanism of Glycyrrhizin isn't

precise, it was found the most effective when given during and after the adsorption period (EC50 300 mg/L) [135].

In another study, the Chinese herbal compound baicalin, derived from *Scutellaria baicalensis*, is found effective in reducing virus load & also it is a cheaper option; more clinical studies should be performed to establish baicalin for the treatment of COVID-19 [134]. Recently a panel was formed by The State Administration of Traditional Chinese Medicine of the People's Republic of China has produced a formula to clear lung mucus and detoxification. The recipe is consists of Astragalus membranaceus, Bupleurum chinense, Mentha Canadensis, Ephedra sinica, Prunus armeniaca, Gypsum Fibrosum, Adlay, Wax gourd, *Platycodon grandiflorum*, *Scutellaria baicalensis*, *Glycyrrhiza uralensis, Flos lonicera, Artemisia apiaceae* [134].

Many medicinal herbs are being used for years in TCM; the suggested herbs/ herbs formula should be concluded in clinical trials to have known good efficacy.

7.2 Ayurveda against COVID-19

Ayurveda, a conventional treatment system, originated more than 3000 years ago. There's a mention of epidemic disease control in The classic Ayurveda text Charaka Samhita where immunity has been considered the main factor in preventing and arresting the disease's progression. The concept of immunity (Bala or strength) in Ayurveda is categorized as natural (Sahaja), chronobiologic (Kalaja), and acquired (Yuktikrut) [136].

COVID-19 positive and older people with other disease conditions are suggested to have 500mg extract or 1-3g powder of Tinospora cordifolia (known as Ashwagandha/ Guduchi Ghana Vati) two times a day with warm water for half to one month, or 10g of Chyawanprasha (an Indian dietary supplement) with warm water or milk once a day [137].

There is one clinical study published on ayurvedic treatment received by only one COVID-19 positive patient living in Newyork. He had severe body ache and fever and eventually lost his taste and smell; by consulting an ayurvedic practitioner in India, he received the following medication; Sudarsana Churna 4 tablets (2 gms), Talisadi Churna 1tsp with honey, Dhanwantara Gutika 2 tablets for 14 days. By following this ayurvedic regimen, he got cured, yet ayurvedic therapy cannot be considered the conventional treatment method for COVID-19 as it's a solo case study and the patient had mild to moderate disease condition which only limited to body ache and fever [138]. Sanjeevani Vati, Chitrakadi Vati, and a combination of Guduchi (Tinospora cordifolia), Shunthi (Zingiber officinale), and Haridra (C. longa) are suggested for the asymptomatic patient to prevent disease progression [139].

A decoction made with some ayurvedic herbs including *T. cordifolia, Z. officinale*, *C. longa, Ocimum sanctum, Glycyrrhiza glabra, Adhatoda vasica, Andrographis paniculata*, *Swertia chirata, Moringa oleifera*, Triphala, and Trikatu is also suggested to a group of patients for their antiviral and protease inhibitor effects [140] and P. Rasayana, Laghu Vasant Malati, Sanjeevani Vati, Tribhuvan keerti rasa, Brihata Vata Chintamani rasa, Mrityunjaya rasa, and Siddha makardhvaja rasa are recommended for mild to severe patients [141,142].

Ayurveda also suggested 'Nasya,' which is the nasal instillation of herbal oils/powders [143] such as butter oil (known as Ghee) and vegetable oils such as sesame or coconut in the nostrils as a possibility to prevent virus entry creating a biofilm barrier. Medicated water, a mixture of single or multiple herbs to the boiling water, is suggested to be consumed as medicine throughout the day. These spices include *Zingiber officinale*, *Glycyrrhiza glabra*, *Cyperus rotundus* rhizomes, *Vetiveria zizanioides*, *Hemisdesmus indicus* roots, *Coriandrum sativum*, and *Cuminum cumin* seeds, *Cinnamomum Verum*, and *Acacia catechu* barks [144].

Ayurvedic medicine has all the potential to be used in conventional treatment, but there is some significant limitation too, one of them is ayurvedic clinicians do not have access to COVID-19 patients in clinical settings [145]. Thus, there is a huge lack of investment and diagnosis concepts in Ayurveda.

