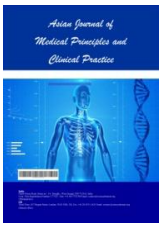

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Potential Interventions and Treatment for Novel Coronavirus: A Literature Review

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Authors' contributions

This work was carried out in collaboration among all authors. Authors LCS and SD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors SS, MAH, MMIK, NHP and AR managed the analyses of the study. Authors LCS, SD and SS managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

The manifestation of a novel coronavirus infection (COVID-19 or 2019-CoV) exert a serious threat to international health and economy. In the inexistence of medication for this virus, there is a quick need to find substitute ways of controlling the spread of disease. We performed internet searches here for all possible treatment methods associated to coronavirus infections and found that

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common treatments, particular treatments for coronavirus and antiviral treatments could be proficient in combating COVID-19. We confer that the nutritional status of each infected patient should be assessed before general treatment is administered. Furthermore, COVID-19 patients should be given convalescent plasma if it is attainable. In conclusion, if the infection is reckless, we recommend that all possible strategies be implemented for controlling the emerging COVID-19.

Keywords: Coronavirus; COVID-19; 2019-CoV; SARS; MERS; potential interventions.

1. INTRODUCTION

The global community is currently facing a big challenge to stop the pandemic outbreak of Coronavirus (COVID-19) which is instigating by SARS-CoV-2 [1]. It was first reported in Wuhan, Hubei, China in December 2019, and expanses rapidly throughout the world, with the World Health Organization announcing a global health emergency on 30 January 2020 [2]. According to WHO, until 27 September 2020, COVID-19 encompasses 213 countries with a total of 33,307,577 cases of disease and a total of 1,002,402 deaths [3].

Coronaviruses (CoVs) they belong to the Orthocoronavirinae subfamily of the family of Coronaviridae, in the order of Nidovirales. The subfamily also consist of: α-coronavirus, β-coronavirus, γ-coronavirus, and delta-coronavirus [4]. In fowls and mammals, coronaviruses mainly cause zoonotic infections and have shown that they can also infect humans in recent decades [5]. Coronavirus lethality was confirmed by the manifestation of severe acute respiratory syndrome (SARS) in 2002 and the outbreak of Middle East respiratory syndrome (MERS) in 2012, when they cross the species barrier and humans became transited [5]. SARS-CoV and MERS-CoV all associated to the β-coronavirus family [6]. Present coronavirus (COVID-19) associated with MERS and SARS coronaviruses was discovered in China at the end of 2019 and evidence of human-to-human transmission among close contacts was found [7]. It is a single-stranded positive-sense RNA [8]. The sequence analysis revealed that COVID-19 has a standard coronavirus genome structure and belongs to a lineage of β-coronaviruses, including SARS-CoV and MERS-CoV [8]. COVID-19 was over 82 per cent similar to SARS-CoV [9,10]. Now COVID-19, with its crippling hand, has spread worldwide. There is no permitted treatment or vaccine for the disease at present. It is very urgent to find a worthy way to inhibit and control the replication and transmission of the virus in the penurity of a specific treatment for this novel virus. We did an online exploration on PubMed and the Web of Science with the keywords SARS, MERS, and coronaviruses. Here, we have summarized the dynamic effect of vitamin and medical treatment on slowing SARS-Cov2 activity and increasing immunity in our body.

2. MATERIALS AND METHODS

2.1 Sources of Data

The information of the paper is based on published data and information. Collection of information was done from documents available mainly in electronic database and on the websites of specialized journal. Several databases, including PubMed, Medline, Google scholar, Cochrane library etc. were searched for literature and extracted data till May 2020. Reference lists of the studies that were included in the analysis were also searched as well.

2.2 Search Strategy

For an appropriate searching keyword like Coronavirus, COVID-19, 2019-CoV, SARS, MERS, Potential Interventions

2.3 Study Selection

Online search was done for primary research articles. Technical papers, special publications and strategic plans published in the international journals were retrieved. Any cross-sectional, case-control, cohort and experimental study on human providing sufficient information on the treatment and control of the emerging COVID-19 was considered eligible for review.

2.4 Nutritional Intervention

As no specific or registered treatment and vaccination is available, our body's defensive system is the only hope to confine coronavirus disease in 2019. For this reason, we need to take dietary supplements or foods containing immunosuppressive vitamins and minerals. There are various vitamins and minerals that enhance our immunity to various viral diseases. They are discussed below:

2.4.1 Vitamin A

The primary fat-soluble vitamin to be identified is vitamin A, and β-carotene is its plant-derived counterpart. Vitamin A is often mentioned to as "anti-infective" vitamin and many of the body's anti-infection defenses depend on sufficient supplies. There are three active forms of vitamin A: retinol, retinal, and retinoic acid. By researchers it is identified that an impaired immune response is caused by a specific nutritional element deficiency [11]. Deficiency of vitamin A is sharply associated with measles and diarrhea [12] and in children with vitamin A deficiency, measles may become serious. Apart from this, Semba et al. [13,14] found that vitamin A supplementation decreased morbidity and mortality in various infectious diseases such as measles, diarrheal disease, pneumonia associated with measles, human immunodeficiency virus (HIV) infection, and malaria. Vitamin A supplementation also gives safeguard against other life-threatening diseases, including malaria, lung disease and HIV complications [14]. Therefore Vitamin A is a hopeful choice for the treatment of this novel coronavirus and for the prevention of lung infection.

