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Running Title: Novel Coronavirus in China

Title: Potential Interventions for Novel Coronavirus in China: A Systematic Review

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Abstract

An outbreak of a novel coronavirus (COVID-19 or 2019-CoV) infection has posed significant threats to international health and the economy. In the absence of treatment for this virus, there is an urgent need to find alternative methods to control the spread of disease. Here, we have conducted an online search for all treatment options related to coronavirus infections as well as some RNA virus infection and we have found that general treatments, coronavirus-specific treatments, and antiviral treatments should be useful in fighting COVID-19. We suggest that the nutritional status of each infected patient should be evaluated before the administration of general treatments and the current children's RNA virus vaccines including influenza vaccine should be immunized for uninfected people and health care workers. In addition, convalescent plasma should be given to COVID-19 patients if it is available. In conclusion, we suggest that all the potential interventions be implemented to control the emerging COVID-19 if the infection is uncontrollable.

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1. Introduction

Coronaviruses (CoVs) belong to the subfamily *Orthocoronavirinae* in the family of *Coronaviridae* in the order *Nidovirales*, and this subfamily including alpha-coronavirus, beta-coronavirus, gamma-coronavirus, and delta-coronavirus [1]. Coronaviruses primarily cause enzootic infections in birds and mammals and, in the last decades, have shown to be capable of infecting humans as well[2]. The outbreak of SARS in 2002 and MERS in 2012 has demonstrated the lethality of coronaviruses when they cross the species barrier and infect humans [2]. SARS-CoV and MERS-CoV all belong to the beta-coronavirus family [3]. Recently, a novel flu-like coronavirus (COVID-19) related to the MERS and SARS coronaviruses was found at the end of 2019 in China [4,5] and the evidence of human-to-human transmission was confirmed among close contacts [6]. The genome of COVID-19 is a single-stranded positive-sense RNA [7]. The sequence analysis showed that the COVID-19 possessed a typical genome structure of coronavirus and belonged to the cluster of beta-coronaviruses including SARS-CoV and MERS-CoV[7]. COVID-19 was more than 82% identical to those of SARS-CoV [8,9]. COVID-19 may spread worldwide with pandemic. Currently, there is no registered treatment or vaccine for the disease. In the absence of a specific treatment for this novel virus, there is an urgent need to find an alternative solution to prevent and control the replication and spread of the virus. We have done an online search on PubMed and Web of Science with the key words of SARS, MERS, and coronaviruses. We summarize and propose therapeutic options available for the treatment of this novel coronaviruses.

Main Text

1. General Treatment for Viral Infection (Table 1)

1.1.Nutritional interventions

1.1.1 Vitamin A

Vitamin A is the first fat-soluble vitamin to be recognized and beta-carotene is its plant-derived precursor. There are three active forms of vitamin A in the body, retinol, retinal, and retinoic acid. Vitamin A as also called “anti-infective” vitamin and many of body’s defenses against infection depend on an adequate supply. Researchers have believed that an impaired immune response is due to deficiency of a particular nutritional element [10]. Vitamin A deficiency is strongly involved in measles and diarrhea [11] and measles can become severe in vitamin A-deficient children. In addition, Semba *et al.* had reported that vitamin A supplementation reduced morbidity and mortality in different infectious diseases, such as measles, diarrheal disease, measles-related pneumonia, human immunodeficiency virus (HIV) infection, and malaria [12]. Vitamin A supplementation also offers some protection against the complications of other life-threatening infections, including malaria, lung diseases, and HIV [13]. Jee *et al.* had reported that low vitamin A diets might compromise the effectiveness of inactivated bovine coronavirus vaccines and render calves more susceptible to infectious disease [14]. The effect of infection with infectious bronchitis virus (IBV), a kind of coronaviruses, was more pronounced in chickens fed a diet marginally deficient in vitamin A than in those fed a diet adequate in vitamin A[15]. The mechanism by which vitamin A and retinoids inhibit measles replication is up-regulating elements of the innate immune response in uninfected bystander cells, making them refractory to productive infection during subsequent rounds of viral replication [16]. Therefore, vitamin A could be a promising option for the treatment of this novel coronavirus and the prevention of lung infection.

1.1.2. B vitamins

B vitamins are water-soluble vitamins and work as part of coenzymes. Each B vitamin has its special functions. For example, vitamin B2 (riboflavin) plays a role in the energy metabolism of all cells. Vitamin B2 deficiency had been suspected to occur among U.S elderly [17]. Keil *et al.* had reported that vitamin B2 and UV light effectively reduced the titer of MERS-CoV in human plasma products [18]. Vitamin B3, also called nicotinamide, could enhance the killing of Staphylococcus aureus through a myeloid-specific transcription factor and vitamin B3 was efficacious in both prophylactic and therapeutic settings [19]. Moreover, vitamin B3 treatment significantly inhibited neutrophil infiltration into the lungs with a strong anti-inflammatory effect during ventilator-induced lung injury. However, it also paradoxically led to the development of significant hypoxemia [20]. Vitamin B6 is also needed in protein metabolism and it participates in over 100 reactions in body tissues. In addition, it also plays important roles in body immune function as well. As shortage of B vitamins may weaken host immune response, they should be supplemented to the virus-infected patients to enhance their immune system. Therefore, B vitamins could be chosen as a basic option for the treatment of COVID-19.

1.1.3. Vitamin C

Vitamin C is another water-soluble vitamin and it is also called ascorbic acid, which means “no-scurvy acid”. Vitamin C is best known for its role in the synthesis of collagen in connective tissues and acts as an antioxidant. Vitamin C also supports immune functions and protects against infection caused by coronavirus [21]. For example, Atherton *et al.* had reported that vitamin C increased the resistance of chick embryo tracheal organ cultures to avian coronavirus infection [22]. Vitamin C may also function as a weak antihistamine agent to provide relief from flu-like symptoms such as sneezing, a running or stuffy nose, and swollen sinuses [23]. Three human controlled trials had reported that there was significantly lower incidence of pneumonia in vitamin C-supplemented groups, suggesting that vitamin C might prevent the susceptibility to lower respiratory tract infections under certain conditions [24]. The COVID-19 had been reported to cause lower respiratory tract infection, so vitamin C could be one of the effective choices for the treatment of COVID-19.

1.1.4. Vitamin D

Vitamin D is not only a nutrient but also a hormone, which can be synthesized in our body with the help of sunlight. In addition to its role in maintaining bone integrity, it also stimulates maturation of many cells including immune cells. A high number of healthy adults have been reported to be with low levels of vitamin D, mostly at the end of Winter season [25]. In addition, people who are housebound, or institutionalized and those who work at night may have vitamin D deficiency, as do many elderly people, who have limited exposure to sunlight [26]. The COVID-19 was first identified in Winter of 2019 and mostly affected middle-aged to elderly people. The virus-infected people might have insufficient of vitamin D. In addition, the decreased vitamin D status in calves had been reported to cause the infection of bovine coronavirus [27]. Therefore, vitamin D could work as anther therapeutic options for the treatment of this novel virus.

1.1.5. Vitamin E

Vitamin E is a lipid-soluble vitamin and it includes both tocopherols and tocotrienols. Vitamin E plays an important role in reducing oxidative stress through binding to free radical as an antioxidant [28]. Vitamin E deficiency had been reported to intensify the myocardial injury of coxsackievirus B3 (a kind of RNA viruses) infection in mice [29] and increased the virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency [30]. In addition, the decreased vitamin E and D status in calves also caused the infection of bovine coronavirus[27].

1.1.6. Omega-3 polyunsaturated fatty acids (PUFA)

Long-chain PUFAs are important mediators of inflammation and adaptive immune responses[31]. Omega-3 and omega-6 PUFAs predominantly promote anti-inflammatory and pro-inflammatory effects. They are precursors of resolvins /protectins and prostaglandins/leukotrienes, respectively [31]. Begin *et al*. had studied plasma lipids levels in patients with AIDS and had found that a selective and specific lack of the long chain PUFAs of omega-3 series, which are found in high concentrations in fish oils [32]. In addition, protectin D1, the omega-3 PUFA-derived lipid mediator, could markedly attenuate influenza virus replication via RNA export machinery. In addition, treatment of protectin D1 with peramivir could completely rescued mice from flu mortality [33]. Leu *et al.* had found that several PUFAs also had anti- hepatitis C virus (HCV) activities [34]. Therefore, Omega-3 including protectin D1, which served as a novel antiviral drug, could be considered for one of the potential interventions of this novel virus, COVID-19.

