



Harmony of operations of some vitamins in controlling the 2019-nCoV virus based on scientific reports

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ABSTRACT

Unlike other related compounds, vitamin D has multi-function operations against 2019-nCoV virus *via* intervention in several parts of its lifecycle. In one hand, this compound induces antimicrobial peptides like cathelicidins and proteins like defensins that lead to lower viral replication rates and also reduces the concentrations of pro-inflammatory cytokines (it causes inflammation that results in multi-organ failure). In the other hand, a vitamin D agonist, calcitriol, modulates the expression of members of the renin-angiotensin system, including angiotensin converting enzymes like ACE2 (the cell receptor for 2019-nCoV viral spike protein). Thus, vitamin D may reduce the spike rate of the virus to the lung cells, resulting in inhibition of the virus in entry stage. About vitamin B series, there is a report that claims vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the 2019-nCoV virus.

Also, vitamins C, and E (anti-oxidants with anti-inflammatory effects) could be effective in inhibiting the damages of the organs caused by the acute immune response (inhibiting the release of high concentrations of free radicals) during COVID-19 as well as boosting the human immune system. It must be mentioned that, in spite of the presented supporting references, this paper is prepared for researcher, not for all people.

1. Introduction

Now, after decades, the entire human race has been faced to a severe outbreak that infected the entire planet in a very short period. The high rate of spreading and mortality, remembers us the *Influenza 1918* [1]; when, there were no enough knowledge and technology, compared to 2020. As will be saved in the recorded history, the outbreak of 2019-nCoV virus from *Wuhan*, China, showed how our knowledge and technologies in controlling and inhibiting the pathogens are low. Thus, the human race has to make a revolution in these areas in order to control the probable outbreaks (or even prediction of junks in near or far future. Due to our present technologies, reaching to a vaccine for 2019-nCoV virus at least takes several months and during this time thousands more would die [2]. On the other hand,

using computer simulation for fast infiltration of potential antivirals [3,4], and subsequently use of relatively effective drugs like remdesivir [5], favipiravir [6] and other ones, for all people of the world is impossible due to accessibility, price, and other related factors. Even use of suggestions from nanotechnology [7] need a lot of in vitro, in vivo, and clinical studies. Indeed, the best way is prevention [8], and as mentioned before, due to our present knowledge, prevention by vaccine takes several months. Thus, it is believed that use of agents for improving the power of the body, increasing the total health and boosting the human immune system may be a beneficial way in this crucial period of time.

In this regard, based on the last recent scientific reports, we have made attempt to investigate the probable effects of vitamins on the bodies' resistance against 2019-nCoV virus,

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and controlling the subsequent infection. Investigating the reports showed, that unlike some other vitamins, vitamin D has multi-function operations against 2019-nCoV via intervention in several parts of its lifecycle. About vitamin B series, there is a report that claims vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the 2019-nCoV virus [9]. On the other hand, vitamins C, and E could be effective in inhibiting the damages of the organs caused by the acute immune response (inhibiting the release of high concentrations of free radicals) during COVID-19 as well as boosting the immune system. Also, as given in following, vitamin A has complex effects on different parts of immune system, and it has an anti-inflammatory influence on the human body, but except only few suggestions [10], there is not any considerable report about its effect on 2019-nCoV virus.

In conclusion, it seems that among all investigated vitamins, vitamin D has the highest effect against the 2019-nCoV virus, and COVID-19 illness. Furthermore, vitamin C could play an anti-inflammatory effect during COVID-19 for prevention of multi organ failure.

2. Vitamin A

Although, there are not considerable reports that specifically investigate the effect of vitamin A on inhibition of 2019-nCoV virus, but there are some reports, which reveal about the effects of vitamin A on regulation and development of the immune system. Reports also discuss about the influences of vitamin A on the functions of various populations of cells of innate and adaptive immune system. On the other hand, it was shown that deficiency of vitamin A confers defects in both innate and adaptive immune compartments, resulting in impair immunity against pathogens [12]. There are some other reports revealing about different response of immune system to vitamin A (Figure 1) deficiency resulting in complex defending mechanism.