2.4.2 B vitamins

Vitamin B complex are water-soluble and act as part of coenzymes. Every B vitamin has its own specific functions. For example, Vitamin B2 (riboflavin) plays a role in energy metabolism of cells. Vitamin B2 deficiency is expected to occur among elderly people in the United States [15]. Vitamin B3, also known as nicotinamide, could enhance the killing of *Staphylococcus aureus* by means of a myeloid-specific transcription factor and has been successful in both the prophylactic and therapical conditions [16]. Vitamin B3 treatment decreased neutrophil infiltration in the lungs with a powerful anti-inflammatory effect during ventilator-induced lung injury. Interestingly, it also driven paradoxically to the development of significant hypoxemia [17]. Vitamin B6 is also important for protein metabolism and is involved in more than 100 reactions in body tissues. It also plays a momentus role in the immune system of the body. The lack of B vitamins can weaken the host's immune response, patients infected with the virus should be complemented to reinforce their immune system. Vitamin B could therefore be chosen as a primary option for treatment with COVID-19 [18].

2.4.3 Vitamin C

Vitamin C is a water-soluble and also called ascorbic acid, meaning 'no-scurvy acid.' Vitamin C is well professed in connective tissues for its role in collagen synthesis and functions as an antioxidant. Vitamin C enhance immune function and helps guard against the infection of coronavirus [19]. Three human controlled trials have reported a apparently lower incidence of pneumonia in vitamin C-supplemented groups, suggesting that vitamin C may, under certain circumstances, prevent susceptibility to lower respiratory tract infections. COVID-19, it has been identified to cause infection of the lower respiratory tract, so vitamin C can be one of the most important COVID-19 treatment options [20]. High proportion of cases requiring intensive care unit (ICU) treatment is one of the primary problems with COVID-19. In a meta-analysis of 12 studies with 1,766 ICU patients, vitamin C attenuated the ICU level by 8% [21]. Another eight studies reported that in patients requiring the longest ventilation, vitamin C reduced the term of the mechanical ventilation [22]. While doses of 0.1 g / day of vitamin C can maintain a normal plasma level in a healthy person [23], much higher doses (1-4 g/day) have been recorded to increase plasma vitamin C levels to within the normal range for critically ill patients [24]. As of February 2020, the clinical characteristics of patients hospitalized with COVID-19-related pneumonia exposed that 26% of patients had been admitted to the Intensive Care Unit (ICU) due to complications such as ARDS and shock [25]. A Randomized Control Trial in the USA in 167 patients with sepsis-related ARDS confirmed that 4-day administration of ~15 g / day of IV vitamin C may reduce mortality in these patients [26].

Fig. 1 show the bioavailability and absorption of natural and synthetic vitamin C. Vitamin C/DHA can be taken as not only as natural but also as synthetic ascorbic acid. Synthetic ascorbic acid can be given orally (with food or without food) or intravenously. Vitamin C or ascorbic acid is partly oxidized in an oxygen environment to dehydroascorbate (DHA). It is transported by two sodium-dependent transporters SVCT1 and SVCT2, while DHA is taken up by the glucose transporter GLUT*n*, where n is 1-3 or 8. Final vitamin C concentration in circulation depends on the route of ingestion and the action of other dietary compounds, including glucose and flavonoids. Flavonoids can block vitamin C absorption but it can decrease

some oxidants and increase the vitamin C/DHA ratio.

2.4.4 Vitamin D

Vitamin D is a hormone which can be synthesized with the assistance of sunlight in our body. It also helps, in addition to its role in preserving bone integrity, the maturation of many cells, including immune cells. Usually at the end of the winter season, low vitamin D levels have been recorded in a significant number of healthy adults [28]. Persons who are homebound or institutionalized and those who work at night may have vitamin D deficiencies, as do certain elderly people with insufficient exposure to sunlight [29]. In the winter of 2019, COVID-19 was reported for the first time and affected mostly middle-aged elderly people. Vitamin D may be inadequate for virus-infected people. In addition, reduced vitamin D status has been reported to contribute to bovine coronavirus infection in calves. More than half of COVID-19 cases and about 70% of COVID-19 deaths were recorded in African American individuals in Chicago, USA, who are most at risk of vitamin D deficiency [30]. Studies have shown that COVID-19 patient's treatment with a high dose of 250,000-500,000 IU vitamin D are safe for manually ventilated, critically ill patients and are associated with reduced hospital length of stay, improved oxygen carrying capacity of the blood and increased levels of hemoglobin [31]. Therefore, Vitamin D work as another intervention for the treatment of this novel virus [32].

Fig. 2 show the mechanism of vitamin D against COVID-19. The active form of vitamin D is calcitriol. It is a fat soluble vitamin which involved in the calcium homeostasis. But it has also role in immune system modulation. SARS-CoV-2 is a beta coronavirus that causes Coronavirus Diseases 2019 (COVID-19). Insufficiency of vitamin D is associated with infections such as acute respiratory tract infections. It has been shown to reduce respiratory tract infections. Vitamin D can reduce the cytokine storm (cytokine release syndrome) that can cause increasing morbidity and mortality in respiratory infection like COVID-19.