1.1.7. Selenium

Selenium is an essential trace element for mammalian redox biology [35]. The nutritional status of host plays a very important role in the defense against infectious diseases [36]. Nutritional deficiency impacts not only the immune response but also the viral pathogen itself [10]. Dietary selenium deficiency that causes oxidative stress in the host can alter a viral genome, so that a normally benign or mildly pathogenic virus can become highly virulent in the deficient host under oxidative stress [10]. Deficiency in selenium also induces not only impairment of host immune system, but also rapid mutation of benign variants of RNA viruses to virulence [37]. Beck *et al.* had reported that selenium deficiency could not only increase the pathology of an influenza virus infection [38], but also drive changes in genome of coxsackievirus, permitting an avirulent virus to acquire virulence due to genetic mutation [39]. It is because that selenium could assist a group of enzymes that, in concert with vitamin E, work to prevent the formation of free radicals and prevent oxidative damage to cells and tissues [37]. It was reported that synergistic effect of selenium with ginseng stem-leaf saponins could induce immune response to a live bivalent infectious bronchitis coronavirus vaccine in chickens [40]. Therefore, selenium supplementation could be an effective choice for the treatment of this novel virus of COVID-19.

1.1.8. Zinc

Zinc is a dietary trace mineral and is important for maintenance and development of immune cells of both the innate and adaptive immune system [41]. Zinc deficiency results in dysfunction of both humoral and cell-mediated immunity and increases susceptibility to infectious diseases [42]. Zinc supplement given to zinc-deficient children could reduce measles-related morbidity and mortality caused by lower respiratory tract infections [43]. Increasing the concentration of intracellular zinc with zinc-ionophores like pyrithione can efficiently impair the replication of a variety of RNA viruses [44]. In addition, the combination of zinc and pyrithione at low concentrations inhibits the replication of SARS-coronavirus (SARS-CoV) [44]. Therefore, zinc supplement may have effect not only on COVID-19 related symptom like diarrhea and lower respiratory tract infection, but also on COVID-19 itself.

1.1.9. Iron

Iron is required for both host and pathogen and iron deficiency can impair host immunity, while iron overload can cause oxidative stress to propagate harmful viral mutations [45]. Iron deficiency has been reported as a risk factor for the development of recurrent acute respiratory tract infections [46]

1.2. Immunoenhancers

1.2.1. Interferons

Interferons (IFNs) have divided into type I and Type II Interferons. As a member of Type I IFN, IFN-alpha is produced very quickly as part of innate immune response to virus infection. IFN- alpha inhibits replication of animal and human coronaviruses [47,48]. The investigation *in vitro* also demonstrated that type I interferons including IFN-beta could inhibit the replication of SARS coronavirus (SARS-CoV) [49]. However, interferon-gamma was reported not to possess antiviral activity against SARS coronavirus [50]. Kuri *et al.* further reported that IFN transcription was blocked in tissue cells infected with SARS-CoV and the cells was able to partially restore their innate immune responsiveness to SARS-CoV after priming with small amounts of IFNs [51]. Moreover, Tan *et al.* had tested the inhibition of SARS coronavirus infection *in vitro* with clinically approved antiviral drugs. They found that the complete inhibition of cytopathic effects of virus was observed with specific subtypes (beta-1b, alpha-n1, alpha-n3, and human leukocyte interferon alpha) in culture [52]. Haagmans *et al.* also reported *in vivo* that pegylated recombinant IFN-α2b, a registered drug for chronic hepatitis C [53], could protect type 1 pneumocytes against SARS coronavirus infection in monkeys (macaques) [54]. The drug given at 3 days before infection could reduce viral replication and lung damage as compared with the control monkeys [55]. It was also considered as a candidate drug for SARS therapy at that time and the effectiveness of synthetic recombinant IFN-alpha for the treatment of SARS patients was demonstrated in a pilot clinical trial [56]. In addition, interferons have also been found to be potent inhibitors of MERS-CoV replication [57]. Moreover, the combination of interferon-alpha-2a with ribavirin was administered to patients with severe MERS-CoV infection and the survival of these patients was improved[57]. These findings suggest that these approved IFN's could be also used for the treatment of this novel coronavirus.

1.2.2. Intravenous gammaglobulin

Intravenous gammaglobulin **(**IVIg) was first developed in the late 1970s [58] and is probably the safest immunomodulating drug available for long-term use in all ages. However, it does have adverse reactions. During the SARS outbreak in 2003, IVIg was used extensively in Singapore. However, one third of critically ill patients developed venous thrombo-embolism including pulmonary embolism despite use of low molecular weight heparin prophylacticly [59]. It was due to the IVIg-induced increase of viscosity in hypercoagulable states of SARS patients [60].

1.2.3. Thymosin alpha-1

Thymosin alpha-1 (Ta1) is a thymic peptide hormone and it has a peculiar ability to restore the homeostasis of immune system [61]. It is was first isolated from thymic tissue in the mid-sixties and it had gained much attention for its immunostimulatory activity [62]. It was chemically synthesized and used in diseases where the immune system was hindered or impaired [63]. Besides its role in thymocyte development, thymosin alpha-1 could also increase resistance to glucocorticoid induced death of the thymocyte [64]. Thymosin alpha-1 could also be used as immune enhancer to SARS patients and it was effective in controlling the spread of the disease [65,66]. Methylprednisolone was often used during the current treatment of COVID-19 and the side effect of corticoid-induced death of thymocytes should be considered. So, it is wise to use thymosin alpha 1 before the administration of methylprednisolone.

1.2.4. Thymopentin

Thymopentin (TP5, munox), a synthetic pentapeptide corresponding to the active site of thymopoietin, had been shown to restore antibody production in old mice [67]. Additionally, it could enhanced the antibody response in human when it was applied subcutaneously three times a week at doses of 50 mg [68]. Moreover, thymopentin could also be used as an adjuvant treatment for non-responders or hyporesponders to hepatitis B vaccination [69].

1.2.5. Levamisole

Levamisole, a synthetic low-molecular-weight compound, is the first member of a new class of drugs which can increase the functions of cellular immunity in normal, healthy laboratory animals [70]. However, levamisole can act as either an immunostimulant agent or an immunosuppressive agent depending upon the dosing and the timing. So, its clinical use should be carefully taken. Joffe *et al.* had reported that levamisole and ascorbic acid treatment *in vitro* could reverse the depressed helper/inducer subpopulation of lymphocyte in measles [71]. Therefore, the use of levamisole could also be considered for the treatment for COVID-19.

1.2.6. Cyclosporine A

Cyclosporine A is a very important immunosuppressive drug and it has been widely used in transplantation. The emerging use of cyclosporine A has greatly improved the survival rates of patients and grafts after solid-organ transplantation [72]. Cyclosporine A is also used for treatment of autoimmune disorders. Luo *et al.* had speculated that nucleocapsid protein (NP) of SARS-CoV played an important role in the process of virus particle assembly and release and it might also bind to human cyclophilin A[73]. Cyclophilin A is a key member of immunophilins acting as a cellular receptor for cyclosporine A[74]. Cyclophilin A has played an important role in viral infection which either facilitates or inhibits their replication [74]. In addition, the inhibition of cyclophilins by cyclosporine A could block the replication of coronavirus of all genera, including SARS-CoV as well as avian infectious bronchitis virus [75]. Therefore, the non-immunosuppressive derivatives of cyclosporine A might serve as broad-range coronavirus inhibitors applicable against the emerging novel virus like COVID-19.

1.2.7. Chinese medicine

Glycyrrhizin is an active component of liquorice roots in Chinese Medicine. Cinatl *et al.* had reported that glycyrrhizin could inhibit the replication of SARS-associated virus *in vitro* and it had already been suggested as an alternative option for treatment of SARS at that time [76]. Baicalin, another Chinese herb, is a flavonoid which is isolated from Radix Scutellaria. Baicalin was also found to have the ability to inhibit SARS-CoV *in vitro* [50]. Ginseng stem-leaf saponins could highly enhance the specific-antibody responses for Newcastle disease virus and infectious bronchitis virus[40]. Therefore, Chinese Medicine could also be considered as choices to enhance host immunity against the infection of COVID-19.

In summary, the general treatment for viral infection including nutritional interventions and all kinds of immunoenhancers has been used to enhance host immunity against RNA viral infections. Therefore, they may also be used to fight COVID-19 infection through correcting the lymphopenia of patients.

2. Coronavirus-Specific Treatments (Table 2)

2.1. Coronaviral protease inhibitors

Chymotrypsin-like (3C-like) and papain-like protease (PLP) are coronavirus encoded proteins. They have essential function for coronaviral replication and also have additional function for inhibition of host innate immune responses. Targeting 3C-like protease (3CLpro) and papain-like protease (PLpro) are more attractive for the treatment of coronavirus [77].

