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Re-examination of An Integrative Treatment Approach for SARS-CoV-2

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Abstract:- The COVID-19 pandemic, caused by the SARS-CoV-2 virus, has reached drastic proportions as infection rates and death tolls continue to skyrocket globally. Due to the hospital and medical staff having to endure supply shortages and strain, appropriate access to quality medical care is becoming increasingly difficult for patients of all demographics. Additionally, no vaccine or treatment approach has been concretely proven although many are undergoing research trials as of the drafting of this review. Because of these factors, doctors and medical professionals are increasingly turning to "compassion treatments," or last-resort methods that have not undergone sufficient clinical trials, to treat their patients. This is absolutely essential in a pandemic, especially with a novel virus such as SARS-CoV-2, however this paper aims to summarize many of these treatment methods for the purpose of providing researchers with materials, as well as a reliable starting point of information for doctors and medical professionals, who might otherwise be forced into potentially hazardous experimentation when patients are in critical condition. It is also important to have an in-depth understanding of the human immune response to the SARS-CoV-2 virus when designing any sort treatment approach. The treatment methods covered by this review include conventional approaches such as mechanical ventilation, corticosteroids, and repurposed drugs such as chloroquine and remdesivir. Alternative treatment approaches are also considered, such as supplemental and intravenous vitamin therapy, convalescent plasma therapy and monoclonal antibodies, and Traditional Chinese Medicine (TCM). In summary, an integrative approach using both the conventional and alternative treatment methods could prove to be the most successful in saving lives during the COVID-19 pandemic.

Keywords:- *COVID-19, SARS-CoV-2, immune response, treatment methods, conventional, alternative, traditional chinese medicine (TCM).*

I. INTRODUCTION

With over 2.5 million cases documented worldwide and the death toll approaching 200,000, the COVID-19 pandemic is a crisis of proportions that has not been seen for over 100 years [1], [2]. Caused by the betacoronavirus SARS-CoV-2, COVID-19 infections are characterized by prevalence of symptoms ranging from fever to lower respiratory symptoms, such as cough and dyspnea, to digestive symptoms and even seemingly unrelated symptoms such as loss of smell and taste [3], [4], [5]. While 80% of COVID-19 cases to date are classified as either asymptomatic or mild, infection can rapidly progress and turn into very serious conditions such as pneumonia, thrombosis, acute respiratory distress syndrome (ARDS), and cytokine storms [4], [6], [7]. Currently, disease mortality is positively correlated with age; however, there have been an increasing number of severe cases that have developed in members of younger demographics [3]. To compound the severity of the disease itself, there are currently global shortages of protective medical gear and supplies needed to treat patients, such as ventilators and respirators, which puts medical professionals in increasingly difficult positions as hospitals have become overwhelmed [8].

This narrative review aims to present as many options with proven scientific background for treating COVID-19 as possible. This paper is a call for researchers, doctors, and other medical professionals to find, and continue finding, creative ways to treat COVID-19 and assist patients in recovery. When met with a pandemic of such massive proportions, the researchers writing this review hypothesize that every treatment option with sound scientific reasoning behind it should be explored in order to develop a patient-centered, holistic approach that can save lives [2]. It should be clearly noted that all of the treatment methods covered in this review are in preliminary stages of research and require more clinical trials to prove their efficacy [3], [4].

II. MATERIALS AND METHODS

For this review, the Google Scholar and NCBI databases as well as the social media platform ResearchGate were used as the main search engines for emerging information surrounding treatment of COVID-19 over the period of one month, as well as background research conducted previously on the treatment methods in question. Search terms included but were not limited to: COVID-19, SARS-CoV-2, antiviral drugs for COVID-19, vitamin therapy and COVID-19, treatment options for COVID-19, and Traditional Chinese Medicine for SARS and COVID-19. Sources were evaluated based on two criteria: whether the source was scientifically sound and not misinformative, and the relevance of the source to the current pandemic. Researchers worked independently on their respective subsections and areas of focus before bringing their work together for review and improvement. All sources used were verified for their validity as well as relevance as information continues to be released surrounding the novel SARS-CoV-2. Finally, the immunological implications of SARS-CoV-2 infections were researched significantly using the aforementioned databases.