2.4.5 Vitamin E

It is lipid soluble, containing both tocopherols and tocotrienols. Vitamin E plays an vital role as an antioxidant in binding free radicals to reduce oxidative stress [34]. The decreased vitamin E and D status in calves also resulted in bovine coronavirus infection [35].

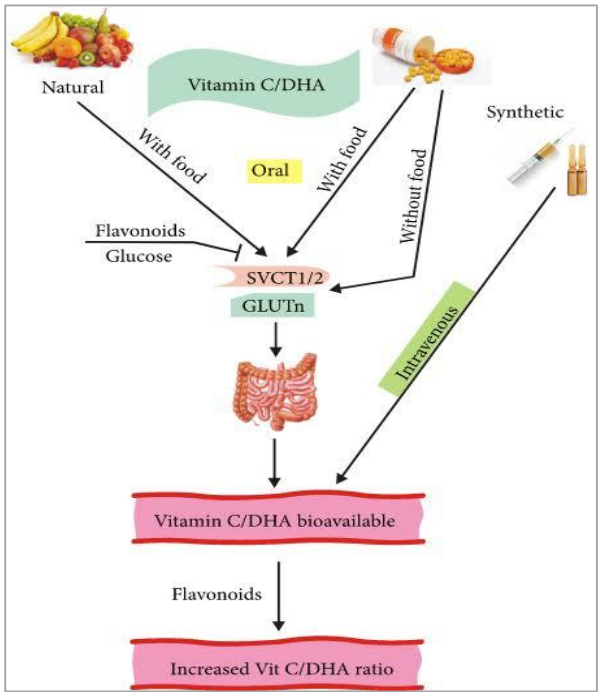

Fig. 1. Absorption and bioavailability of natural and synthetic vitamin C [27]
Source: https://static-01.hindawi.com/articles/omcl/volume-2019/7286737/figures/7286737.fig.002.svgz

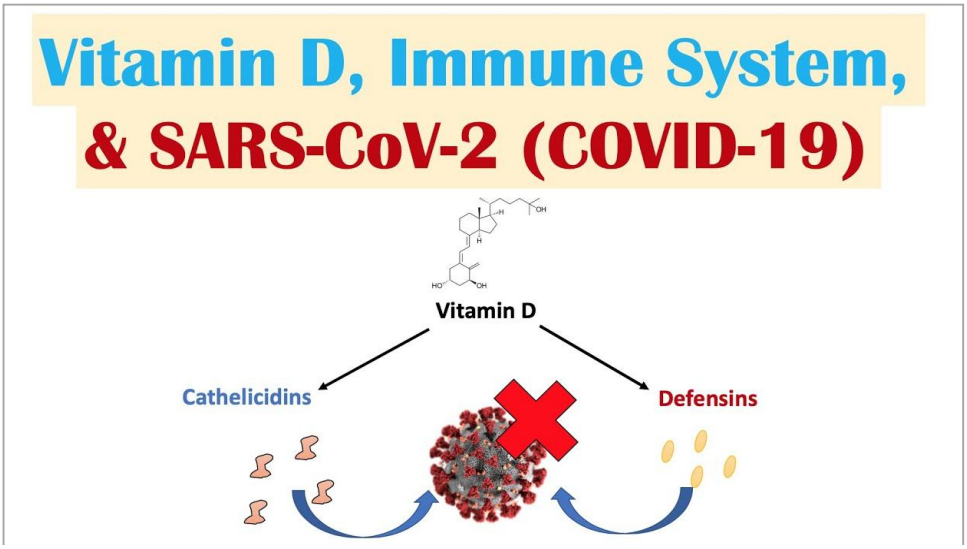

Fig. 2. The defensive mechanism of Vit D against COVID-19 [33]
Source: https://i.ytimg.com/vi/zd_oGkGJr04/hqdefault.jpg

2.4.6 Omega-3 polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs) are main mediators of adaptive immune responses and inflammation. Omega-3 and Omega-6 PUFAs mainly enhance anti-inflammatory and pro-inflammatory effects [36]. Leu et al. found that anti-hepatitis C virus (HCV) activity was also present in some PUFAs. Omega-3 including protein D1 used as an antiviral drug, could be considered for one of the potential interventions of this new virus, COVID-19 [37].

2.4.7 Selenium

Selenium is an important trace element for mammalian redox biology. In defending against infectious diseases, the host 's nutritional status plays a very effective role [38]. Synergistic effect of selenium with ginseng stem-leaf saponins has been reported to augument an immune response to live a bivalent infectious bronchitis coronavirus vaccine in chickens. Selenium also used without combination of acetylcysteine or CoQ10 in critical ill patients admitted to the ICU (septic & non-septic) [39]. In a meta-analysis, patients with advanced diseases, Manzanares and colleagues [40] did not find a clear beneficial impact on mortality but found a decrease in diseases in non-septic patients in a sub-group review. Selenium supplementation can also be an alternative for the treatment of this novel COVID-19 virus [41].