2.1.1. Chymotrypsin-like (3C-like) inhibitors

2.1.1.1. Cinanserin

Cinanserin, an old drug, is well-known for serotonin receptor antagonist. It could inhibit the 3 chymotrypsin-like (3C-like) protease and was a promising inhibitor of replication of SARS-CoV [78]. The 3CLpro was also been found to be encoded in COVID-19 [7]. Therefore, Cinanserin may be a better choice for the treatment of COVID-19 infection.

2.1.1.2. Flavonoids

Flavonoids are an important class of natural products and have several subgroups, which include chalcones, flavones, flavonols and isoflavones [79]. Flavonoids have many functions besides antioxidant effects and they also have antiviral abilities. Shimizu *et al.* had found that flavonoids from Pterogyne Nitens could inhibit the entry of hepatitis C Virus [80]. Jo *et al.* had suggested that the anti-coronavirus activity of some flavonoids (Herbacetin, rhoifolin and pectolinarin) was due to the inhibition of 3C-like protease (3CLpro) [81]. Other flavonoids (Herbacetin, isobavachalcone, quercetin 3-β-d-glucoside, and helichrysetin) were also found to be able to block the enzymatic activity of MERS-CoV/3CLpro [82]. Moreover, Ryu *et al.* had reported that biflavonoids from Torreya Nucifera also brought inhibition effect of SARS-CoV /3CL (pro) [83].

2.1.2. Papain-like protease (PLP) inhibitors

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

2.1.2.1. Diarylheptanoids

Diarylheptanoids is a natural product and is extracted from the stem bark of Alnus japonica. It had been found to be able to inhibit papain-like protease of SARS-CoV [77].

Therefore, cinanserin together with flavonoids and other natural compounds could be chosen as alternative choices to fight COVID-19 infection through targeting coronaviral proteases.

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

Angiotensin-converting enzyme-2 (ACE2) is a type I integral membrane protein which functions as a carboxypeptidase and is the first human homologue of ACE [84]. ACE2 efficiently hydrolyses the potent vasoconstrictor angiotensin II to angiotensin (1-7) and it has been implicated in hypertension, cardiac function, heart function and diabetes [84]. In addition, ACE2 is also a functional receptor of SARS-CoV and it mediates virus entry into the cell through binding with spike (S) protein [85,86]. The S protein of SARS-CoV is a type I surface glycoprotein and is responsible for the binding to cellular receptors. In addition, S protein mediates the fusion of viral and host membranes [87]. Zhou *et al.* reported that COVID-19 used ACE2 as a solely receptor for the entry, but did not use other coronavirus receptors, aminopeptidase N and dipeptidyl peptidase, for the entry. Blocking the binding of S protein to ACE2 is important for the treatment of SARS CoV infection [88].

2.2.1. Human monoclonal antibody

Sui *et al.* had found one recombinant human monoclonal antibody (mAb) (single-chain variable region fragments, scFvs 80R) against the S1 domain of S protein of SARS-CoV from two nonimmune human antibody libraries. The mAb could efficiently neutralize SARS-CoV and inhibit syncytia formation between cells expressing the S protein and those expressing the SARS-CoV receptor ACE2 [89].

2.2.2. Chloroquine

Chloroquine is a 9-aminoquinoline known since 1934. Apart from its well-known antimalarial effects, the drug also has many interesting biochemical properties including antiviral effect. In addition, it had been used against viral infection [90]. Moreover, chloroquine was also found to be a potent inhibitor of SARS coronavirus infection through interfering with ACE2, one of cell surface binding sites for S protein of SARS-CoV [91].

2.2.3. Emodin

Emodin is an anthraquinone compound derived from genus *Rheum* and *Polygonum* and it is also a virucidal agent [92]. Emodin could significantly block the interaction between the S protein of SARS-CoV and ACE2. Therefore, emodin might abolish SARS-CoV infection by competing the binding site of S protein with ACE2 [93].

2.2.4. Promazine

Promazine, anti-psychotic drug, shares a similar structure with emodin. It has been found to exhibit the significant effect in inhibiting the replication of SARS-CoV [94]. As compared to emodin, promazine exhibited potent inhibition of the binding of S protein to ACE2. These findings suggested that emodin and promazine might be able to inhibit SARS-CoV infectivity through blocking the interaction of S protein and ACE2 [93]. Therefore, the monoclonal antibody (scFv80R), chloroquine, emodin, and promazine could be used as alternative choices for the treatment of COVID-19.

2.2.5. Nicotianamine

Nicotianamine is an important metal ligand in plants [95] and it is found a novel angiotensin-converting enzyme 2 inhibitor in soybean [96]. So, it is another potential option to be used to reduce the infection of COVID-19.

3. Antiviral Treatments (Table 3)

3.1. Ribavirin

Ribavirin, a broad-spectrum antiviral agent, is routinely used to treat hepatitis C. During the outbreak of SARS, ribavirin was used extensively for most cases with or without concomitant use of steroids in Hong Kong [97]. However, there was considerable skepticism from overseas and local experts on the efficacy of ribavirin [98]. Because there was a report mentioned that ribavirin had no significant activity against SARS-CoV *in vitro*[52] and the use of ribavirin was found to be associated with significant toxicity, including hemolysis (in 76%) and decrease in hemoglobin (in 49%) [99]. However, Morgenstern *et al.* had reported that ribavirin and interferon-beta synergistically inhibited the replication of SARS-associated coronavirus in animal and human cell lines [49]. In view of adverse reactions and the lack of *in vitro* efficacy, the use of ribavirin should be seriously considered for the treatment of COVID-19, even in combination with other antiviral drugs.

3.2. Lopinavir (LPV)/ritonavir (RTV) (Kaletra)

The combination of lopinavir with ritonavir is widely used as a boosted protease inhibitor in the treatment of HIV infection [100]. LPV is usually combined with RTV to increase lopinavir half-life through the inhibition of cytochrome P450 [101]. Chu *et al.* had found that the use of LPV/RTV with ribavirin in the treatment of SARS was associated with better outcome [102]. Kim *et al.* had also reported a successful case of MERS-CoV disease treated with triple combination therapy LPV/RTV, ribavirin, and IFN-alpha 2a in South Korea [103]. Regarding to this novel virus, COVID-19, Kim's triple combination therapy should be considered as an option at the early stage of disease.

3.3. Remdesivir

Remdesivir (RDV), a nucleoside analogue GS-5734, had been reported to inhibit human and zoonotic coronavirus *in vitro* and to restrain severe acute respiratory syndrome coronavirus (SARS-CoV) *in vivo* [104]. Recently, the antiviral activity of RDV and IFN-beta was found to be superior to that of LPV/RTV-IFN-beta against MERS-CoV *in vitro* and *in vivo*[101]. In addition, RDV could improve pulmonary function and reduce lung viral loads and severe lung pathology in mice, which was impossible for LPV/RTV-IFN-beta [101].Recently, a first COVID-19 infected case was reported in the United States and the use of remdesivir was administered when the patient's clinical status was getting worsen [105]. Therefore, the use of RDV with IFN-beta could be a better choice for the treatment of COVID-19 comparing with that of the triple combination of LPV/RTV-IFN-beta. However, the randomized and controlled trials are still needed to determine the safety and efficacy of remdesivir.

3.4. Nelfinavir

Nelfinavir is a selective inhibitor of HIV protease, which is responsible for post-translational processing of HIV propeptides [106]. Yamamoto had found that nelfinavir could strongly inhibit the replication of SARS coronavirus (SARS-CoV) [107]. Therefore, nelfinavir could also be an option for the treatment of COVID-19.

3.5 Arbidol

Arbidol (ARB) is a Russian-made small indole-derivative molecule and is licensed in Russia and China for prophylaxis and treatment of influenza and other respiratory viral infections [108]. Arbidol had been found to be able to block viral fusion against influenza A and B viruses as well as hepatitis C virus [109]. Arbidol could also inhibit hepatitis C virus by blocking hepatitis C virus entry and replication *in vitro* [110]. In addition, arbidol and its derivatives, arbidol mesylate, had been reported to have antiviral activity against the pathogen of SARS in the cell cultures and arbidol mesylate was nearly 5 times as effective as arbidol in reducing the reproduction of SARS virus in the cultured cells [111].