7.3 Traditional herbal medicines against COVID-19

Artemisia annua has grabbed our attention; it has been using widely in the past in many regions of Africa and Asia for malaria, viral infection, and cancer treatment [146, 147]. For example, the president of Madagascar has called it a cure for COVID-19 where it is known as COVID Organic drink containing *Artemisia annua* extract. The main ingredients that fight against COVID-19 are called artemisinin, and another one is synthetic Artesunate 2 derived from *Artemisia annua* [148].

The Artemisia annua found effective against SARS-CoV-2, especially Artesunate 2, has a higher toxicity than Artemisinin though there is also a chance for people who will be having artemisia annua extract may develop resistance to Plasmodium falciparum (Malaria causing parasite). A more clinical trial is required to establish it as an active pharmaceutical ingredient [148,149].

A study conducted by Khaerunnisa et al. [150] found some medicinal plants (*Capsicum annuum*, *Curcuma longa*, *Mentha longıfolia*, *Olea europaea*, *Phoenix hanceanaand*, *Camellia Sinensis)* effective against coronavirus. Glucoside, Curcumin, Oleuropein, Luteolin-7, Epicatechingallate, Catechin, Demethoxycurcumin, glucoside, and Apigenin-7 are some antiviral agents extracted from plants as mentioned earlier have shown inhibiting effects on COVID-19 Mopar protein [150]. However, more investigations are required to ensure their application.

In another article mentioned the extracts of *Ganoderma lucidum* (IC50:41.9 μg/mL), *Coriolus Versicolor* (IC50:108.4μg/mL), and *Sinomenium acutum* (IC50:198.6 μg/mL) confirmed their inhibition against SARS-CoV RNA polymerase enzyme in a dose-dependent manner which disrupted viral replication [151].

8. Oxygen support or Ventilation of patients during COVID-19 treatment

COVID-19 patients with oxygen saturation below 93% are given oxygen support. In these cases, mostly oxygen support is provided with noninvasive devices such as continuous positive airway pressure (CPAP) and bilevel positive airway pressure ventilators (BiPAP), where oxygen passes through a tube via a face mask. However, in the cases of acute respiratory distress, oxygen supports are given with an invasive mechanical ventilator via intubation [152]. The scarcity of oxygen was the most common

fear among all of the countries. We found that High-flow nasal oxygen (HFNO) reduces ICU requirements, hospitalization duration, and adverse reactions associated with invasive mechanical ventilation [153].

9.0 Vaccines

Vaccination is the most feasible way to prevent diseases. Unfortunately, vaccines are not available during the pandemic as the duration to develop a vaccine is 12-15 years. If we look at previous cases, we will see that the Ebola epidemic outbreak occurred in 2013, and it took three years to enter into the phase I clinical [154] and six years to get market authorization [155]. However, in the case of SARS-CoV-2, the genetic sequence was published on January 11, 2020 [156], and in early April 2021, 632 clinical trials have been registered; among them, 24 are in phase IV [157], which is relatively rapid and short duration to develop any vaccine but as the pandemic toll on massive mortality scientist all over the world is trying to create COVID-19 vaccine as early as possible. However, now there are no authorized vaccines available only vaccines from Pfizer-BioNTech, Moderna, and Johnson & Johnson are permitted for emergency use. SARS CoV-2, the spike (S) glycoprotein, is a crucial target for vaccines, therapeutic antibodies, and diagnostics [158], but other approaches for vaccine formulation against SARS-COV-2. We have shortly described here some SARS-CoV-2 vaccine candidates currently at an advanced stage in clinical trials, and some are being taken worldwide.

9.1 mRNA Based Vaccines

mRNA-based vaccines are significant for it's highly flexible, scalable, inexpensive, short production cycle, cold-chain free, and immunogenic in various conditions [159].

