

# Coronavirus (COVID-19): preventive measures and potential interventions

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**Abstract:** *Novel viral eruption originating in Wuhan city (Hubei, China) has spread internationally reaching all continents in an unexpectedly very short time, posing a great burden on global transportation, health, and economy. This mini-review article aimed at focusing on the available preventive measures and therapeutic interventions taking into account that there is a limited scientific resource of information and lack of specific established vaccination yet We searched Iraq Virtual Science Library (IVSL), PubMed, Cochrane Library MEDLINE, EMBASE, and the Chinese Biomedical Database (CBM), for the 3 target words 'COVID-19, coronavirus, 2019-CoV' and we included only articles in English in the study. The outcome of this study is important nationally and globally providing information about general measures and possible interventions relevant to public and health professionals. This review concludes that the nutritional status of the patient together with proper diagnosis should be the priority of the management plan provided that the loci is within the outbreak area and available flu vaccines should be used by unaffected health-care providers and children.*

**Keywords:** *coronavirus, COVID-19, outbreak, preventive measures.*

## 1. INTRODUCTION:

Coronavirus (COVID-19) is a pleomorphic RNA virus that belongs to Coronavirinae c subfamily, more specifically from beta-coronavirus genus<sup>1</sup>(Figure 1). Coronaviruses are primarily zoonotic pathogens that infect animals including birds and mammals. However, it has been reported that several types of coronaviruses can cause respiratory, gastrointestinal, hepatic, renal and even neurologic infections in humans with a range of clinical manifestations from no symptoms to sever symptoms mandates admission to the intensive care unit. CoV OC43 and CoV 229E are examples of the coronaviruses that cause infections in people with competent immune system, while the types that are associated with the outbreaks of severe acute respiratory syndrome (SARS-CoV) in 2002 and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) in 2012 are examples of highly pathologic types of coronaviruses<sup>2</sup>. Recently an outbreak of a new flu-like coronavirus occurred in Wuhan state of Hubei province in China<sup>3,4</sup>. The evidence suggested a high human-to-human transmissibility rate through droplets<sup>5</sup>. Genomic analysis revealed that COVID-19 is a single stranded RNA and confirmed that it belongs to beta-coronavirus cluster<sup>6</sup>.

Hitherto there is few vaccine incompletely approved for protection against COVID-19 around the world and also there is no specific medicine for treatment or eradication of this pandemic viral infection. This mini-review article is aimed to enhance the understanding of the ongoing COVID-19 outbreak and address the currently available strategies and medical interventions to limit the spread of the virus and decrease its severity by listing the general preventive measures and interventions followed during MERS and SARS dissemination.

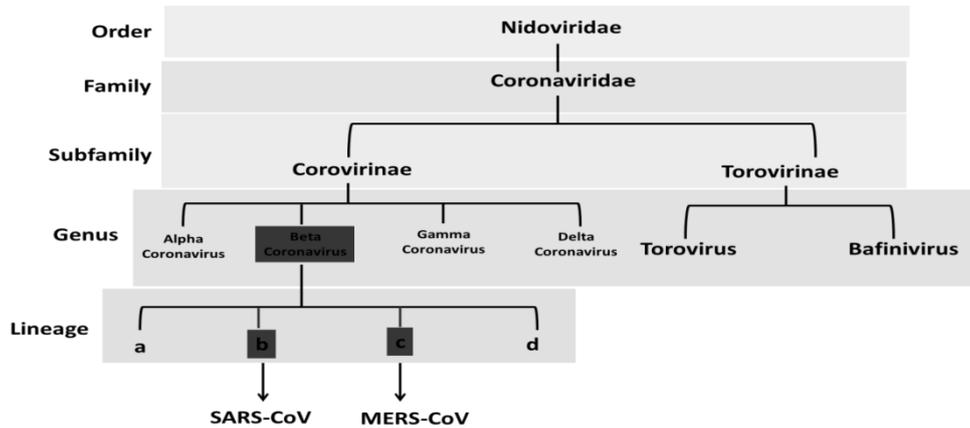


Figure 1. New classification scheme for members of *Coronaviridae*.