2.4.8 Zinc

In the diet zinc is a trace mineral and is important for the maintenance and development of immune cells in both the innate and adaptive immune systems. Zinc deficiency causes immunity dysfunction, both humoral and cell-mediated, and rises susceptibility to infectious diseases [42]. A low level of zinc in older adults (serum Zn < 0.7 mg / L) has reported to be a risk factor for pneumonia [43]. A combination of zinc and pyrithione at lower concentrations confines the replication of SARS coronavirus (SARS-CoV). A research paper found that four COVID-19 outpatients aged 26–63 were treated with zinc salt lozenges [44]. They took doses between 115 to 184 mg Zn/day for 10 to 14 days and they recovered [45]. Another study reported that three COVID-19 patients 38–74 years of age with additional gut manifestations received zinc sulphate (220 mg Zn daily for 5 days) along with hydroxychloroquine and azithromycine [46] and the patients recovered. Therefore, zinc supplementation can have an outcome not only on symptoms related to COVID-19, such as diarrhea and lower respiratory tract infection, but also on COVID-19 itself [47].

2.4.9 Iron

Iron is needed for both the host and the pathogen, and iron deficiency can weaken host immunity, while iron overload can promote harmful viral mutations by causing oxidative

stress. Iron deficiency has been identified as a risk factor for the upliftment of recurrent acute respiratory tract diseases [48]. A report suggests that iron chelation medicines, such as deferoxamine, may helpful for the treatment of Covid-19 in combination with anti-viral medicines. Deferoxamine reduced the level of IL-6 and in vitro endothelial inflammation, which could mitigate the severity of COVID-19 infection as endothelial inflammation is one of the major factors leading to multi-organ harm and failure [49].

2.5 Coronavirus-Specific Treatments

2.5.1 Coronaviral protease inhibitors

In blocking viral replication, viral protease inhibitors are exceptionally successful. Protease inhibitors that interrupt coronavirus replication (CoV), including severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS), provide a promising platform for the development of anti-coronaviral therapies [50]. Papain-like protease (PLP) and chymotrypsin-like (3C-like) protease are those proteins which are coronavirus encoded proteins. They have significant functions for coronaviral replication and also have an additional role in inhibiting the host's inherent immune responses. For coronavirus treatment, targeting 3C-like protease (3CLpro) and papain-like protease (PLpro) are more precise [51].

2.5.2 Chymotrypsin-like (3C-like) inhibitors

2.5.2.1 Cinanserin

As an ancient drug, Cinanserin is well recognized for being the key antagonist to the serotonin receptor. It has been a effectual inhibitor of the replication of severe acute respiratory coronavirus syndrome (SARS-CoV) and also restricts 3-chymotrypsin-like (3C-like) protease [52]. It was also found that the 3CLpro had been encoded in COVID-19 [53]. So, Cinanserin may be a better alternative for treating COVID-19 infection.

2.5.2.2 Flavonoids

Flavonoids are products which occur naturally. Particularly they belong to a group of secondary plant metabolites commonly found in fruits and vegetables with a polyphenolic structure [54]. There are some subgroups, including chalcones, flavones, flavonols, and isoflavones [55]. Apart from antioxidant effects flavonoids have many functions, and they do have antiviral capabilities [56]. Jo et al. reported that the anti-coronavirus behavior of some flavonoids (herbacetin, rhoifolin, and pectolinarin) was due to the inactivation of 3C-like protease (3CLpro)(54). Some flavonoids (herbacetine, isobavachalcone, quercetin 3-β-d-glucoside, and helichrysetin) have also been found to interupt the enzymatic activity of MERS-CoV/3CLpro [57].

2.5.3 Papain-like protease (PLP) inhibitors

Papain-like protease (PLP) the human coronavirus is a novel viral-encoded deubiquitinase and an interferon antagonist for inhibition of the host's innate antiviral immune response.

2.5.3.1 Diarylheptanoids

Diarylheptanoids are a natural product which is attained from the stem bark of Alnus japonica. The papain-like SARS-CoV protease was set to be inhabitable [51]. Cinanserin, along with flavonoids and other natural compounds, may therefore be chosen as an subsitute means of combating COVID-19 infection by targeting coronaviral proteases.

2.5.4 Spike (S) protein-angiotensin-converting enzyme 2 (ACE2) blockers

Angiotensin-converting enzyme 2 (ACE2) was revealed in 2000. ACE2 is a type I transmembrane protein built up of 805 amino acids and has two domains: a catalytic amino-terminal domain and a catalytic carboxy-terminal domain [58,59]. ACE2 practically hydrolyzes angiotensin II to angiotensin (1-7) and has been involved in hypertension, diabetes, and heart function [60]. ACE2 has been identified as a functional receptor for SARS-CoV, which interposes virus entry into the cell by binding to spike (S) protein [61,62]. SARS-CoV spike protein is type I surface glycoprotein and is capable of binding to cellular receptors. The S protein also treats the fusion of the viral and host membranes [63]. Zhou et al. [64] narrated that COVID-19 used ACE2 as the only receptor for entry, but did not use other coronavirus receptors such as aminopeptidase N and dipeptidyl peptidase for entry. Mitigating the binding of S protein to ACE2 is crucial in the treatment of SARS CoV infection.