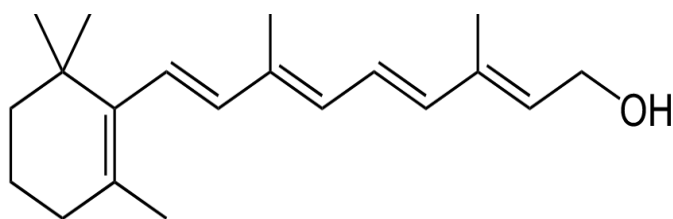


Figure 1. the chemical structure of Retinol (vitamin A1-alcohol)

As an example, high level dietary of vitamin A had not altered clinical outcome of viral pneumonia for influenza, but it enhanced the salivary *Immunoglobulin A* response and diminished the *Immunoglobulin G* response to influenza infection [13]. Up to date, we could not find any significant report about the direct intervention of vitamin A on inhibition of 2019-nCoV.

3. Vitamin C

Vitamin C or ascorbic acid (Figure 2) with its antioxidant properties can effectively prevent activation of cytokine and neutrophils in the lungs (those could hurt the alveolar capillaries). Also, vitamin C prevents the formation of neutrophil extracellular traps, which causes neutrophil activation. In addition, it leads a certain protective effect on influenza infects; while, few investigations showed that vitamin C deficiency is related to increase of severity of influenza. Also, in a non-randomized trial, a number of people used a high-dose vitamin C, and the results showed that in the high-dose of vitamin, the patients did not show a better clinical outcome [14]. On the other hand, some researchers suggest comprehensive experiments of the effect of vitamin C on COVID-19, due the previous reports about the vitamin C influence on pneumonia [15].

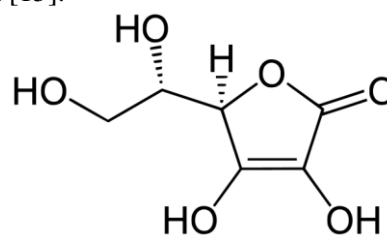


Figure 2. Chemical structure of ascorbic acid.

Another investigation made by Erol, proposes an anti-oxidation interventional mechanism for operation of vitamin C in COVID-19 patients. It also says, the COVID-19 patients with the breathing difficulty could be candidates for a high dose intravenous vitamin C treatment during the early period of the infection. While, the osmotic cell death of immune cells, which would generate a local inflammation in alveolar medium, is a concern that could be raised due to high-dose vitamin C treatment [16]. Also, WHO suggests more discussions on the effect of high dose vitamin C for COVID-19 patients, due to the effect of high dose Vitamin C (50mg/kg/6hrs) in preventing mortality from acute lung injuries as compared to some other compounds [17].

On the other hand some researchers believe that the moderate amounts of vitamin C supplementation could be choice for prevention of COVID-19 [18]. Also, Zhang believes, that vitamin C could be one of the suitable option for the treatment of COVID-19, due to lower respiratory tract infection (caused by 2019-nCoV virus) [19].

Due to these, it could be concluded that high dose-vitamin C may be a choice when high level symptoms of COVID-19 emerged; while this vitamin could not inhibit the 2019-nCoV, at least as well as 25-hydroxy vitamin D (mentioned in following).

4. Vitamin D

A review on the following reports shows that vitamin D (Figure 3) has a significant effect on controlling of 2019-

nCoV virus via intervention in different parts of the virus life cycle. For example, the last recent studies show that (like SARS-CoV), the 2019-nCoV virus spikes to the angiotensin converting enzyme 2 (ACE-2) of human lung cell, and subsequently enters there [20]. On the other hand, some other reports reveal that expression of ACE2 could be modulated by a vitamin D agonist, calcitriol. As an instance, Zhang and co-workers reported that a vitamin D agonist, calcitriol, modulated the expression of members of the renin-angiotensin system, including angiotensin I-converting enzymes (ACE and ACE2), renin and Ang II [21].