3.6. Nitric oxide

Nitric oxide (NO) is a gas with diverse biological activities and is produced from arginine by NO synthases. NO is able to interact with superoxide, forming peroxynitrite, which, in turn, can mediate bactericidal or cytotoxic reactions [112]. In addition, NO had played an important role in regulating airway function and in treating inflammatory airway diseases [113]. Rossaint *et al.* reported that the beneficial effects of NO inhalation could be observed in most patients with severe acute respiratory distress syndrome (ARDS) [114]. NO was also found to inhibit the synthesis of viral protein and RNA [115]. Moreover, Akerström *et al.* had reported that organic NO donor, S-nitroso-N-acetylpenicillamine, could significantly inhibit the replication cycle of SARS-CoV in a concentration-dependent manner [116]. Therefore, the NO inhalation could be also chosen as an option for treatment of severely COVID-19 infected patients.

4. Other Compounds (Table 3)

4.1. Alpha-lipoic acid

Alpha-lipoic acid (ALA), a naturally occurring disulfide compound, acts as a cellular coenzyme and has been applied for the treatment of polyneuropathies and hepatic disorders for years [117]. ALA, as an antioxidant, has played a pivotal role in scavenging free radicals to protect against oxidative damage in several diseases [118]. In addition, ALA also had its capability to enhance intracellular glutathione (GSH) levels[118] and to normalize the oxidative stress induced by Dexamethasone in chicken [119]. Wu *et al.* also reported that the oxidative stress in host cells was an important factor in infectivity of human coronavirus 229E and the glucose-6-phosphate dehydrogenase (G6PD) deficiency was another factor that enhanced human coronavirus 229E infection [120]. Addition of alpha-lipoic acid to G6PD-knockdown cells could attenuate the increased susceptibility to human coronavirus 229E infection [120]. Interestingly, Baur *et al.* also found that alpha-lipoic acid was effective to inhibit the replication of HIV-1[121]. In summary, we speculate that ALA could be also used as an optional therapy for this new virus.

4.2. Estradiol and phytoestrogen

Females, generally, mount more robust immune responses to viral challenge than males, which can result in more efficient virus clearance [122]. Epidemiological studies showed that males experiencing higher rate of incidence and case fatality compared with females after SARS-CoV infection[123,124]. During MERS outbreak, the disease occurrence rate in men was almost twice as much as in women and the case fatality rate was the same as the occurrence rate among men and women [125]. In addition, Channappanavar *et al.* had reported that male mice were more susceptible to SARS-CoV infection compared with age-matched female mice. However, the mortality was increased in female mice when the ovariectomy was done or the estrogen receptor antagonist was given [126]. Wei *et al.* also found that serum levels of prolactin (PRL), follicle stimulating hormone (FSH), and luteinizing hormone (LH) of SARS patients were significantly higher than those of control groups, while estradiol (E2), pregnancy hormone (P), and thyroid stimulating hormone (TSH) were considerably lower than those of normal controls [127]. Interestingly, estrogenic compounds had been found to reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors [128]. In addition, resveratrol, a phytoestrogen from grape seeds and red wine, had been reported to be a potent anti-MERS agent *in vitro* [129]. Therefore, 17β-Estradiol or phytoestrogen could also be an alternative option to be considered for the treatment of COVID-19.

4.3. Mucroporin-M1

Mucroporin-M1 is a scorpion venom-derived peptide and has broad-spectrum virucidal activity against many viruses including measles, influenza H5N1 viruses, and SARS-CoV [130]. Therefore, this peptide could also be used for the treatment of COVID-19 infection as well as the new drug design to target COVID-19.

Conclusion

In this review, we summarize all the potential interventions for COVID-19 infection according to previous treatments of SARS and MERS. We have found that the general treatments are very important to enhance host immune response against RNA viral infection. The immune response has often been shown to be weakened by inadequate nutrition in many model systems as well as in human studies. However, the nutritional status of the host, until recently, has not been considered as a contributing factor to the emergence of viral infectious diseases. Therefore, we propose to verify the nutritional status of COVID-19 infected patients before the administration of general treatments. In addition, we also found coronavirus-specific treatments and antiviral treatments were very useful for the treatment of SARS and MERS. They should also be considered as potential treatments for COVID-19 infection. The other compounds should also be chosen as alternative options for the treatment as well as new drug designs.

To complete eradication of virus infection, the COVID-19 related vaccines are warranted. The vaccine development for SARS had already attracted the attention of many scientists in the past. Avian infectious bronchitis virus (IBV) is similar to SARS-CoV and both viruses belong to coronavirus. IBV is in group 3 and SARS belongs to group 4 [131]. Bijlenga *et al.* had suggested that avian live virus IBV vaccine (strain H) be used to treat SARS in 2005[55]. However, preliminary test in monkeys should be taken before the startup. Interesting, children are seldom attacked by

COVID-19 as well as SARS-CoV. It may be due to the required vaccine program for every child. The RNA-virus vaccines and the adjuvants in vaccine program may help children escape from the infection. Therefore, the RNA-virus related vaccines including measles (MeV), polio, Japanese encephalitis virus, influenza virus, and rabies related vaccines, could be used as most promising alternative choices to prevent human-to-human transmission through immunizing health care workers and non-infected population as well.

Recombinant measles vaccine expressing S protein of SARS and MERS were also tried by many researchers. Escriou *et al.* had generated live-attenuated recombinant measles vaccine (MV) candidates expressing the membrane-anchored S protein of SARS-CoV (SARS-CoV-S-vaccine) and they had found that the vaccine could induce highest titers of neutralizing antibodies and protected immunized animals from intranasal infectious challenge with SARS-CoV [132]. Bodmer *et al.* had reported that two live-attenuated measles virus vaccines either expressing S protein or N protein of MERS-CoV could induce robust and multifunctional T cell responses in mouse model [133]. Frantz *et al.* also mentioned that recombinant measles vaccine could induce stronger and T helper 1 (Th1)-biased responses [134].

Regarding to a short-term protection and prevention of viral infection, passive immunotherapy should not be neglected [135]. Monoclonal antibody therapy is one of the best forms for passive immunotherapy. A human IgG1 monoclonal antibody (mAb), CR3014, had been generated and it had been found to be reactive with whole inactivated SARS coronavirus. In addition, CR3014 could be used as prophylaxis for SARS coronavirus infection in ferrets [136]. However, CR3014 was found to be able to block the interaction in parent SARS-CoV strain, but not in escape variants. This led the ineffectiveness of CR3014 to prevent infection in human. CR3022 was another monoclonal antibody and it had been found to neutralize CR3014 escape viruses[136]. The combination of CR3014 and CR3022 had also been reported to have the potential to control immune escape [135]. However, the clinical trial of CR3022 with CR3014 had never been tried due to the high cost of manufacturing.

Convalescent plasma can also be called a passive immunotherapy. It is usually chosen when there are no specific vaccines or drugs available for emerging infection-related diseases [137]. Arabi *et al.* had tested the feasibility of convalescent plasma therapy as well as its safety and clinical efficacy in critically ill MERS patients. They found that convalescent plasma had an immunotherapeutic potential for the treatment of MERS-CoV infection [138]. In addition, convalescent plasma from recovered SARS patients had also been reported to be useful clinically for treating other SARS patients [139,140]. Importantly, the use convalescent plasma or serum was also suggested by World Health Organization (WHO) under Blood Regulators Network when vaccines and antiviral drugs was unavailable for an emerging virus. In summary, these findings suggest that the current children's RNA-virus related vaccines are the best alternative methods to be used to vaccinate the uninfected people and health care workers. Convalescent plasma should be routinely used for the treatment of COVID-19 infected critically sick patients if it is available. The avian IBV vaccine is also be another choice for clinical trial if its safety has been approved in monkeys. Therefore, we suggest that all the potential interventions be implemented to control the emerging COVID-19 if the infection is uncontrollable.

Conflicts of Interest:

The authors declare that they have no conflict of interest.

References

1 Banerjee, A., Kulcsar, K., Misra, V., Frieman, M. & Mossman, K. Bats and Coronaviruses. *Viruses* **11**, doi:10.3390/v11010041 (2019).

2 Schoeman, D. & Fielding, B. C. Coronavirus envelope protein: current knowledge. *Virol J* **16**, 69, doi:10.1186/s12985-019-1182-0 (2019).

3 Zumla, A., Hui, D. S. & Perlman, S. Middle East respiratory syndrome. *Lancet* **386**, 995-1007, doi:10.1016/S0140-6736(15)60454-8 (2015).

4 Cohen, J. & Normile, D. New SARS-like virus in China triggers alarm. *Science* **367**, 234-235, doi:10.1126/science.367.6475.234 (2020).

5 Zhu, N. *et al.* A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*, doi:10.1056/NEJMoa2001017 (2020).

6 Li, Q. *et al.* Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus-Infected Pneumonia. *N Engl J Med*, doi:10.1056/NEJMoa2001316 (2020).