## 2. POTENTIAL INTERVENTIONS

The available medical remedies for treatment of COVID-19 are based on the best of our knowledge and available information on the previous experience dealing with the latest outbreaks of the viruses such as SARS and MERS that belong to the same beta coronavirus subgroup.

## 3. IMPROVEMENT OF NUTRITIONAL STATUS

### 3.1. Vitamins

Generally vitamins are helpful in improving the immune system as it is vital for maintaining the leukocyte function. Vitamin C is also important for iron absorption, and maintaining adequate iron homeostasis, which would boost the immune system and reduce the vulnerability to microbial infections<sup>7,8</sup>. Vitamin A could be used to improve the immune system against the novel coronavirus. It has been used formerly for patients with different viral infection (e.g. measles and HIV) with encouraging outcomes<sup>9</sup>. Vitamin C has been used in a clinical trial as add-on-therapy for patients with pneumonia and the outcome showed improvement in overall results compared to control group. Moreover, experimental application of vitamin C on tracheal culture of chick embryo elicited a dramatic response in avian coronavirus infection<sup>10</sup>. No current study confirmed that vitamin D supplements would reduce the risk of coronavirus infection, maintaining blood level of vitamin D between 20 to 30 ng/mL by getting adequate sun exposure (at least three times a week for about 30 minutes), consuming vitamin D-fortified products (such as most types of milk, certain other dairy foods), or taking a vitamin D supplement is a good, safe, preventative measure for protecting against a variety of respiratory infections. To maintain healthy levels, only 400 to 800 IU (15

to 20 mcg) is required daily, Yet, to boost low levels, higher doses of about 2,000 IU daily should be considered. However, very high doses, (such as 100,000 IU taken monthly) may not be quite useful and could even increase the risk of respiratory infections in some people<sup>11,12</sup>. It has also been reported that bovine coronavirus is often associated with vitamin D deficiency and supplementation of it reduced the symptoms and improved the general clinical features<sup>13</sup>. The virulence behavior of coxsackievirus B3 has been linked to a great extent to vitamin E deficiency<sup>14</sup>. B vitamin supplementation has been greatly linked to improvement of MERS coronavirus indicated by reduced plasma titer test results<sup>15</sup>. These outcomes have greatly improved various types of respiratory diseases and could find application in novel COVID-19.

### **3.2. Minerals**

Minerals like calcium, magnesium, and zinc are vital to several bodily processes. Minerals play a key role in maintaining the activity of a large number of enzymes that are imperative for biological oxidation-reduction (redox) system<sup>16</sup>. Magnesium and zinc have been reported to boost immune system and may help to reduce inflammation. While inflammation is a normal immune response, long term or chronic inflammation could damage the human health and promote the development of many diseases like cancer and heart diseases<sup>17,18</sup>. Supplementation with magnesium has been shown to reduce markers of chronic inflammation, such as C-reactive protein (CRP) and interleukin 6 (IL-6)<sup>19</sup>. On the other hand, magnesium deficiency has been linked to chronic inflammation. Zinc plays a vital role in the development and physiological function of immune cells and thereby help to protect the body against microbial infection<sup>17,20,21</sup>. Selenium deficiency has been associated with virulence effect of respiratory infection with coxsackievirus and facilitates viral genetic mutation leading to more host virulence attack<sup>14</sup>. Zinc does have antiviral properties and was shown to have inhibitory activity on replication of SARS coronavirus<sup>22</sup>. Iron deficiency has been considered as an extra factor contributing to respiratory viral virulence effects<sup>23</sup>. These information encourage application of minerals in novel COVID-19 as a potential intervention alongside with other available remedies.