III. IMMUNE RESPONSE TO SARS-COV-2 INFECTIONS

In spite of the modest volume of evidence regarding the human immune response to SARS-CoV-2, inferences based on the previous epidemics of Sudden Acute Respiratory Syndrome (SARS)-CoV and Middle-Eastern Respiratory Syndrome (MERS)-CoV, may shed some light or, in the very least, pave the way towards a better understanding of infections with this novel betacoronavirus. Genetically, SARS-CoV2 is more closely related to the two bat-associated coronaviruses, bat-SL-CoVZC45 and bat-SL-CoVZXC2 (88%), than to SARS-CoV (79%) and MERS-CoV (50%) coronaviruses [9]. Although there are notable differences in certain amino-acid residues, the SARS-CoV2 receptor binding domain is structurally similar to that of SARS-CoV; thus far, it is known that SARS-CoV2 enters cells that express angiotensin-converting enzyme (ACE) 2, present on the surface of type 2 alveolar cells, renal tract, the heart, and the gastrointestinal tract [9], [10], [11]. Thus far, the hypothetical yet highly plausible course of infection is that the infection commences once the virus passes the respiratory mucosa and reaches the pulmonary tissue [12]. SARS-CoV2 then enters the pulmonary cells expressing ACE2 and likely uses the lung tissue to enter the bloodstream, causing viremia [12]. Once inside the host's bloodstream, the virus easily disseminates to the organs abundant in ACE2+ cells. Notably, the first stage of infection is rather silent, the virus is able to dampen or invade host immune defences, leading to a delay in symptom onset of approximately 7- or 8-days post-infection [12]. Although finer details behind the immune response at the innate and adaptive level are still unclear, similarities between the novel betacoronavirus and SARS-CoV and MERS-CoV, offer potential clues into the immune response and subsequent immunopathology of this infection.

A. Innate Immunity: Innate immune response to RNA viruses

In the context of innate immunopathology of COVID-19, fatal and severe cases of this diseases are marked with high neutrophil count, an elevated D-dimer, and an increase in pro-inflammatory cytokines such as interleukin-6, monocyte chemoattractant protein 1 (MCP-1/CCL2), and tumour necrosis factor alpha (TNF-α) [12]. [13], [14], 15]. Concordantly to this inflammatory immunopathology, elevated C-reactive protein further hallmarks this disease. SARS-CoV2 and SARS-CoV use ACE2 as an entry point into cells [16], contrasted with MERS-CoV, which uses dipeptidyl peptidase (DPP)-4 for entry [15]. The success of SARS-CoV2 as a pathogen may likely be resolved at the level of the innate immune response at the pathogen entry site. Pathogen-associated molecular patterns (PAMPs) that are recognized by endosomal pattern recognition receptors (PRRs) in the case of RNA viruses, are either viral dsRNA of replication intermediates [17]. These PAMPs are recognized by endosomal RNA receptors, the cytosolic RNA sensor - retinoic acid-inducible gene I (RIG-I)/melanoma differentiation-associated protein (MDA) 5-, TLR3 and TLR7 (de Wit et al., 2016). Once the viral PAMPs are recognized, production of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κB) and interferon regulatory factor (IRF)-3 commence, which, in turn, stimulates the production of interferon alpha (IFN-α) and other pro-inflammatory cytokines [17]. Once IFN-α is successfully secreted, it will initiate the JAK-STAT pathway via the interferon alpha/beta receptor (IFNAR) which, in turn, will initiate the phosphorylation of STAT1 and STAT2 [17]. IRF-9 will form a complex with the phosphorylated STAT1/2, and initiate transcription of IFN-induced genes once the complex has been successfully translocated into the nucleus [17]. The successful completion of this cascade leads to a competent innate immune response able to efficiently suppress viral infections at the entry stage [13]. It is known that SARS-CoV efficaciously interferes with this signalling cascade by using its structural and functional proteins (M, N, ORF); this resultant of this is either dampening of IFN signalling or evasion of the immune response [18]. Thus, approximately 7 to 8 days upon infection, rampant inflammation can be expected at infected sites as means of recapitulation for the immune response delay [12], [13].The same appears to be true for SARS-CoV2 infections [12], [19], [20].