2.5.5 Human monoclonal antibody

Monoclonal antibodies are well established as a promising class of anti-infectious disease drugs and have shown therapeutic efficacy for many viruses by targeting vulnerable sites on viral surface proteins [65]. Coronavirus neutralizing antibodies specifically target the trimeric spike (S) glycoproteins on the viral surface that facilitate entry into host cells. There are two functional subunits of the S protein which negotiate cell attachment (the S1 subunit, consisting of four core domains S1A through S1D) and fusion of the viral and cell membrane (the S2 subunit). The receptor interaction site in S1 is often attacked by powerful neutralizing antibodies, where interactions between receptors are disabled [66-70]. A human monoclonal antibody (mAb 47D11) that has sharply inhibited SARS-S and SARS2-S pseudotyped VSV infection has been identified by Wang, Chunyan, et al. An authentic SARS CoV and SARS CoV-2 infection of VeroE6 cells has also been found to be neutralized [25].

2.5.6 Chloroquine and Hydroxychloroquine

Chloroquine has been named 9-aminoquinoline since 1934. The drug also has numerous major biochemical properties, such as well-known antimalarial activity, antiviral effects, etc. [71]. Chloroquine has also been found to be an effective SARS coronavirus infection inhibitor by interacting with ACE2, a cell surface binding site for the SARS-CoV spike protein [72]. Chloroquine and hydroxychloroquine are significant against SARS-CoV-2 and have been confirmed to be effective in Chinese COV-19 patients, according to Gautret et al. [73]. However, recently the FDA said that hydroxychloroquine and chloroquine can cause abnormal heart rhythms, such as prolongation of the QT interval and ventricular tachycardia (an extremely rapid heart rate). These risks may rises if such medicines are combined with other medicines known to extend the QT interval, including the antibiotic azithromycin, which is also used in certain COVID-19 patients without FDA approval [74].

Fig. 3 show the mechanism of Chloroquine/Hydroxychloroquine against COVID-19. Chloroquine/ Hydroxychloroquine has multiple effects on cellular function such as i) alkalinizes vacuolar pH, ii) it's a zinc ionophore, iii) choloroquine binds to sialic acid. All these functions are the antiviral action against COVID-19. Spike protein of SARS-CoV-19 bind to the endosome through ACE-2 receptor. Then the endosome eventually transverse through the cytosome and fused to lysosome. Then the virus can enter the lysosome and can acts with the lysosome and allowing it to infect. The chloroquine/ hydroxychloroquine can block the process of entrance of the virus.

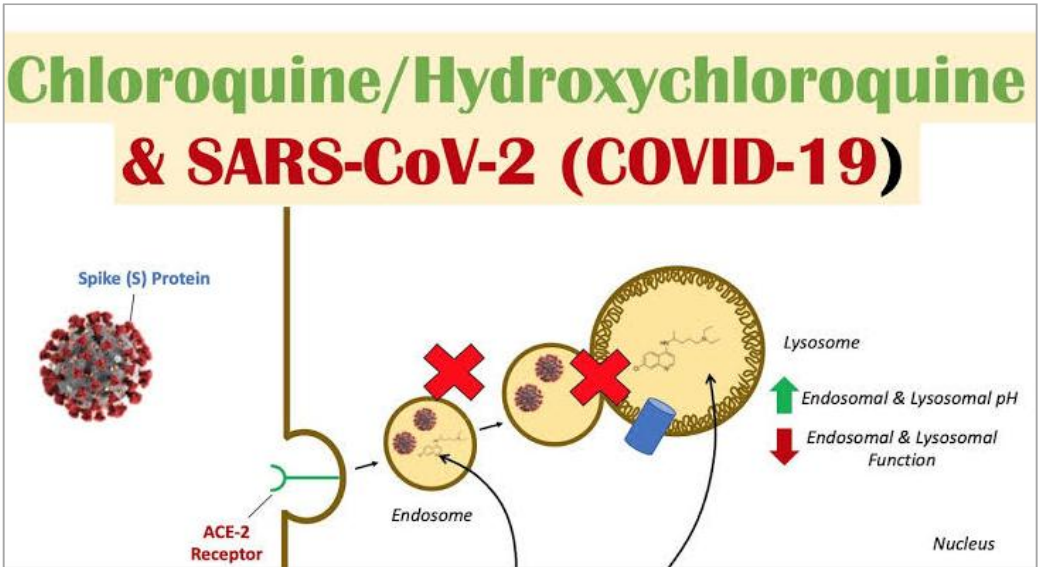

Fig. 3. The mechanism of Choloroquine against COVID-19 [75]
Source: https://i.ytimg.com/vi/S6kPUFseTWQ/maxresdefault.jpg

2.5.7 Emodin

Emodin is an anthraquinone equivalent as well as a virucidal agent, attained from genus Rheum and Polygonum. Ho et al. reported that emodin significantly blocked the S protein and ACE2 interaction in a dose-dependent manner. It was also found to inhibit S protein-pseudotype retrovirus infectivity in Vero E6 cells. These findings indicated that emodin in SARS treatment can be considered as a possible lead therapeutic agent [76].