### **3.3. OMEGA3 (Polyunsaturated fatty acids)**

The long-chain polyunsaturated fatty acids derived from fish oils, particularly eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) have a myriad of biological effects. Epidemiological studies have shown the beneficial effects of dietary and supplementary omega-3 (n-3) fatty acids which may include effects on lipid profile<sup>24</sup>, platelet function<sup>25</sup>, endothelial and vascular integrity<sup>26</sup>, cardiac function, oxidative stress<sup>27</sup>, pro- and anti-inflammatory cytokines<sup>28</sup>, and most importantly immune function<sup>26</sup>. It has been documented that plasma levels of OMEGA3 is lower than the normal levels in patients with AIDS compared to healthy control subjects<sup>29</sup>. Another study reported that OMEGA3 have therapeutic effect in hepatitis C patients<sup>30</sup>. Therefore, these data could encourage the use of OMEGA3 in the management of COVID-19 patients.

## **4. Immune enhancer therapeutic agents**

### **4.1. Interferon (IFN)**

The replication of SARS coronavirus and hepatitis C virus has been inhibited by IFN<sup>31,32,33</sup>. Kuri *et al.* (2009) reported that IFN potentiates the host immune response to the viral infection and suggested that conditioning the host with small doses of IFN might be an option to protect against such viral infections<sup>34</sup>. Moreover, *in vitro* cell-cultured studies confirmed the effectiveness of priming infected cells with IFN before viral exposure; the result indicated protection of IFN-primed host cells from viral virulence attack compared to cells that were not exposed to IFN<sup>34,35</sup>. A well designed experimental study conducted on monkeys infected with SARS-coronavirus concluded that injection of monkeys with IFN for 3 days prior to the exposure to the viral infection would protect against viral virulence activities<sup>36</sup>.

### **4.2. Gamma globulin ( $\gamma$ -globulin)**

$\gamma$ -globulin is the safest and most effective immunomodulating agent and is being extensively used in SARS outbreak in pandemic areas<sup>37</sup>. However, the side effect of thromboembolism and pulmonary embolism should be considered<sup>38,39</sup>.

### **4.3. Thymosin alpha-1 (Thymosin- $\alpha$ 1)**

Thymosin- $\alpha$ 1 has been used in patients with SARS-coronavirus as an immune enhancer; boosting the immune response with this factor has reduced the spread of infection<sup>28</sup>. Thymosin- $\alpha$ 1 could also be used in glucocorticoid-induced thymocyte injury imparting protection of thymocyte; these findings are important for indication of thymosin in COVID-19 patients treated with methylprednisolone for controlling respiratory symptoms<sup>40</sup>.

### **4.4. Thymopentin**

The mode of action of this factor is based on enhancing antibody production by the host system<sup>41</sup> and it has been applied for treatment of hepatitis viral infection<sup>42</sup>.

### **4.5. Levamisole**

T-cell function has been promoted using levamisole and combined use with ascorbic acid demonstrated positive *in vitro* results in measles<sup>43</sup>. These results could be part of treatment of COVID-19.

## **5. Human monoclonal antibodies**

Recombinant human monoclonal antibodies against specific protein (involved in viral entry, fusion, and replication) could be utilized as an additional techniques to tackle the disease. This effect has been utilized in the treatment of SARS-outbreaks<sup>44</sup>.

## **6. Convalescent plasma**

Passive immunotherapy is based on using plasma from recovered or convalescent people who contain viral-specific antibodies against viral infection<sup>45</sup>. Convalescent plasma collected from MERS and SARS patients has clinically improved viral-infected patients<sup>46,47</sup>. This idea could be applied against COVID-19.

## 7. Specific antiviral therapy

The currently available antiviral agents have been shown to be effective against aggressive coronavirus outbreaks, some of them have been tried out to combat a panel of single-strand RNA viruses. Those include the related coronaviruses SARS and MERS, and hence COVID-19 would very likely be included in their antiviral spectrum.

### 1. Ribavirin (guanosine analogue)

Ribavirin has been effectively used against hepatitis C and SARS<sup>48</sup>. *In vitro* study on cell line culture revealed that the replication of SARS has been inhibited by a combination of ribavirin and interferon-beta [31].