B. Adaptive Immunity: Lessons from SARS-CoV

Although any conclusions on adaptive immunity currently must be made based on modest clinical evidence and with caution, lymphopenia seems to be the hallmark of COVID-19, particularly during the initial stages of infection [3]. Lymphopenia may be closely linked to disease severity, as ICU COVID-19 patients have a notable decrease in overall lymphocytes, yet an overall increase in inflammatory markers (IL-6, CRP). Mounting a competent and well-balanced Th1 immune response is key in combating infections with intracellular pathogens, ergo its involvement

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in viral infections is paramount. Although the intricacies of the immune response to SARS-CoV2 await comprehensive elucidation, similarities between this novel betacoronavirus and SARS-CoV have become apparent in the context of adaptive immunity [21]. Seroconversion in SARS-CoV patients commences around the fourth day after infection, whilst the adaptive response is hallmarked with long-lasting IgG and neutralizing antibodies up to two years upon infection [21]. In a cohort study of 173 patients with SARS-CoV2 infection, seroconversion was observed in the first 7 days of illness, with an antibody presence of <40%. However, 15 days after the onset of clinical disease, antibody levels progressed to 100.0%, 94.3% and 79.8% for Ab, IgM and IgG respectively [20]. Such findings solidify the inference that lymphopenia, owed to viral immune evasion or immune suppression, is present within the first days of disease. Resolving this infection, therefore, hinges on a competent interferon-mediated immune response. In a study that included 6 mothers with COVID-19 pneumonia who gave birth via Caesarean section in their third trimester, antibodies were found in the serum of 6 infants [22]. RT-PCR test for SARS-CoV2 was negative for blood samples of all 6 infants, indicating absence of SARS-CoV2. Interestingly, the proinflammatory cytokine IL-6 was notably increased in all 6 infants [22]. Furthermore, COVID-19 symptoms were absent from all 6 infants upon birth, as the study reported. The mothers had elevated levels of IgG and IgM and, concordantly to these findings, abnormally high levels of IgG and IgM were found in two infants (<10 AU/mL); an IgG level of 125.5 was found in the first infant, whilst the second infant had an IgG level of 113.91 AU/mL and IgM level of 16.25 AU/mL [22]. Whether the presence of these antibodies conferred protective immunity against SARS-CoV2 remains unknown. Furthermore, three infants were reported to have normal IgM levels yet elevated IgG levels (75.49,73.19, 51.38 AU/mL respectively); elevated IgG was consistent for all 3 mothers, whereas higher IgM levels were recorded in only 2 mothers [22]. Presence of IgM in infant sera was, indeed, unusual, however it is possible that the virus managed to cross the placenta at some point during gestation, causing the foetus to produce IgM, regardless of the negative RT-PCR results. It will be interesting to see whether antibody epitopes for SARS-CoV2 are generally for structural proteins (envelope, spike, membrane, and nucleocapsid), which is the case for SARS-CoV infections. It should be noted that fatal groups infected with SARS-CoV had an elevated Th2 serum cytokine level, particularly IL-4, IL-5 and IL-10, implying a possible disbalance of the Th1 and Th2 immune responses as causative factors in negative outcomes in SARS, but also possibly in SARS-CoV-2 [23].

IV. TREATMENT METHODS BEING CONSIDERED AND UNDERGOING RESEARCH

A. Conventional treatment approaches - Mechanical Ventilation

Current allopathic treatment approaches primarily involve the use of mechanical ventilators and corticosteroids, while doctors and researchers explore drugs that can potentially be used. Mechanical ventilators are used to treat certain respiratory conditions that can cause various complications, and such problems result in people being rendered unable to breathe properly [24]. Patients should first be treated with oxygen therapy before intubation is considered [4]. The current recommendation for patients who need to be intubated is to use a low tidal volume and pressure, with an increased number of breaths per minute (up to 35) in order to protect the lungs from harmful ventilation effects [25]. When patients experience acute respiratory distress syndrome (ARDS), which may happen during the COVID-19 pandemic, patients are put onto a mechanical ventilator, because this is a highly critical condition where the patient is not able to breathe without mechanical assistance [26]. During the COVID-19 pandemic, many patients had been put on mechanical ventilators because many of them have developed ventilator-associated pneumonia. Some researchers state that antibiotics might have been overused when it comes to ventilator-associated pneumonia, and the reason is due to patients being more exposed to getting adverse effects when it comes to the respiratory system, and developing a faster resistance to antibiotics [27].