In another report, Grant and co-workers, claimed that vitamin D (Figure 2) could reduce the risk of 2019-nCoV or influenza infections through several different mechanisms. Those mechanisms would include inducing antimicrobial peptides like cathelicidins and proteins like defensins that lead to lower viral replication rates and also reducing concentrations of pro-inflammatory cytokines (it produces the inflammation that injures the lungs).

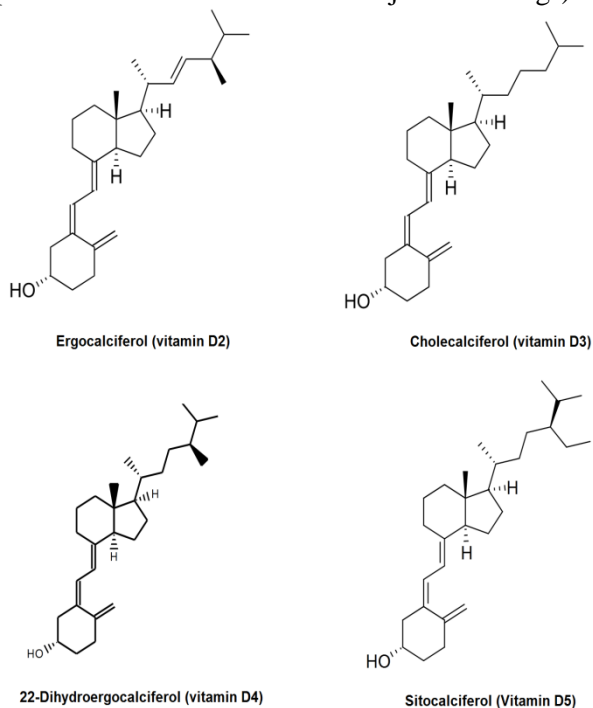


Figure 3. chemical structures for vitamin D family.

Moreover, they discuss about several clinical trials or observational studies reporting about vitamin D supplementation as a reducer of the risk of influenza. They emphasized that the outbreak of COVID-19 occurred in winter, a time when 25-hydroxyvitamin D concentrations are very low; that is, the number of infected people in the Southern Hemisphere near the end of summer are low. On the other hand, it is found that vitamin D deficiency contributes to acute respiratory distress syndrome (ARDS); and its fatality rates increases with age and with chronic disease co-morbidity, both of which are associated with lower amounts of 25-hydroxyvitamin D concentration. In addition, they

recommend taking 10,000 IU/d of vitamin D₃ for a limited period to rapidly raise 25(OH)D concentrations, followed by 5000 IU/d to those at risk of influenza or COVID-19 [22].

In another report, Smith and colleagues reported that Vitamin D levels are significantly low in the aging population especially in some European countries. On the other hand, the most vulnerable group of people for COVID-19 is the aged group. Thus, the researchers of the work suggested Vitamin D for protection against SARS-CoV2 infection [23].

Also, Braiman suggests a possible relationship between COVID-2019 and vitamin D deficiency. He claims this relationship could be stronger when one compares the low rates of vitamin D deficiency in Scandinavian countries to their low rates of death among COVID-19 patients (compared to the other countries). However, low-latitude nations that reveal the highest rates of death related to COVID-19 (like Indonesia and the Philippines) have previously reported about high surface of vitamin D deficiency. He concluded that, public-health authorities all around the world have to urgently develop an inexpensive but rigorous experimental test of his hypothesis about the relationship between COVID-19 mortality and vitamin D deficiency [24].