2.5.8 Promazine

Antipsychotics are medical drugs obtainable on prescription and approved for the treatment of types of mental health conditions that include psychotic events in their symptoms. Promazine is a first-generation antipsychotic drug [77]. The structure of promazine and emodin is analogous. It was found to have a momentus impact on inhibiting the replication of SARS CoV [78].

2.5.9 Nicotianamine

In plants nicotianamine is a crucial metal-ligand. It also found as a novel angiotensin-changeable enzyme-2 inhibitor in soybean [79,80]. So, this could be another possible way to alleviate the infection of COVID-19.

2.6 Antiviral Drugs

2.6.1 Ribavirin

Ribavirin is an antiviral agent and interferes with the replication of DNA and RNA viruses. Ribavirin not only interferes with polymerases, but also interferes with RNA capping to prevent RNA degradation [81]. Ribavirin has a well-established history of usage during the outbreak of SARS [82]. The pathology of COVID-19 is comparable to the 2003 SARS-CoV & 2013 MERS-CoV and due to this similarity previous treatment guidance can guide the current outbreak of 2019-nCoV [83]. It has been reported that there is no significant activity of ribavirin against SARS-CoV in vitro [84]. Treatment with a combination of chloroquine and ribavirin may give some avail to an outbreak due to the immediate availability of drugs. Ribavirin and interferon-beta have been reported to prevent the replication of SARS-associated coronavirus in animal and human cell lines [85]. Despite the lack of in vitro efficacy, the usage of ribavirin should be seriously considered for COVID-19 treatment, even in combination with other antiviral medicines.

2.6.2 Lopinavir (LPV)/ritonavir (RTV) (Kaletra)

Lopinavir/ ritonavir (LPV / RTV), a protease inhibitor, is extensively used in the clinical treatment of HIV-1 infection [86]. Patients with HIV-1 infection may receive an effective response like the reduction of viral load in plasma and the improvement of immunity by combining LPV / r with other antiviral drugs. The combination of LPV / RTV and ribavirin has been reported to result in a excellent outcome in the treatment of SARS [87]. Another study in South Korea shows that combination therapy with LPV / RTV, ribavirin, and IFN-alpha 2a has shown a better result in the treatment of MERS-CoV [88]. Therefore, triple combination of LPV/RTV, ribavirin, and IFN-alpha 2a should be considered as an option in COVID-19 treatment.

2.6.3 Remdesivir

Remdesivir is a nucleotide analog drug that prevents viral RNA polymerases. Remdesivir is active against certain families of viruses, including coronaviruses (SARS-CoV & MERS-CoV) [89]. It was found that the antiviral activity of RDV and IFN-beta showed a better result than LPV / RTV-IFN-beta against MERS-CoV in vitro and *in vivo* [86]. A study revealed that 68% of patients with severe COVID-19 treated with remdesivir showed clinical improvement [86]. Remdesivir could be a good choice in the treatment of COVID-19. To find out the efficiency and safety of remdesivir further trials are very necessary.

Fig. 4 show the mechanism of Remdesivir against COVID-19. It is an antiviral agent and shown to have activity in-vitro against SARS-CoV-2 (COVID-19) and other coronaviruses (SARS-CoV, MERS-CoV). Spike protein of SARS-CoV-19 bind to the endosome through ACE-2 receptor. The endosome fuses lysosome. This process is known as endocytosis. The virus then exceeds in the lysosome and unveils viral RNA. Viral RNA is the genetic code of coronavirus. Then it makes RNA-dependent RNA polymerase (RDRP) protein. Then it makes more viral RNA and then new viral proteins. Remdesivir enters into the cell and metabolized to its active form GS-441524. Remdesivir and its active form GS-441524 inhibit the production of viral RNA.

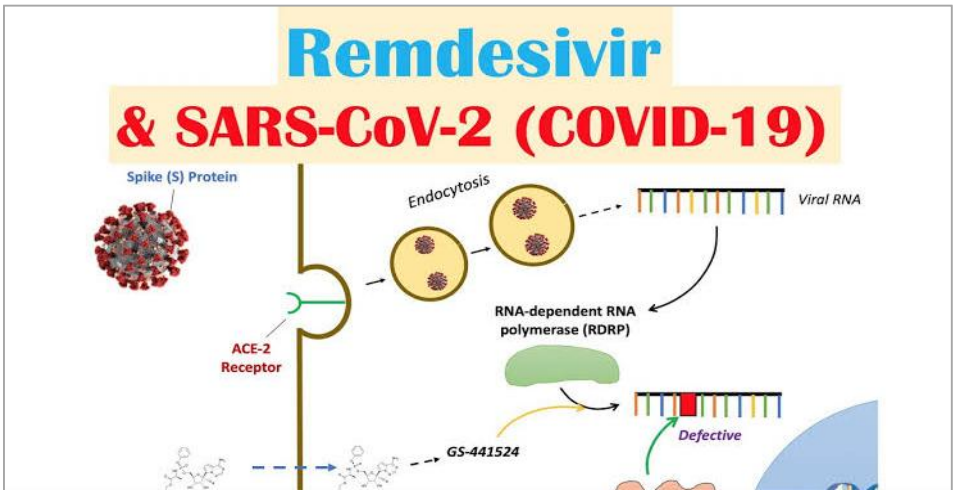

Fig. 4. The mechanism of Remdesivir [90]
Source: https://i.ytimg.com/vi/PXWUDX9C0xw/maxresdefault.jpg