B. The Controversial Chloroquine and Hydroxychloroquine

One drug being considered for its potential inhibitory action of SARS-CoV-2 is hydroxychloroquine (HCQ). Research conducted on Chinese patients who had contracted COVID-19 demonstrated that hydroxychloroquine had an anti-SARS-CoV-2 effect when performing in vitro tests, and its clinical safety proved better than chloroquine [28]. The oral absorption of hydroxychloroquine into the human body has been found to be very efficient. It is reported that hydroxychloroquine is less toxic compared to chloroquine (CQ), but if the dosage is increased for treatment more than it should be, poisoning is very likely to happen [29]. However, there has not been sufficient research for this drug, as one popular study stating the efficacy of the use of hydroxychloroquine and azithromycin combined to treat COVID-19, failed to provide patient follow-up results [28], [30]. Side effects may occur when taking too much of chloroquine and hydroxychloroquine, although current data has not shown any type of severe damage to the body. Both CQ and HCQ are metabolized in the liver, and it is possible if there is a larger intake, there is risk of liver poisoning, which is why they have to be prescribed carefully to patients who may have liver failure as a potential comorbidity [30].

C. Glucocorticoids

Glucocorticoids such as hydrocortisone have routine use in the treatment of pneumonia, especially in patients with adrenal insufficiency [31]. These steroids are generally 21 carbons long and produced by the adrenal cortex [32]. Early on in the COVID-19 pandemic, they were suggested as a treatment in the case of severe pneumonia. Methylprednisolone was stated to be appropriate for use among severe cases or patients who had a rapidly progressing infection [4]. However, prolonged use of glucocorticoids can cause numerous side effects such as peptic ulcers, hypertension, psychological symptoms, uncomfortable withdrawal, and even long-term effects such as the development of Cushing's syndrome [32]. Current recommendations for treating SARS-CoV-2-induced pneumonia with glucocorticoids are to not exceed 2 mg per kg of body weight per day [4].

D. Other Drugs Under Consideration

Several additional drugs are being explored for use against SARS-CoV-2, the most notable being the antiviral drug Remdesivir. Preliminary studies have shown that Remdesivir has the ability to inhibit SARS-CoV-2, and compassion treatment of critical COVID-19 patients have yielded 68% successful results thus far [33]. As an adenosine analogue, remdesivir functions on a pharmacological level by terminating viral replication too early when incorporated into the RNA replication chain [34]. While more clinical trials for Remdesivir are absolutely essential, few side effects have been reported up to this point, which suggests that this form of treatment may provide effective and safe treatment for more critical patients [35]. Other drugs such as Lopinavir, Ribavirin, Penciclovir, Nitazoxanide, interferon drugs, Favipiravir, and Nafamostat have undergone assay-based testing against SARS-CoV-2, but results have been mixed and the half-cytotoxic concentrations (CC50) of these drugs have been higher than Remdesivir or CQ and HCQ [34]. These drugs also can present higher side effects and can potentially worsen cytokine storms [36].

V. ALTERNATIVE METHODS FOR TREATING COVID-19

Due to its status as a novel virus, concrete treatment protocols have not been developed yet for SARS-CoV-2. Antiviral drugs and antibodies have been explored but only experimentally, and no drug has undergone the necessary research to prove it can successfully treat 2019-nCoV, even though studies are rapidly being conducted delving into the antiviral properties of drugs such as chloroquine [4], [28]. Vaccines are only in preliminary trials, and potential antibody treatments are still in the initial phase [35]. Because of this, many doctors at the onset of the outbreak began to explore the potential of using alternative treatment options such as traditional chinese medicine (TCM) or other herbal therapies [4]. This section will provide as detailed a summary as possible on the phytotherapeutic options that could have single or multiple actions in treating COVID-19, whether by strengthening the immune system, managing the symptoms it presents, or having a direct antiviral effect. It should be noted that in the largest pandemic until the current COVID-19 outbreak, the Spanish flu epidemic of 1918, was successfully treated using herbal medicines by many herbal practitioners and physicians within certain hospitals, and some medical and natural practitioners even achieved a death rate as low as 0.6% [2]. When exploring the potential of natural medicine for treating any disease, including COVID-19, it is important to note that plant-based medicine, unlike many standard allopathic drugs, works with a wide range of mechanisms within the body rather than with a specific pathogenic target [2], [4].