7 Chen, Y., Liu, Q. & Guo, D. Coronaviruses: genome structure, replication, and pathogenesis. *J Med Virol*, doi:10.1002/jmv.25681 (2020).

8 Zhang, N. *et al.* Recent advances in the detection of respiratory virus infection in humans. *J Med Virol*, doi:10.1002/jmv.25674 (2020).

9 Chan, J. F. *et al.* Genomic characterization of the 2019 novel human-pathogenic coronavirus isolated from a patient with atypical pneumonia after visiting Wuhan. *Emerg Microbes Infect* **9**, 221-236, doi:10.1080/22221751.2020.1719902 (2020).

10 Guillin, O. M., Vindry, C., Ohlmann, T. & Chavatte, L. Selenium, Selenoproteins and Viral Infection. *Nutrients* **11**, doi:10.3390/nu11092101 (2019).

11 Kantoch, M., Litwinska, B., Szkoda, M. & Siennicka, J. [Importance of vitamin A deficiency in pathology and immunology of viral infections]. *Rocz Panstw Zakl Hig* **53**, 385-392 (2002).

12 Semba, R. D. Vitamin A and immunity to viral, bacterial and protozoan infections. *Proc Nutr Soc* **58**, 719-727, doi:10.1017/s0029665199000944 (1999).

13 Villamor, E. *et al.* Vitamin A supplements ameliorate the adverse effect of HIV-1, malaria, and diarrheal infections on child growth. *Pediatrics* **109**, E6, doi:10.1542/peds.109.1.e6 (2002).

14 Jee, J. *et al.* Effects of dietary vitamin A content on antibody responses of feedlot calves inoculated intramuscularly with an inactivated bovine

coronavirus vaccine. *Am J Vet Res* **74**, 1353-1362, doi:10.2460/ajvr.74.10.1353 (2013).

15 West, C. E., Sijtsma, S. R., Kouwenhoven, B., Rombout, J. H. & van der Zijpp, A. J. Epithelia-damaging virus infections affect vitamin A status in chickens. *J Nutr* **122**, 333-339, doi:10.1093/jn/122.2.333 (1992).

16 Trottier, C., Colombo, M., Mann, K. K., Miller, W. H., Jr. & Ward, B. J. Retinoids inhibit measles virus through a type I IFN-dependent bystander effect. *FASEB J* **23**, 3203-3212, doi:10.1096/fj.09-129288 (2009).

17 Powers, H. J. Riboflavin (vitamin B-2) and health. *Am J Clin Nutr* **77**, 1352-1360, doi:10.1093/ajcn/77.6.1352 (2003).

18 Keil, S. D., Bowen, R. & Marschner, S. Inactivation of Middle East respiratory syndrome coronavirus (MERS-CoV) in plasma products using a riboflavin-based and ultraviolet light-based photochemical treatment. *Transfusion* **56**, 2948-2952, doi:10.1111/trf.13860 (2016).

19 Kyme, P. *et al.* C/EBPepsilon mediates nicotinamide-enhanced clearance of Staphylococcus aureus in mice. *J Clin Invest* **122**, 3316-3329, doi:10.1172/JCI62070 (2012).

20 Jones, H. D. *et al.* Nicotinamide exacerbates hypoxemia in ventilator-induced lung injury independent of neutrophil infiltration. *PLoS One* **10**, e0123460, doi:10.1371/journal.pone.0123460 (2015).

21 Hemila, H. Vitamin C and SARS coronavirus. *J. Antimicrob. Chemother.* **52**, 1049-1050, doi:10.1093/jac/dkh002 (2003).

22 Atherton, J. G., Kratzing, C. C. & Fisher, A. The effect of ascorbic acid on infection chick-embryo ciliated tracheal organ cultures by coronavirus. *Arch Virol* **56**, 195-199, doi:10.1007/bf01317848 (1978).

23 Field, C. J., Johnson, I. R. & Schley, P. D. Nutrients and their role in host resistance to infection. *J Leukoc Biol* **71**, 16-32 (2002).

24 Hemila, H. Vitamin C intake and susceptibility to pneumonia. *Pediatr Infect Dis J* **16**, 836-837, doi:10.1097/00006454-199709000-00003 (1997).

25 Tangpricha, V., Pearce, E. N., Chen, T. C. & Holick, M. F. Vitamin D insufficiency among free-living healthy young adults. *Am J Med* **112**, 659-662, doi:10.1016/s0002-9343(02)01091-4 (2002).

26 Holick, M. F. Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. *Am J Clin Nutr* **80**, 1678S-1688S, doi:10.1093/ajcn/80.6.1678S (2004).

27 Nonnecke, B. J. *et al.* Acute phase response elicited by experimental bovine diarrhea virus (BVDV) infection is associated with decreased vitamin D and E status of vitamin-replete preruminant calves. *J Dairy Sci* **97**, 5566-5579, doi:10.3168/jds.2014-8293 (2014).

28 Galmes, S., Serra, F. & Palou, A. Vitamin E Metabolic Effects and Genetic Variants: A Challenge for Precision Nutrition in Obesity and Associated Disturbances. *Nutrients* **10**, doi:10.3390/nu10121919 (2018).

29 Beck, M. A. *et al.* Vitamin E deficiency intensifies the myocardial injury of coxsackievirus B3 infection of mice. *J Nutr* **124**, 345-358, doi:10.1093/jn/124.3.345 (1994).

30 Beck, M. A. Increased virulence of coxsackievirus B3 in mice due to vitamin E or selenium deficiency. *J Nutr* **127**, 966S-970S, doi:10.1093/jn/127.5.966S (1997).

31 Cai, C. *et al.* Macrophage-Derived Extracellular Vesicles Induce Long-Lasting Immunity Against Hepatitis C Virus Which Is Blunted by Polyunsaturated Fatty Acids. *Front Immunol* **9**, 723, doi:10.3389/fimmu.2018.00723 (2018).

32 Begin, M. E., Manku, M. S. & Horrobin, D. F. Plasma fatty acid levels in patients with acquired immune deficiency syndrome and in controls. *Prostaglandins Leukot Essent Fatty Acids* **37**, 135-137, doi:10.1016/0952-3278(89)90110-5 (1989).

33 Morita, M. *et al.* The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. *Cell* **153**, 112-125, doi:10.1016/j.cell.2013.02.027 (2013).

34 Leu, G. Z., Lin, T. Y. & Hsu, J. T. Anti-HCV activities of selective polyunsaturated fatty acids. *Biochem Biophys Res Commun* **318**, 275-280, doi:10.1016/j.bbrc.2004.04.019 (2004).

35 Rayman, M. P. Selenium and human health. *Lancet* **379**, 1256-1268, doi:10.1016/S0140-6736(11)61452-9 (2012).

36 Beck, M. A. & Matthews, C. C. Micronutrients and host resistance to viral infection. *Proc Nutr Soc* **59**, 581-585, doi:10.1017/s0029665100000823 (2000).

37 Harthill, M. Review: micronutrient selenium deficiency influences evolution of some viral infectious diseases. *Biol Trace Elem Res* **143**, 1325-1336, doi:10.1007/s12011-011-8977-1 (2011).

38 Beck, M. A. *et al.* Selenium deficiency increases the pathology of an influenza virus infection. *FASEB J* **15**, 1481-1483 (2001).

39 Beck, M. A., Shi, Q., Morris, V. C. & Levander, O. A. Rapid genomic evolution of a non-virulent coxsackievirus B3 in selenium-deficient mice results in selection of identical virulent isolates. *Nat Med* **1**, 433-436, doi:10.1038/nm0595-433 (1995).

40 Ma, X., Bi, S., Wang, Y., Chi, X. & Hu, S. Combined adjuvant effect of ginseng stem-leaf saponins and selenium on immune responses to a live bivalent vaccine of Newcastle disease virus and infectious bronchitis virus in chickens. *Poult Sci* **98**, 3548-3556, doi:10.3382/ps/pez207 (2019).

41 Maares, M. & Haase, H. Zinc and immunity: An essential interrelation. *Arch Biochem Biophys* **611**, 58-65, doi:10.1016/j.abb.2016.03.022 (2016).

42 Tuerk, M. J. & Fazel, N. Zinc deficiency. *Curr Opin Gastroenterol* **25**, 136-143, doi:10.1097/MOG.0b013e328321b395 (2009).

43 Awotiwon, A. A., Oduwole, O., Sinha, A. & Okwundu, C. I. Zinc supplementation for the treatment of measles in children. *Cochrane Database Syst Rev* **6**, CD011177, doi:10.1002/14651858.CD011177.pub3 (2017).