### 2. Lopinavir (LPV)/ritonavir (RTV) protease inhibitor

A combination of LPV/RTV has been applied originally for HIV infection<sup>49</sup>. The combination has also shown efficacy in SARS eruption<sup>50</sup>. The efficacy against MERS has been enhanced by addition of ribavirin and interferon- $\alpha$  to the above combination<sup>51</sup>.

### 3. Remdesivir (RDV) nucleotide analogs

*In vivo* application of RDV has shown antiviral efficacy against SARS and zoonotic coronavirus<sup>52</sup>. A combination of RDV and IFN-beta has shown a great efficacy against MERS in both *in vitro* and *in vivo* studies<sup>53</sup>. RDV reduces pulmonary dysfunctionality and reduced viral-host opsonization and entry during active phase of respiratory viral infections<sup>53</sup>. RDV has been used for severe cases of the recent COVID-19 outbreak<sup>54</sup>.

### 4. Nelfinavir protease inhibitor

Nelfinavir has been shown to effectively inhibit SARS coronavirus infection. It selectively inhibits HIV protease, a post-translational processing protein<sup>55</sup>.

## 8. Herbal remedies

1. **Cinanserin** is a formerly used serotonin receptor that has shown good capability to inhibit chemotrypsin-like protease and might be a promising inhibitory agent for coronavirus replication<sup>56</sup>.

2. **Flavonoids** are herbal-derived antioxidant and antiviral products. Flavonoids have been shown to inhibit hepatitis C viral entry<sup>57</sup>.

3. **Emodin** is a herbal-derived product characterized by its mechanism of action by inhibition of the viral entry proteins (S protein and ACE protein)<sup>58, 59</sup>.

4. **Diarylheptanoids (DAH)** is a herbal extract and it has been reported that it inhibits the protease of SARS-CoV<sup>60</sup>. DAH share inhibitory activity on viral infection with emodin and flavonoids.

5. **Nicotianamine (NA)** is a plant-derived medicine and has been suggested to carry a potential to reduce COVID-19 infection<sup>61</sup>. The mode of action is being related to ACE inhibition<sup>62</sup>.

### 6. Chinese herbal medicine

- **Mucroporin:** a virucidal protein isolated from the venom of scorpion with efficacy against measles, SARS-CoV, and influenza H5N1 viruses<sup>63</sup>.

- **Glycyrrhizin:** liquorice-derived product with inhibitory effects on SARS replication<sup>64</sup>.

- **Baicalin:** herbal-isolated flavonoids reported by investigators as inhibitors of SARS virus, Newcastle disease virus and infectious bronchitis virus<sup>32</sup>.
- **Ginseng stem-leaf saponins:** encourage the immune response in viral infections of live chicken<sup>65</sup>.

## 9. Other compounds

### 1. Chloroquine

Chloroquine has been used for treatment of viral infection<sup>66</sup>. Its mode of action is based on the inhibition of spike protein of angiotensin-converting enzyme interfering with viral binding sites of SARS-coronavirus<sup>67</sup>.

### 2. Promazine

Promazine is originally a neuroleptic agent and it has shown efficacy in treatment of SARS through inhibiting viral replication<sup>59</sup>. Promazine has also shown to potentially inhibit the binding of S protein to ACE2<sup>68</sup>. These actions could be utilized to apply these agents for COVID-19 therapy.

### 3. Arbidol

The mode of action of arbidol is based on inhibition of viral fusion step through inhibiting viral entry and replication; its efficacy against hepatitis C and influenza A and B virus has been reported<sup>69,70</sup>. *In vitro* cell culture techniques indicate that arbidol shows inhibitory effect against replication of SARS virus<sup>71</sup>, an action which could be utilized against COVID-19 virus.