A. The effects of Vitamins and Minerals on the Immune System

For many years, research has shown that without proper immune response, even the slightest infection can prove fatal and, when looking at what really helps modulate immune response and is absolutely essential to effective immune function, vitamins and minerals play the most important role [37]. Vitamin C possesses a unique ability in that it acts as a prooxidant for immune cells and an antioxidant for lung epithelial cells [38]. A recent review on the SARS-CoV-2 pandemic and the current treatment options being explored mentioned vitamin C may have a useful preventative action [39]. However, its capabilities within the human body may go beyond prevention. Vitamin C is being explored for its potential use as an intravenous high-dose treatment against ARDS and sepsis caused by SARS-CoV-2 or other infections, two very serious and often fatal conditions that tend to be associated with critical COVID-19 cases [38]. IV vitamin C treatment should be monitored very closely and it is recommended to take a glucocorticoid, such as hydrocortisone, treatment alongside the vitamin to reduce inflammation as a result of osmotic cell death which can occur when this type of treatment in cases of pneumonia [38], [40].

Another very important vitamin in sustaining the body while trying to fight off a viral infection is vitamin D. Vitamin D helps the primary lung epithelial cells by regulating genes with important innate immune functions [41], [42]. Many people already have vitamin D deficiencies which results in weaker immune systems, especially for those that have autoimmune disease or live in colder climates [41]. Another important factor in vitamin D deficiency is age, which proves important when considering SARS-CoV-2 infections, as higher age and mortality are positively correlated [43]. However, those more at-risk or with reduced access to sunlight for a SARS-CoV-2 infection can take a high supplemental dose of up to 10,000 IU per day, especially patients with primary basic diseases such as coronary heart disease, diabetes, or hypertension [39], [43]. Vitamin D, specifically its metabolite 1,25 dihydroxyvitamin D, plays several roles in immune response generation, especially in T cell response modulation and an inhibitor of cytokines [44], which could possibly indicate potential for prevention of cytokine storms during a SARS-CoV-2 infection. Furthermore, intravenous vitamin D has been used for treating pneumonia patients, and caused a statistically significant decrease in hospital stay duration of patients requiring ventilation in intensive care [43].

Zinc is an essential micronutrient used in DNA synthesis and cell proliferation that may have potential as a supplement during treatment of SARS-CoV-2 infections [45]. This micronutrient is very essential in the elderly due to the possible decrease in absorption efficiency which could result in a much weaker immune system, which can even result in a greater risk of developing an autoimmune disease and pneumonia [46]. It is also involved in the regulation of innate and adaptive immune responses, cell signaling, and production of immune cells [47]. One hypothesis suggests that combining zinc with the drugs CQ and HCQ may produce better outcomes, especially in patients with a zinc deficiency, since the drugs bind extracellular zinc to lysosomes which then interferes with RNA-based viral replication, and zinc has proven antiviral activity against several viruses [45].

B. Convalescent Plasma Therapy and the Potential of Monoclonal Antibodies to Treat COVID-19

With the severity and rapid progression of the COVID-19 pandemic, convalescent plasma therapy containing immunoglobulins from patients who had previously survived and improved after battling SARS-CoV-2 has become a last-resort therapy [48]. However, this form of treatment may prove more effective than many other treatment methods; one study reported in February, 2020 reported that 91 out of 157 patients treated using plasma therapy within 48 hours of treatment [49]. Monoclonal antibodies have evidence from the previous SARS and MERS coronavirus outbreaks, and they function by binding to the ACE2 receptor of human cells, which prevents the SARS-COV-2 virus from binding there [50]. Researchers arguing for these kinds of therapies present them as an effective strategy to combat any emerging epidemic or pandemic in addition to SARS-CoV-2 [49], [50].