44 te Velthuis, A. J. *et al.* Zn(2+) inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog* **6**, e1001176, doi:10.1371/journal.ppat.1001176 (2010).

45 Wessling-Resnick, M. Crossing the Iron Gate: Why and How Transferrin Receptors Mediate Viral Entry. *Annu Rev Nutr* **38**, 431-458, doi:10.1146/annurev-nutr-082117-051749 (2018).

46 Jayaweera, J., Reyes, M. & Joseph, A. Childhood iron deficiency anemia leads to recurrent respiratory tract infections and gastroenteritis. *Sci Rep* **9**, 12637, doi:10.1038/s41598-019-49122-z (2019).

47 Pei, J., Sekellick, M. J., Marcus, P. I., Choi, I. S. & Collisson, E. W. Chicken interferon type I inhibits infectious bronchitis virus replication and associated respiratory illness. *J Interferon Cytokine Res* **21**, 1071-1077, doi:10.1089/107999001317205204 (2001).

48 Turner, R. B., Felton, A., Kosak, K., Kelsey, D. K. & Meschievitz, C. K. Prevention of experimental coronavirus colds with intranasal alpha-2b interferon. *J Infect Dis* **154**, 443-447, doi:10.1093/infdis/154.3.443 (1986).

49 Morgenstern, B., Michaelis, M., Baer, P. C., Doerr, H. W. & Cinatl, J., Jr. Ribavirin and interferon-beta synergistically inhibit SARS-associated coronavirus replication in animal and human cell lines. *Biochem Biophys Res Commun* **326**, 905-908, doi:10.1016/j.bbrc.2004.11.128 (2005).

50 Chen, F. *et al.* In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. *J Clin Virol* **31**, 69-75, doi:10.1016/j.jcv.2004.03.003 (2004).

51 Kuri, T. *et al.* Interferon priming enables cells to partially overturn the SARS coronavirus-induced block in innate immune activation. *J Gen Virol* **90**, 2686-2694, doi:10.1099/vir.0.013599-0 (2009).

52 Tan, E. L. *et al.* Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs. *Emerg Infect Dis* **10**, 581-586, doi:10.3201/eid1004.030458 (2004).

53 Manns, M. P. *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a

randomised trial. *Lancet* **358**, 958-965, doi:10.1016/s0140-6736(01)06102-5 (2001).

54 Haagmans, B. L. *et al.* Pegylated interferon-alpha protects type 1 pneumocytes against SARS coronavirus infection in macaques. *Nat Med* **10**, 290-293, doi:10.1038/nm1001 (2004).

55 Bijlenga, G. Proposal for vaccination against SARS coronavirus using avian infectious bronchitis virus strain H from The Netherlands. *J Infect* **51**, 263-265, doi:10.1016/j.jinf.2005.04.010 (2005).

56 Loutfy, M. R. *et al.* Interferon alfacon-1 plus corticosteroids in severe acute respiratory syndrome: a preliminary study. *JAMA* **290**, 3222-3228, doi:10.1001/jama.290.24.3222 (2003).

57 Mustafa, S., Balkhy, H. & Gabere, M. N. Current treatment options and the role of peptides as potential therapeutic components for Middle East Respiratory Syndrome (MERS): A review. *J Infect Public Health* **11**, 9-17, doi:10.1016/j.jiph.2017.08.009 (2018).

58 Bussel, J. B. & Szatrowski, T. P. Uses of intravenous gammaglobulin in immune hematologic disease. *Immunol Invest* **24**, 451-456, doi:10.3109/08820139509062794 (1995).

59 Lew, T. W. *et al.* Acute respiratory distress syndrome in critically ill patients with severe acute respiratory syndrome. *JAMA* **290**, 374-380, doi:10.1001/jama.290.3.374 (2003).

60 Dalakas, M. C. & Clark, W. M. Strokes, thromboembolic events, and IVIg: rare incidents blemish an excellent safety record. *Neurology* **60**, 1736-1737, doi:10.1212/01.wnl.0000074394.15882.83 (2003).

61 Matteucci, C. *et al.* Thymosin alpha 1 and HIV-1: recent advances and future perspectives. *Future Microbiol* **12**, 141-155, doi:10.2217/fmb-2016-0125 (2017).

62 Costantini, C. *et al.* A Reappraisal of Thymosin Alpha1 in Cancer Therapy. *Front Oncol* **9**, 873, doi:10.3389/fonc.2019.00873 (2019).

63 Pica, F. *et al.* Serum thymosin alpha 1 levels in normal and pathological conditions. *Expert Opin Biol Ther* **18**, 13-21, doi:10.1080/14712598.2018.1474197 (2018).

64 Baumann, C. A., Badamchian, M. & Goldstein, A. L. Thymosin alpha 1 antagonizes dexamethasone and CD3-induced apoptosis of CD4+ CD8+ thymocytes through the activation of cAMP and protein kinase C dependent second messenger pathways. *Mech Ageing Dev* **94**, 85-101, doi:10.1016/s0047-6374(96)01860-x (1997).

65 Gao, Z. C. *et al.* [Clinical investigation of outbreak of nosocomial severe acute respiratory syndrome]. *Zhongguo Wei Zhong Bing Ji Jiu Yi Xue* **15**, 332-335 (2003).

66 Kumar, V., Jung, Y. S. & Liang, P. H. Anti-SARS coronavirus agents: a patent review (2008 - present). *Expert Opin Ther Pat* **23**, 1337-1348, doi:10.1517/13543776.2013.823159 (2013).

67 Duchateau, J., Servais, G., Vreyens, R., Delespesse, G. & Bolla, K. Modulation of immune response in aged humans through different administration modes of thymopentin. *Surv Immunol Res* **4 Suppl 1**, 94-101 (1985).

68 Duchateau, J., Delespesse, G. & Bolla, K. Phase variation in the modulation of the human immune response. *Immunology today* **4**, 213-214, doi:10.1016/0167-5699(83)90028-2 (1983).

69 Zaruba, K., Rastorfer, M., Grob, P. J., Joller-Jemelka, H. & Bolla, K. Thymopentin as adjuvant in non-responders or hyporesponders to hepatitis B vaccination. *Lancet* **2**, 1245, doi:10.1016/s0140-6736(83)91284-9 (1983).

70 Renoux, G. The general immunopharmacology of levamisole. *Drugs* **20**, 89-99, doi:10.2165/00003495-198020020-00001 (1980).

71 Joffe, M. I., Sukha, N. R. & Rabson, A. R. Lymphocyte subsets in measles. Depressed helper/inducer subpopulation reversed by in vitro treatment with levamisole and ascorbic acid. *J Clin Invest* **72**, 971-980, doi:10.1172/JCI111069 (1983).

72 Ziaei, M., Ziaei, F. & Manzouri, B. Systemic cyclosporine and corneal transplantation. *Int Ophthalmol* **36**, 139-146, doi:10.1007/s10792-015-0137-8 (2016).

73 Luo, C. *et al.* Nucleocapsid protein of SARS coronavirus tightly binds to human cyclophilin A. *Biochem Biophys Res Commun* **321**, 557-565, doi:10.1016/j.bbrc.2004.07.003 (2004).

74 Dawar, F. U., Tu, J., Khattak, M. N., Mei, J. & Lin, L. Cyclophilin A: A Key Factor in Virus Replication and Potential Target for Anti-viral Therapy. *Curr Issues Mol Biol* **21**, 1-20, doi:10.21775/cimb.021.001 (2017).

75 Pfefferle, S. *et al.* The SARS-coronavirus-host interactome: identification of cyclophilins as target for pan-coronavirus inhibitors. *PLoS Pathog* **7**, e1002331, doi:10.1371/journal.ppat.1002331 (2011).

76 Cinatl, J. *et al.* Glycyrrhizin, an active component of liquorice roots, and replication of SARS-associated coronavirus. *Lancet* **361**, 2045-2046, doi:10.1016/s0140-6736(03)13615-x (2003).

77 Park, J. Y. *et al.* Diarylheptanoids from Alnus japonica inhibit papain-like protease of severe acute respiratory syndrome coronavirus. *Biol Pharm Bull* **35**, 2036-2042, doi:10.1248/bpb.b12-00623 (2012).

78 Chen, L. *et al.* Cinanserin is an inhibitor of the 3C-like proteinase of severe acute respiratory syndrome coronavirus and strongly reduces virus replication

in vitro. *J Virol* **79**, 7095-7103, doi:10.1128/JVI.79.11.7095-7103.2005 (2005).