### 4. Angiotensin-converting enzyme (ACE)

ACE is an important receptor for coronavirus entry and facilitate viral-host membrane fusion<sup>72,73,74</sup>. ACE inhibition inhibits SARS-viral (coronavirus) infection and could be effective for recent COVID-19 infection outbreaks<sup>72,73,75</sup>.

### 5. Nitric oxide

Because nitric oxide inhibits viral RNA and protein synthesis and has been shown to be effective in inhibition of SARS viral replication<sup>69,70</sup>, therefore; nitric oxide inhalation by the patient could be helpful in suppression of COVID-19 viral replication.

### 6. Alphalipoic acids (ALA)

ALA is an important antioxidant and cellular coenzyme with great functional role in redox and immunological reactions. ALA has provided important protective effects against human coronavirus infection<sup>71</sup>. ALA also inhibit HIV-1 viral replication<sup>72</sup>.

### 7. Estradiol and phytoestrogen

Investigators have reported that estrogen provides protective effect against viral infections through improvement of immune system<sup>73</sup>. *In vitro* studies conducted on age-matched male versus female mice exposed to SARS virus confirmed that the incidence and mortality rate among male mouse was higher than female ones. Additionally, the fatality rate was increased

in female mouse following ovariectomy or mouse exposure to anti-estrogen therapy<sup>74</sup>. Statistical studies confirmed that the incidence and mortality rate are higher among male SARS patients than females with nearly same fatality rate. The incidence rate of MERS during eruption phase was almost twice in males compared to females<sup>75</sup>. Estrogenic drugs inhibit influenza A viral replication in primary nasal epithelial cells from the female donor (no action was found when nasal epithelial cells were derived from the male donor)<sup>76</sup>. *In vitro* experimental studies confirmed that resveratrol (phytoestrogen) has shown potent anti-MERS activity<sup>77</sup>. These information encourage the application of estrogenic compounds in COVID-19 patients.

## **10. Preventive measures**

Preventive measures should be taken seriously by the local authorities during viral eruption. Personal protective equipment should be used by health care providers to decrease the chance of infection. Close contact with patients should be avoided or reduced to a minimum and hand washing should be more frequent than usual to expel the virus and avoid transmission (reference WHO website and CDC website).

### **10.1. Hand washing**

Hand washing with soap and water for 20 seconds after coughing, sneezing, going to toilet, and before eating should be performed time to time especially during outdoor times soap could be replaced by hand sanitizer containing 60% alcohol.

### **10.2. Respiratory hygiene**

Sick subjects should wear surgical masks to avoid transmission to healthy subjects; this will prevent or decrease the droplets released during talking, coughing and sneezing; in case of unavailability of masks due to increased demand, sneezing and coughing should be on tissues. Health care providers should always wear masks and the following points needs to be considered for wearing a mask.

- 1- Mask should cover mouth and nose properly and should not be touched during use.
- 2- Mask should be removed from lace and not front to avoid hand contact with the mask from high area of the mask (front side), and should be discarded appropriately.
- 3- Hands should be washed after mask removal.
- 4- Mask should be replaced by a new one and should never be re-used.

### **10.3. Self-isolation**

Sick individuals should consider the following important items:

- Avoid contact with other people in different high-risk areas, including work, public area, school, public transportation means, taxis, and ride sharing vehicles
- Keep in touch with health care providers for advise
- Isolation required from other family members (personal items and bathrooms should not be shared)
- Household cleaners should be used to clean contact surfaces every time after use

#### 10.4. Vaccine research

There is great interest globally to develop a vaccine against COVID-19, however, the time required for experimental optimization and result validation in laboratory animals is the rate limiting step to confirm vaccine-effectiveness. There is several attempts to develop a new vaccine by the end of 2020 or early 2021.

#### 11. Conclusion

In the present article, we outlined the available intervention which might potentially be used for the management of COVID-19 virus. This mini-review confirmed that general nutritional status of the subject and using immune enhancers together with self-hygiene and isolation are the corner stone for the treatment of COVID-19.

#### CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest in the manuscript.

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