C. Prevalence of Traditional Chinese Medicine to Treat COVID-19

Aside from known treatments for viral diseases as antiviral treatment, antibiotic therapy, corticosteroid therapy and classical symptomatic therapy [4], it has been proven that traditional Chinese medicine (TCM) has been highly effective throughout the years of fighting different viruses [51]. The main principle on which TCM works can also be labeled as personalized medicine, as different herbal blends are used to specifically and individually treat the patient based on syndrome differentiation. In TCM it is taught that prevention before illness is always better than treatment after getting ill [52]. According to studies of Jin et al., some examples of the herbs used are in form of perfumed Chinese herb bags (clove, fineleaf schizonepeta herb, Perilla frutescens, Atractylodes lancea, cinnamon, biond magnolia flower, Asarum sieboldii, and Elettaria cardamomum); those can also be in the form of Chinese herbs for a foot bath (vulgaris, carthamus, and dried ginger); Chinese herbs for prophylaxis: Astragalus mongholicus, rhizoma atractylodis macrocephalae, saposhnikovia divaricata, Cyrtomium fortunei, honeysuckle, dried tangerine or orange peel, eupatorium, and licorice; Medical tea: perilla leaf, agastache leaf, dried tangerine or orange peel, amomum tsao-ko, and ginger. Additionally, one of the most important mentions by Jin et al. is Chinese patent medicine: Huoxiang Zhengqi capsule or Huoxiang Zhengqi Shui (in half dose), proven to be highly efficient in prevention and prophylaxis [4]. These all are proven to have positive effects in viral disease prevention and symptom management.

In the case of COVID-19, one of the main issues is pneumonia [53]. Pneumonia is the world's leading cause of death in young children and elderly people [54]. Throughout history, and according to ancient literature confirmed by modern research, TCM have been reported to cure viral pneumonia [52], [55], [56]. For decades now, in China and many other Asian countries, Traditional Chinese Medicine has been widely used both for prevention and treatment of viral pneumonia [57]. A good example includes an outbreak in spring 2003 in Hong Kong where TCM herbs like Folium mori, Flos chrysanthemi, Semen armeniacae amarum, Fructus forsythiae, Herba menthae, Radix platycodonis, Radix glycyrrhizae, Rhizoma phragmitis, Radix scutellariae, Folium isatidis, Radix astragali and Radix saposhnikoviae have been used for prevention and treatment of SARS-CoV [51]. Additionally, extracts such as Lycoris radiata (ethanolic extract), Artemisia annua (ethanolic extract), Pyrrosia lingua (chloroform extract), and Lindera aggregata (ethanolic extract), are used in SARS prevention and therapy [58]. Excluding these, the most commonly used anti-virus herbs in TCMs are Scutellaria baicalensis Georgi - Baicalein and root; Polygonum cuspidatum Sieb. Et Zucc Rootstalk and root; Flos Lonicerae Japonica and Fructus Forsythiae flower and fruit [55]. Recent researches reported that the main mode of action of TCMs is by modulating immune response boosting body resistance against virus and other pathogens [57], [59], [60]. For even further confirmation, according to research done by Luo et al. (2019) based on historical records SARS and H1N1 influenza prevention, TCM herbal formula could be an alternative approach for prevention of COVID-19 in high-risk populations [61]. The individual actions of the herbs that make up the herbal formulae used in TCM and other herbal disciplines (phytotherapeutics) could also be used for COVID-19 treatment, but that is beyond the scope of this review and must be covered by another paper.

VI. DISCUSSION AND CONCLUSION

It is important to put the emphasis on the fact that an official cure or vaccine against SARS-COV-2 is yet to be discovered; all methods, medications and herbs mentioned in this paper are for the purpose of treating symptoms and helping prevent of COVID-19. Doctors and medical professionals have used these treatment methods with mixed success, and there currently is no universal cure for COVID-19 [33]. It may be advisable to continue using an integrative approach, considering all potential treatment options for the good of the patient [4]. Conventional treatment approaches should be used cautiously when necessary, and not without consideration of potential side effects [4]. Alternative treatment approaches should not be forgotten during any research undertaken to treat or cure this virus as plant-based therapies have been utilized throughout

history for their medical properties and great potential for treating all varieties of diseases and infections, including very serious illnesses and pandemics [2]. It is well known by now that individual actions of the herbs that make up the herbal formulae used in TCM and other herbal disciplines (phytotherapeutics) were proven to have effect in coronavirus infections [58]. Additionally, intravenous therapies like immunoglobulin, monoclonal antibodies, and vitamin therapy may prove life saving especially in more at-risk patients [48], [49], [50]. In conclusion, the purpose of this paper was to give insight into the potential of conventional and alternative methods of treatment for the purpose of finding the best way to fight COVID-19 pandemics and give ideas for further research on this topic.

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