79 Panche, A. N., Diwan, A. D. & Chandra, S. R. Flavonoids: an overview. *J Nutr Sci* **5**, e47, doi:10.1017/jns.2016.41 (2016).

80 Shimizu, J. F. *et al.* Flavonoids from Pterogyne nitens Inhibit Hepatitis C Virus Entry. *Sci Rep* **7**, 16127, doi:10.1038/s41598-017-16336-y (2017).

81 Jo, S., Kim, S., Shin, D. H. & Kim, M. S. Inhibition of SARS-CoV 3CL protease by flavonoids. *J Enzyme Inhib Med Chem* **35**, 145-151, doi:10.1080/14756366.2019.1690480 (2020).

82 Jo, S., Kim, H., Kim, S., Shin, D. H. & Kim, M. S. Characteristics of flavonoids as potent MERS-CoV 3C-like protease inhibitors. *Chem Biol Drug Des* **94**, 2023-2030, doi:10.1111/cbdd.13604 (2019).

83 Ryu, Y. B. *et al.* Biflavonoids from Torreya nucifera displaying SARS-CoV 3CL(pro) inhibition. *Bioorg Med Chem* **18**, 7940-7947, doi:10.1016/j.bmc.2010.09.035 (2010).

84 Warner, F. J., Smith, A. I., Hooper, N. M. & Turner, A. J. Angiotensin-converting enzyme-2: a molecular and cellular perspective. *Cell Mol Life Sci* **61**, 2704-2713, doi:10.1007/s00018-004-4240-7 (2004).

85 Li, W. *et al.* Angiotensin-converting enzyme 2 is a functional receptor for the SARS coronavirus. *Nature* **426**, 450-454, doi:10.1038/nature02145 (2003).

86 Dimitrov, D. S. The secret life of ACE2 as a receptor for the SARS virus. *Cell* **115**, 652-653, doi:10.1016/s0092-8674(03)00976-0 (2003).

87 Simmons, G. *et al.* Characterization of severe acute respiratory syndrome-associated coronavirus (SARS-CoV) spike glycoprotein-mediated viral entry. *Proc Natl Acad Sci U S A* **101**, 4240-4245, doi:10.1073/pnas.0306446101 (2004).

88 Yeung, K. S., Yamanaka, G. A. & Meanwell, N. A. Severe acute respiratory syndrome coronavirus entry into host cells: Opportunities for therapeutic intervention. *Med Res Rev* **26**, 414-433, doi:10.1002/med.20055 (2006).

89 Sui, J. *et al.* Potent neutralization of severe acute respiratory syndrome (SARS) coronavirus by a human mAb to S1 protein that blocks receptor association. *Proc Natl Acad Sci U S A* **101**, 2536-2541, doi:10.1073/pnas.0307140101 (2004).

90 Savarino, A., Boelaert, J. R., Cassone, A., Majori, G. & Cauda, R. Effects of chloroquine on viral infections: an old drug against today's diseases? *Lancet Infect Dis* **3**, 722-727, doi:10.1016/s1473-3099(03)00806-5 (2003).

91 Vincent, M. J. *et al.* Chloroquine is a potent inhibitor of SARS coronavirus infection and spread. *Virol J* **2**, 69, doi:10.1186/1743-422X-2-69 (2005).

92 Alves, D. S., Perez-Fons, L., Estepa, A. & Micol, V. Membrane-related effects underlying the biological activity of the anthraquinones emodin and barbaloin. *Biochem Pharmacol* **68**, 549-561, doi:10.1016/j.bcp.2004.04.012 (2004).

93 Ho, T. Y., Wu, S. L., Chen, J. C., Li, C. C. & Hsiang, C. Y. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. *Antiviral Res* **74**, 92-101, doi:10.1016/j.antiviral.2006.04.014 (2007).

94 Zhang, X. W. & Yap, Y. L. Old drugs as lead compounds for a new disease? Binding analysis of SARS coronavirus main proteinase with HIV, psychotic and parasite drugs. *Bioorg Med Chem* **12**, 2517-2521, doi:10.1016/j.bmc.2004.03.035 (2004).

95 Trampczynska, A., Bottcher, C. & Clemens, S. The transition metal chelator nicotianamine is synthesized by filamentous fungi. *FEBS Lett* **580**, 3173-3178, doi:10.1016/j.febslet.2006.04.073 (2006).

96 Takahashi, S., Yoshiya, T., Yoshizawa-Kumagaye, K. & Sugiyama, T. Nicotianamine is a novel angiotensin-converting enzyme 2 inhibitor in soybean. *Biomed Res* **36**, 219-224, doi:10.2220/biomedres.36.219 (2015).

97 Wenzel, R. P. & Edmond, M. B. Managing SARS amidst uncertainty. *N Engl J Med* **348**, 1947-1948, doi:10.1056/NEJMp030072 (2003).

98 Cyranoski, D. Critics slam treatment for SARS as ineffective and perhaps dangerous. *Nature* **423**, 4, doi:10.1038/423004a (2003).

99 Booth, C. M. *et al.* Clinical features and short-term outcomes of 144 patients with SARS in the greater Toronto area. *JAMA* **289**, 2801-2809, doi:10.1001/jama.289.21.JOC30885 (2003).

100 Tsang, K. & Zhong, N. S. SARS: pharmacotherapy. *Respirology* **8 Suppl**, S25-30, doi:10.1046/j.1440-1843.2003.00525.x (2003).

101 Sheahan, T. P. *et al.* Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV. *Nat Commun* **11**, 222, doi:10.1038/s41467-019-13940-6 (2020).

102 Chu, C. M. *et al.* Role of lopinavir/ritonavir in the treatment of SARS: initial virological and clinical findings. *Thorax* **59**, 252-256, doi:10.1136/thorax.2003.012658 (2004).

103 Kim, U. J., Won, E. J., Kee, S. J., Jung, S. I. & Jang, H. C. Combination therapy with lopinavir/ritonavir, ribavirin and interferon-alpha for Middle East respiratory syndrome. *Antivir Ther* **21**, 455-459, doi:10.3851/IMP3002 (2016).

104 Agostini, M. L. *et al.* Coronavirus Susceptibility to the Antiviral Remdesivir (GS-5734) Is Mediated by the Viral Polymerase and the Proofreading Exoribonuclease. *mBio* **9**, doi:10.1128/mBio.00221-18 (2018).

105 Holshue, M. L. *et al.* First Case of 2019 Novel Coronavirus in the United States. *New England Journal of Medicine*, doi:10.1056/NEJMoa2001191 (2020).

106 Jarvis, B. & Faulds, D. Nelfinavir. A review of its therapeutic efficacy in HIV infection. *Drugs* **56**, 147-167, doi:10.2165/00003495-199856010-00013 (1998).

107 Yamamoto, N. *et al.* HIV protease inhibitor nelfinavir inhibits replication of SARS-associated coronavirus. *Biochem Biophys Res Commun* **318**, 719-725, doi:10.1016/j.bbrc.2004.04.083 (2004).

108 Blaising, J., Polyak, S. J. & Pecheur, E. I. Arbidol as a broad-spectrum antiviral: an update. *Antiviral Res* **107**, 84-94, doi:10.1016/j.antiviral.2014.04.006 (2014).

109 Boriskin, Y. S., Leneva, I. A., Pecheur, E. I. & Polyak, S. J. Arbidol: a broad-spectrum antiviral compound that blocks viral fusion. *Curr Med Chem* **15**, 997-1005, doi:10.2174/092986708784049658 (2008).

110 Pecheur, E. I. *et al.* The Synthetic Antiviral Drug Arbidol Inhibits Globally Prevalent Pathogenic Viruses. *J Virol* **90**, 3086-3092, doi:10.1128/JVI.02077-15 (2016).

111 Khamitov, R. A. *et al.* [Antiviral activity of arbidol and its derivatives against the pathogen of severe acute respiratory syndrome in the cell cultures]. *Vopr Virusol* **53**, 9-13 (2008).

112 Robbins, R. A. & Grisham, M. B. Nitric oxide. *Int J Biochem Cell Biol* **29**, 857-860, doi:10.1016/s1357-2725(96)00167-7 (1997).

113 Barnes, P. J. Nitric oxide and airway disease. *Ann Med* **27**, 389-393, doi:10.3109/07853899509002592 (1995).

114 Rossaint, R. *et al.* Efficacy of inhaled nitric oxide in patients with severe ARDS. *Chest* **107**, 1107-1115, doi:10.1378/chest.107.4.1107 (1995).

115 Hui, D. S. An overview on severe acute respiratory syndrome (SARS). *Monaldi Arch Chest Dis* **63**, 149-157, doi:10.4081/monaldi.2005.632 (2005).