2.6.4 Nelfinavir

Nelfinavir is considered to be a safe antiviral medicine and has been commonly used as an HIV-1 protease inhibitor. It is used with the combination of other antiretroviral drugs [91]. A study has reported that nelfinavir can significantly prevent SARS-CoV replication in Vero E6 cells [92]. This can also be a better option in the treatment of COVID-19 patients.

2.6.5 Arbidol

Arbidol is a medicine that has been used mostly in the treatment of influenza and other respiratory viral infections. It has an antiviral effect on early in vitro SARS-CoV viral replication [93]. It was found that combination of arbidol with LPV/RTV can delay the progression of lung lesions and lowers the possibility of respiratory and gastrointestinal transmission for decreasing the viral load of COVID-19 [94]. Therefore arbidol can also be effective in COVID-19 cases.

2.6.6 Nitric oxide

Nitric oxide (NO) is a biologically active, short-lived and a gaseous product. NO is formed by NO synthases from arginine. NO reacts with superoxide and releases peroxynitrite, which may mediate bactericidal or cytotoxic reactions [95]. Research has revealed that the replication cycle of severe acute respiratory syndrome coronavirus (SARS CoV) is prevented by in vitro NO [96]. In addition to preventing the replication cycle of severe acute respiratory syndrome, NO also inhibits the synthesis of viral proteins and RNA. In order to treat COVID-19 patients, nitric oxide may be an option.

2.6.7 Doxycycline

Doxycycline is a tetracycline of second-generation. It has both antimicrobial and anti-inflammatory activities [97,98]. Doxycycline in combination with chloroquine was found to prevent the entry of SARS-CoV-1 in cells in a previous study [99]. So doxycycline can also be effective in COVID-19 treatment.

2.7 Other Compounds

2.7.1 Alpha lipoic acid

Alpha lipoic acid (ALA), is a naturally-occurring disulfide compound. It works as a cellular coenzyme and also has been used in the treatment of polyneuropathies and hepatic disorders for years. ALA played a important function as an antioxidant in scavenging free radicals to safeguard against oxidative damage in various diseases [100]. Consequently, ALA had the capacity to enhance levels of intracellular glutathione (GSH) [100] and to normalize the oxidative stress induced by Dexamethasone in chicken [101]. Wu et al. stated that oxidative stress in host cells was a important factor for human coronavirus 229E infection. Another factor for rising the infectivity was the deficiency of glucose-6-phosphate dehydrogenase (G6PD) [102]. The addition of alpha lipoic acid to G6PD knockdown cells can decrease the increased

susceptibility to infection with human coronavirus 229E [102]. Interestingly, Baur et al. also revealed alpha-lipoic acid to be effective in inhibiting HIV-1 replication [103]. We speculate that ALA also could be used for this new virus as an optional therapy.

2.7.2 Estradiol and phytoestrogen

In general, females have stronger immune responses to the viral problem than males, which can lead to more proper viral clearance [18]. From epidemiological study it is found that after SARS-CoV infection males experience a higher incidence rate and case fatality rate compared to females [104,105]. During MERS outbreak, the rate of disease occurrence in men was nearly twice that in women and the case fatality rate among men and women was the identical as the occurrence rate [106]. Channappanavar et al. revealed that male mice were more vulnerable to infection with SARS-CoV compared to female mice matched in age., However, mortality in female mice was increased when the ovariectomy was done or the estrogen receptor antagonist was given [107]. Wei et al. [108] also stated that SARS patients had significantly higher serum levels of prolactin (PRL), follicle-stimulating hormone (FSH), and luteinizing hormone (LH) than control groups, while estradiol (E2), pregnancy hormone (P), and thyroid-stimulating hormone (TSH) were considerably lower than normal controls. Notably, estrogenic compounds were found to decrease the replication of influenza A virus in primary human nasal epithelial cells from female donors, but not in male donors [109]. Resveratrol, a phytoestrogen from grape seeds and red wine, had been reported to be a potent in vitro anti-MERS agent [110]. So, 17β-Estradiol or phytoestrogen may also be considered an substitute choice for the treatment of COVID-19.

2.7.3 Mucroporin-M1

In recent years, outbreaks of SARS-CoV, influenza A (H5N1, H1N1) and measles viruses have enhanced serious concerns about the available measures to control emerging and re-emerging viral infectious diseases [111]. Mucroporin is the primary cationic host defense peptide from the venom of the *Lychas mucronatus* scorpion [112]. Mucroporin-M1 has a spacious range of virucidal activity against many viruses, including H5N1, measles and SARS-CoV viruses [111]. To treat the COVID-19 infection, Mucroporin-M1 also could be applied.