BNT162b2 vaccine

Four vaccines were developed by BioNTech, Pfizer, and Fosun Pharma named BNT162a1, BNT162b1, BNT162b2 BNT162c2 to a different antigen and mRNA format but similar to immune responses [160]. Following a worldwide Phase, three clinical trials with about 95% efficacy BNT162b2 vaccine received emergency use approval from FDA and were taken by almost 89 countries, including Argentina, Denmark, Bangladesh, Israel, the UK, the USA, and many other countries worldwide [161]. BNT162b2 is a nucleoside-modified messenger RNA virus that encodes SARS-C0V-2 spike glycoprotein after administering two shots of 30-µg doses BNT162b2 elicits a high amount of neutralizing antibody titers, stout antigen-specific CD4+ and CD8+ T-cell responses against SARS-CoV-2. Currently, it is the only vaccine that got approval for emergency use for people aged under 16 (12 to 15 years) with 100% efficacy [162].

The main disadvantage of BNT162 is that it requires a freezing temperature which is below −80 ◦C to store, and its potency gets reduced after five days of thawing. These limitations are the challenges to transport this vaccine to isolated areas and other countries [163].

Moderna (mRNA-1273) vaccine

The mRNA-1273 vaccine is developed by the US National Institute of Allergy and Infectious Diseases (NIAID) Vaccine Research Center and Moderna, Inc. [164] & shortlisted by WHO for emergency use for 53 countries [161]. Moderna Inc. has claimed to achieve 94.5% efficacy in Phase 3 clinical trials. It is formulated with synthetic mRNA encapsulated in Lipid nanoparticle (LNP) that codes for the whole pre-fusion stabilized spike protein (S) of SARS-CoV-2 [162]. The advantage of this vaccine is it's comparatively safe as it is not made with any inactivated pathogen or any sub-units of the live pathogen [165], and the disadvantage is its low shelf life, low stability also a ten times lower transfection rate than viral vectors [164, 166].

CVnCoV vaccine

CVnCoV is an mRNA-based vaccine developed by CureVac biopharmaceuticals. CVnCoV is made with optimized mRNA that codes a stabilized spike protein(S) similar to mRNA-1273 and BNT162. The vaccine has two doses that require to be administered within 28 days. It is currently in Phase 2/3 clinical trials but not yet approved for use also; there is no established reference for pediatric and pregnancy-related safety ball [156, 161].

9.2 DNA Based Vaccines

DNA vaccines stimulate adaptive immune responses in the host that encode the antigen and an adjuvant. Therefore, DNA vaccines have better stability, shelf-life than mRNA vaccines [168]. However, there is some disadvantage and low immunogenicity and requirement to pass nuclear membrane for transcription [169].

INO-4800 vaccine

INO-4800 is an artificially engineered DNA-based vaccine developed by Inovio Pharmaceuticals. It is formulated targeting at SARS-CoV-2 S-protein and administered intramuscularly or intradermally using a smart device called Cellectra [162]. INO-4800 translates into proteins to introduce an immune response inside the host body [168, 170]. A phase 2/3 trial is currently going on in the USA to determine its safety, tolerability, and immunogenicity in up to 6578 healthy individuals [168].

bac-TRL-Spike Vaccine

The bacTRL-Spike vaccine is an orally administered vaccine that contains live Bifidobacterium longum containing synthetic plasmid DNA that encodes the S-protein of SARS-CoV-2 [171]. A phase-1 clinical trial will evaluate the safety, immunogenicity, and tolerability of the bacTRLSpike vaccine in healthy adults in Australia [172].

GX-19 vaccine

GX-19 is a DNA-based vaccine designed by the biotech company Genexine Inc. in South Korea and is currently under Phase 2 clinical trials in humans. GX-19 is administered in two doses within 28 days [162].

9.3 Viral Vector Vaccines

Viral vector vaccines consist of a recombinant virus that is attenuated to reduce pathogenicity, and they can be either replicating or non-replicating [173]. They are characterized by solid immunogenicity and safety [174] and low-titer production, tumorigenicity, and host pre-immune condition [173].