116 Akerstrom, S. *et al.* Nitric oxide inhibits the replication cycle of severe acute respiratory syndrome coronavirus. *J Virol* **79**, 1966-1969, doi:10.1128/JVI.79.3.1966-1969.2005 (2005).

117 Sachse, G. & Willms, B. Efficacy of thioctic acid in the therapy of peripheral diabetic neuropathy. *Horm Metab Res Suppl* **9**, 105-107 (1980).

118 Tibullo, D. *et al.* Biochemical and clinical relevance of alpha lipoic acid: antioxidant and anti-inflammatory activity, molecular pathways and therapeutic potential. *Inflamm Res* **66**, 947-959, doi:10.1007/s00011-017-1079-6 (2017).

119 El-Senousey, H. K. *et al.* Effects of dietary vitamin C, vitamin E, and alpha-lipoic acid supplementation on the antioxidant defense system and immune-related gene expression in broilers exposed to oxidative stress by dexamethasone. *Poult Sci* **97**, 30-38, doi:10.3382/ps/pex298 (2018).

120 Wu, Y. H. *et al.* Glucose-6-phosphate dehydrogenase deficiency enhances human coronavirus 229E infection. *J Infect Dis* **197**, 812-816, doi:10.1086/528377 (2008).

121 Baur, A. *et al.* Alpha-lipoic acid is an effective inhibitor of human immuno-deficiency virus (HIV-1) replication. *Klin Wochenschr* **69**, 722-724, doi:10.1007/bf01649442 (1991).

122 Marriott, I. & Huet-Hudson, Y. M. Sexual dimorphism in innate immune responses to infectious organisms. *Immunol Res* **34**, 177-192, doi:10.1385/IR:34:3:177 (2006).

123 Karlberg, J., Chong, D. S. & Lai, W. Y. Do men have a higher case fatality rate of severe acute respiratory syndrome than women do? *Am J Epidemiol* **159**, 229-231, doi:10.1093/aje/kwh056 (2004).

124 Leong, H. N. *et al.* SARS in Singapore--predictors of disease severity. *Ann Acad Med Singapore* **35**, 326-331 (2006).

125 Alghamdi, I. G. *et al.* The pattern of Middle East respiratory syndrome coronavirus in Saudi Arabia: a descriptive epidemiological analysis of data from the Saudi Ministry of Health. *Int J Gen Med* **7**, 417-423, doi:10.2147/IJGM.S67061 (2014).

126 Channappanavar, R. *et al.* Sex-Based Differences in Susceptibility to Severe Acute Respiratory Syndrome Coronavirus Infection. *J Immunol* **198**, 4046-4053, doi:10.4049/jimmunol.1601896 (2017).

127 Wei, L. *et al.* Endocrine cells of the adenohypophysis in severe acute respiratory syndrome (SARS). *Biochem Cell Biol* **88**, 723-730, doi:10.1139/O10-022 (2010).

128 Peretz, J., Pekosz, A., Lane, A. P. & Klein, S. L. Estrogenic compounds reduce influenza A virus replication in primary human nasal epithelial cells derived from female, but not male, donors. *Am J Physiol Lung Cell Mol Physiol* **310**, L415-425, doi:10.1152/ajplung.00398.2015 (2016).

129 Lin, S. C. *et al.* Effective inhibition of MERS-CoV infection by resveratrol. *BMC Infect Dis* **17**, 144, doi:10.1186/s12879-017-2253-8 (2017).

130 Li, Q. *et al.* Virucidal activity of a scorpion venom peptide variant mucroporin-M1 against measles, SARS-CoV and influenza H5N1 viruses. *Peptides* **32**, 1518-1525, doi:10.1016/j.peptides.2011.05.015 (2011).

131 Cavanagh, D. Severe acute respiratory syndrome vaccine development: experiences of vaccination against avian infectious bronchitis coronavirus. *Avian Pathol* **32**, 567-582, doi:10.1080/0307945031000162119 8 (2003).

132 Escriou, N. *et al.* Protection from SARS coronavirus conferred by live measles vaccine expressing the spike glycoprotein. *Virology* **452-453**, 32-41, doi:10.1016/j.virol.2014.01.002 (2014).

133 Bodmer, B. S., Fiedler, A. H., Hanauer, J. R. H., Prufer, S. & Muhlebach, M. D. Live-attenuated bivalent measles virus-derived vaccines targeting Middle East respiratory syndrome coronavirus induce robust and multifunctional T cell responses against both viruses in an appropriate mouse model. *Virology* **521**, 99-107, doi:10.1016/j.virol.2018.05.028 (2018).

134 Frantz, P. N., Teeravechyan, S. & Tangy, F. Measles-derived vaccines to prevent emerging viral diseases. *Microbes Infect* **20**, 493-500, doi:10.1016/j.micinf.2018.01.005 (2018).

135 ter Meulen, J. *et al.* Human monoclonal antibody combination against SARS coronavirus: synergy and coverage of escape mutants. *PLoS Med* **3**, e237, doi:10.1371/journal.pmed.0030237 (2006).

136 ter Meulen, J. *et al.* Human monoclonal antibody as prophylaxis for SARS coronavirus infection in ferrets. *Lancet* **363**, 2139-2141, doi:10.1016/S0140-6736(04)16506-9 (2004).

137 Marano, G. *et al.* Convalescent plasma: new evidence for an old therapeutic tool? *Blood Transfus* **14**, 152-157, doi:10.2450/2015.0131-15 (2016).

138 Arabi, Y. *et al.* Feasibility, safety, clinical, and laboratory effects of convalescent plasma therapy for patients with Middle East respiratory syndrome coronavirus infection: a study protocol. *Springerplus* **4**, 709, doi:10.1186/s40064-015-1490-9 (2015).

139 Cheng, Y. *et al.* Use of convalescent plasma therapy in SARS patients in Hong Kong. *Eur J Clin Microbiol Infect Dis* **24**, 44-46, doi:10.1007/s10096-004-1271-9 (2005).

140 Soo, Y. O. *et al.* Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. *Clin Microbiol Infect* **10**, 676-678, doi:10.1111/j.1469-0691.2004.00956.x (2004).

Table 1. General Supportive Treatments	
Options	**Virus targeted and functions related**
1.1. Nutritional interventions	
1.1.1. Vitamin A	Measles virus, human immunodeficiency virus, avian coronavirus
1.1.2. B vitamins	MERS-CoV; ventilator-induced lung injury
1.1.3. Vitamin C	Avian coronavirus; lower respiratory tract infections
1.1.4. Vitamin D	Bovine coronavirus
1.1.5. Vitamin E	Coxsackievirus, bovine coronavirus
1.1.6. Omega-3 polyunsaturated fatty acids (PUFA)	Influenza virus, human immunodeficiency virus
1.1.7. Selenium	Influenza virus, avian coronavirus; viral mutations
1.1.8. Zinc	Measles virus, SARS-CoV
1.1.9. Iron	Viral mutations
1.2. Immunoenhancers	
1.2.1. Interferons	SARS-CoV, MERS-CoV
1.2.2. Intravenous gammaglobulin	SARS-CoV
1.2.3. Thymosin alpha-1	Increase resistance to glucocorticoid induced death of thymocyte

1.2.4. Thymopentin	Restore antibody production
1.2.5. Levamisole	Immunostimulant agent or immunosuppressive agent
1.2.6. Cyclosporine A	SARS-CoV, avian infectious bronchitis virus
1.2.7. Chinese medicine	SARS-CoV, avian infectious bronchitis virus

Table 2. Coronavirus-Specific Treatments
2.1 Coronavirus protease inhibitors
2.1.1 Chymotrypsin-like (3C-like) inhibitors
2.1.1.1. Cinanserin
2.1.1.2. Flavonoids
2.1.2 Papain-like protease (PLP) inhibitors
2.1.2.1 Diarylheptanoids
2.2. Spike (S) protein-angiotensin-converting enzyme 2 (ACE2) blockers or S protein inhibitors
2.2.1. Human monoclonal antibody (mAb)
2.2.2. Chloroquine

2.2.3. Emodin
2.2.4. Promazine
2.2.5. Nicotianamine

Table 3. Antiviral Treatments and Other Compounds
3. Antiviral treatments
3.1. Ribavirin
3.2. Lopinavir (LPV)/ritonavir (RTV) (Kaletra)
3.3. Remdesivir
3.4. Nelfinavir
3.5 Arbidol
3.6. Nitric oxide
4. Other compounds
4.1. Alpha-lipoic acid
4.2. Estradiol and phytoestrogen
4.3. Mucroporin-M1