2.8 Management from Conventional Medicine

Currently, there is a limited evidence from randomized clinical trials to support any conventional medicine as vaccine or pharmacological therapy for the treatment and prevention of coronavirus [113,114]. Antiviral treatment and corticosteroids used in SARS and other outbreaks are considering now-a-days in many countries to fight against coronavirus.

2.8.1 Corticosteroids

Previously, corticosteroids were used in H1N1 viral pneumonia and severe community acquired pneumonia with possible mortality reduction in patients who developed acute respiratory diseases [115,116]. It was used in SARS aiming to suppress cytokine storm to prevent clinical deterioration arise from host immunopathological response in the second phase. Corticosteroids use on the current outbreak was widely reported [117,118].

2.8.2 Ivermectin

Ivermectin is a mostly used medication for the treatment and management of many neglected tropical diseases [119]. The drug has an outstanding safety record, with over 2.5 billion doses delivered over the past 30 years, and its ability to reduce malaria transmission by killing mosquitoes is under examination in several trials around the world [120]. Ivermectin obstructs in vitro replication of certain positive, single-stranded RNA viruses, namely dengue virus (DNV), Zika virus, yellow fever virus and other viruses [121]. Caly et al. recently revealed that ivermectin is a potent inhibitor of in vitro replication of the severe acute respiratory coronavirus 2 (SARS-CoV-2) [122]. Within 48h, the single treatment of this drug was able to reduce the virus in culture by up to 5000 times. No further reductions were recorded with a further increase in the time span, i.e. to 72h. However, no toxicity was found at any time with the drug [123]. As most RNA viruses are IMPα / β1 dependent during infection, Ivermectin acts on it and inhibits the import with increased antiviral response [122,123].

2.8.3 Favipiravir

Favipiravir is commonly used against influenza and also has been used successfully in other infectious conditions [124]. Favipiravir targets

RNA viruses by inhibiting RNA-dependent RNA polymerase [125]. It was the first drug approved for coronavirus treatment in China. The use of Favipiravir as a treatment for coronavirus was approved by The National Medical Products Administration of China. The drug has reportedly shown efficacy in treating the disease with minimal side effects in a clinical trial involving 70 patients. The clinical trial was carried out in China's Shenzhen city of the Guangdong province [126].

2.8.4 Plasma therapy

It is no new idea to use convalescent plasma to treat viral diseases. It had already been tried in the beginning of the 20th century [127]. It was a time when there was no effective antiviral agent. Since then, several attempts have been made at convalescent plasma therapy [128]. Convalescent plasma or immunoglobulin is used as a last resort to increase the survival rate of SARS patients, whose condition continued to deteriorate following pulsed methylprednisolone therapy. Some studies of patients treated with convalescent plasma showed a shorter hospital stay and lower mortality than those not treated with convalescent plasma [8]. In 2014, the demeanor of convalescent plasma collected from patients who had recovered from Ebola virus disease was recommended by WHO as an empirical treatment during outbreaks [8].

Previously, plasma therapy has been used as a treatment to severe acute respiratory syndrome (SARS), influenza, Ebola virus, and Middle East respiratory syndrome coronavirus (MERS-CoV), and it seems to have achieved 'not-bad' results, although not always successful [128].

2.9 Other Possible Therapeutic Interventions

2.9.1 Androgen-deprivation therapy

Androgen-deprivation therapy can be an option against SARS-CoV-2. A study was done with prostate cancer patients receiving ADT (androgen-deprivation therapy) and not receiving ADT. This study indicates that prostate cancer patients receiving ADT had a lower risk of COVID-19 (SARS-CoV-2) 9than others prostate cancer patients not receiving ADT [129].

2.9.2 Anti-histamine

Histamine is an endogenous biogenic amine that acts as a local mediator in the immune system. It is distributed in the cells and is present in high concentrations in the lungs, skin, and gastrointestinal tract. Few studies were done to see the effect of anti-histamine in the patients with the symptom of COVID-19. One study reveals that patients had the improvements with the symptoms of COVID-19 when administered high dose oral famotidine therapy [130].

3. CONCLUSION

COVID-19 has narrow pharmacological therapeutic options due to the lack of evidence from well-designed clinical trials, similar to other outbreaks of any newly detected virus. In this study, we outlined all possible COVID-19 infection interventions based on former treatments for SARS and MERS. However, we have found that for increasing the host's immune response to viral RNA infection, general treatments are very important. In several model systems as well as in human studies the immune response has also been exibited to be compromised by inadequate nutrition. However, the host's nutritional status was not seen as a contributing factor to the emergence of viral infectious diseases. Therefore, we propound to test the nutritional status of patients infected with COVID-19 before general treatment is provided. Additionally, we have put in that coronavirus-specific treatments and antiviral therapies were very effective for SARS and MERS treatments. These may also be considered as feasible treatments for a COVID-19 infection. The other compounds should also be chosen as variant options for the treatment as well as new drug designs.

DISCLAIMER

The products used for this research are commonly and predominantly use products in our area of research and country. There is absolutely no conflict of interest between the authors and producers of the products because we do not intend to use these products as an avenue for any litigation but for the advancement of knowledge. Also, the research was not funded by the producing company rather it was funded by personal efforts of the authors.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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