ChAdOx1 nCoV-19 vaccine

The ChAdOx1 nCoV-19 vaccine is developed by Oxford University and manufactured by AstraZeneca Inc, which is also referred to as AZD-1222/ Vaxzevria, which is formulated with adenovirus vector ChAdOx1 containing the gene of the whole spike protein of SARS-CoV-2 [161, 175]. It is also manufactured in INDIA under the name Covishield by the Serum Institute of India [161]. It induces abundant humoral and cell-mediated immunity against SARS-CoV-2 [175, 176]. This same vaccine is being manufactured in India named COVISHIELD by the Serum Institute of India [162].
Its manufacturer confirmed its efficacy and safety profile with zero hospitalization on December 8, 2020. AZD-1222 is currently in emergency use in the USA, UK, India, and other 112 countries [161, 175]

Gamaleya: Sputnik V

The Russian vaccine, Gam-COVID-VacLyo is a non-replicating viral vector, has been developed by the Gamaleya Institute of Epidemiology and Microbiology in Moscow, Russia, which is also known as Sputnik V. By approving the SARS-CoV-2 Vaccine Gam-COVID-VacLyo with 91.6% efficacy rate on August 24, 2020, Russian became the first country that has approved the COVID-19 vaccine [180]. It is an intramuscular vaccine formulated with two recombinant adenovirus vectors (Ad5 and Ad26). Sputnik V is currently approved for use in 68 different countries. The vaccine is significantly safe and strongly immunogenic as it produces strong humoral and cellular immune responses, but the main limitation of this virus could be pre-existing immunity in the human populace [161, 180, 181].

Ad5-nCoV: Cansino

Ad5-nCoV is a non-replicating recombinant type-5 adenovirus (Ad5) vector vaccine, also referred to as Convidecia, developed by the Cansino Biologics and Beijing Institute of Biotechnology, China [179]. It is tolerable, immunogenic, and induces the T-cell response from day 14 post-vaccination, and the humoral response was found at peak day 28 post-vaccination. However, some mild adverse reactions are noticed, including fatigue, fever, headache, and muscle pain [182,162]. Therefore, on June 25, 2020, China's Central Military Commission approved the use of Ad5-nCoV as an "especially needed drug" in China, and currently, it is approved in seven other countries, including Argentina, Chile, Ecuador, Hungary, Malaysia, Mexico, Pakistan [161, 183].

Janssen COVID-19 Vaccine (Ad26.COV2.S)

Janssen COVID-19 vaccine was developed by Janssen Biotech, Inc and approved on February 27, 2021, by FDA for emergency use; It is given as a single intramuscular single dose to people aged above 18 [184]. It is a recombinant vaccine based on modified human adeno vector 26; it replicates the spike protein of the SARS-CoV-2 virus. It is also known

as Ad26.COV2.S, Ad26COVS1, JNJ-78436735. The vaccine has been found effective 66% in mild symptomatic cases, 85% in moderate to severe cases, and 100% in preventing death/hospitalization, but it was reported to have thrombocytopenia with low platelets in six people after the vaccine administration to more than 6.8 million doses, and due to this the United States officials held the rollout of Janssen vaccine. However, it was resumed after declaring it a sporadic event[185]. Janssen vaccine is not FDA authorized yet but approved for emergency use in 52 countries [161, 186].

9.4 Protein Subunit-Based Vaccines

Protein Subunit vaccines for SARS-CoV-2 viruses depend on inducing immune response to prevent perfusion of S-spike protein to the host ACE2 receptor [187]. SARS-CoV-2 protein subunit vaccines can be classified into three categories, RBD-based vaccines, S-based vaccines, and virus-like particle (VLP) vaccines, and show potent immunogenic effects if administered with molecular adjuvants [188].

NVX-CoV2373 Vaccine

NVX-CoV2373 is a protein-based recombinant vaccine developed by Novavax, USA. The vaccine was formulated with the coronavirus spike (S) protein using Novavax's recombinant nanoparticle technology with their patented saponin-based Matrix-M adjuvant to improve the immune response and production of the maximum level neutralizing antibodies. It contains purified protein antigen that can neither replicate nor can cause the disease. NVX-CoV2373 is currently in evaluation in two pivotal Phase 3 trials in India, the United Kingdom of Great Britain, Northern Ireland, Mexico, Puerto Rico, United States of America [161,163]. Novavax has received funding of USD 384-million from the Coalition for Epidemic Preparedness Innovations (CEPI) [179] and USD 1.6 billion from the U.S. government [163].