Alipio, reported that by increasing the serum 25-hydroxy vitamin D level in the human body, the clinical outcomes were improved; while, by decreasing this serum level, the clinical outcomes of COVID-2019 patients, were not satisfactory [25]. Also, Nonnecke and friends claimed that the decrease in vitamin D and vitamin E levels in cattle would lead to bovine corona virus infection [26]

McCartney and Byrne, believe that vitamin D deficiency would contribute to increase of the risk of respiratory infection including Covid-19. They suggest that older, patients, nursing home residents and other vulnerable such as compromised immune function, darker skins, vegetarians and vegans, overweight, smokers and healthcare workers, be urgently supplemented with a dosage of 20-50µg/d of vitamin D, in order to enhance their resistance to Covid-19[27].

5. Vitamin E

Vitamin E (Figure 4) is not a single specific compound, indeed this is a group of fat soluble molecules that include four tocotrienols and four tocopherols. The deficiency of vitamin E, is also rare and it usually happen due to the problems in digesting dietary fat rather than from a diet low in vitamin E [28].

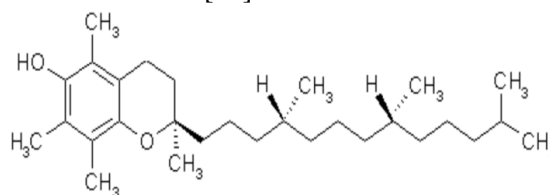


Figure 4. The R,R,R- alpha-tocopherol form of vitamin E

Based on recent clinical reports, Wang and co-workers [29], believe that the therapeutic time for COVID-19 infection is considerably longer than fourteen days. They think long-time viral stimulation would lead (in vivo) intensive immunological reactions, immune-cell infiltration and cytokine storm. Meanwhile, some immunocytes especially macrophages and neutrophils could lead to production of a number of reactive oxygen species (ROS) like, superoxide anion, hydrogen peroxide, and hydroxide. On the other hand, specified amounts of ROS are crucial for regulating immunological responses and subsequently for clearing viruses; while, the excessive amounts of ROS could oxidize the membrane lipids and also the cellular proteins. In continue, this process would damage the virus-infected cells as well as normal cells in lung, and heart, and some other organs [29].

Therefore, potential anti-oxidative therapies by using inexpensive medicinal antioxidants like Vitamin C (L-ascorbic acid) and Vitamin E (due to their reductive hydrogen atoms which could react with, and neutralize ROS) may be proposed as alleviate cardiogenic casualties caused by COVID-19 [30]

Law, believes that in a certain time, using the steroids and antibiotics must be ceased, and those should be replaced by medical doses of anti-oxidants like Vitamin E, and C in order to neutralize the remaining lysozymes and cytokines for the regenerating of the body cell in various damaged organs [31].

In summary, due to the recent reports, vitamin E modulates the response of the immune system, in part by decreasing the inflammation, and also by boosting the immune system [32], while, unlike vitamin D, vitamin E could not have an antiviral effect against 2019-nCoV.

6. Conclusion

In conclusion, the last recent scientific reports, show us, that unlike some other vitamins, vitamin D has considerable effects on 2019-nCoV virus *via* intervention in several points of its lifecycle. In the case of vitamin B series, there is a report that claims vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the 2019-nCoV virus. On the other hand, vitamins C, and E could be effective in inhibiting the damages of the organs caused by the acute immune response (inhibiting the release of high concentrations of free radicals) during COVID-19 as well as boosting the immune system. Also, vitamin A has complex effects on different parts of immune system, and it has an anti-inflammatory influence on the human body, but except only a few suggestions, there is not any considerable report about its direct effect on 2019-nCoV virus.

Finally, it is due that, among all investigated vitamins, vitamin D has the highest effects against the 2019-nCoV virus. Furthermore, vitamin C could play an anti-inflammatory effect during COVID-19 for prevention of multi organ failure.

Conflict of interests

The authors declare that there is no any conflict of interests.

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