PittCoVacc vaccine

PittCoVacc Vaccine (Pittsburgh CoronaVirus Vaccine) is a Micro-Needle Array (MNA) based recombinant SARS-CoV-2 vaccine developed by the University of Pittsburgh School of Medicine. It is administered in a method called a micro-needle array. In this method, a fingertip-sized patch of 400 tiny needles made entirely of sugar and the protein is administered, which delivers the spike protein pieces of the virus into the skin where immunogenicity is strongest. PittCoVacc is still in the preclinical phase.[179,189,190].

SCB-2019 vaccine

Clover Biopharmaceuticals develop the SCB-2019 vaccine formulated with S-Trimer protein and any of these two adjuvants such as AS03 or CpG/Alum; it showed high humoral and cellular response immune responses against SARS-CoV-2, with robust viral neutralizing activity. At present, in Australia, Phase 1 clinical trial is going on it[191].

9.5 Triple Antigen Vaccine

743 Premas Biotech in India developed the triple antigen vaccine. This multi-antigenic
744 VLP vaccine prototype has been created with the recombinant spike protein, membrane,
745 and envelope protein of SARS-CoV-2, co-expressing in an engineered Saccharomyces
746 cerevisiae expression platfo (D-Crypt™) [192]. It is comparatively easy to produce and
747 cost-effective; it is successful in animal testing, expressing immune response by
748 neutralizing antibody against SARS-CoV-2 and now in talks to take it in advance stage
749 [193].

750 *9.6 Inactivated Vaccines*

751 **BBIBP-CorV Vaccine**

752 BBIBP-CorVwas developed by the Beijing Institute of Biological Products and
753 Sinopharm in China. It is created with the inactivated 19nCoV-CDC-Tan-HB02 (HB02)
754 strain isolated from SARS-CoV-2 inside Vero cells. This vaccine showed strong humoral
755 and very mild common adverse effects, including pain and fever [194]. Phase 3 clinical
756 trials for BBIBP-CorV started in the United Arab Emirates in July and showed 86%
757 efficacy, and now it is approved for emergency use in 53 countries, including United
758 Arab Emirates [195].

759 **CoronaVac Vaccine**

760 CoronaVac is an inactivated viral vector vaccine developed by Sinovac Research
761 and Development Co., China [196]. Other vaccines usually use the spike protein for
762 antibody production, but the whole killed SARS-CoV-2 virus is used to formulate the
763 CoronaVac vaccine, and the entire region of the virus induces antibody production [197].
764 CoronaVac is the second Chinese vaccine approved by WHO with a 79% efficacy rate
765 and is currently in emergency use in 32 countries [161, 197].

766 **10. Conclusion and future directions**

767 This article presents a trenchant recapitulation of the current state of knowledge
768 and practice applying for the prevention and management of COVID-19. In this review
769 we have tried to present a landscape of the therapeutic options available till date and
770 different practices performed by the medical practitioners and patients. We believe this
771 write-up will contribute to the researchers worldwide to get an entire scenario and help
772 them fix their primacy of the research arena for COVID-19. Some emergency vaccines are
773 now available in limited quantity such as, Moderna, Pfizer, Johnson & Johnson,
774 Sinopharm, etc. which are mostly taken by the people worldwide. Yet, one of the major
775 drawbacks of these vaccines is we don't know indeed how long these vaccines will
776 protect us from getting infected due to the short duration of research. Among the
777 therapeutics mentioned above, ribavirin, remdesivir, tocilizumab, interferon, a Chinese
778 herb Artemisia annua have been found promising than others. Exercises/ yoga, Taking
779 earlier mentioned immune-boosting foods, multivitamins, etc play a vital role in
780 prophylactic of the disease.

781 The world isn't healed yet, but our current knowledge, medication, and awareness can
782 help us survive this pandemic. With this article, we tried to contribute to this current
783 struggling period so the commoners can ameliorate the disease condition and scientists

784 can get a birds' eye view of the current situation and take forward their research and
785 experiments.

786 **Supplementary Materials:** The following are available online at www.mdpi.com/xxx/s1, Figure S1:
787 title, Table S1: title, Video S1: title.

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801

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