

## AN OVERVIEW OF THE GLOBAL OUTBREAK OF CORONAVIRUS DISEASE (COVID-19) INCLUDING THE ROLE OF VITAMIN D AND BEST POSSIBLE MANAGEMENT IN THE LIGHT OF UNANI MEDICINES : A REVIEW

Rabia Khan<sup>1\*</sup>, Yasmeen Shamsi<sup>2</sup>, Khursheed Ahmed Ansari<sup>3</sup>,  
Amreen<sup>4</sup>, Araf Fatima<sup>4</sup>, Nuzhat Praveen<sup>1</sup>, Mehvish Alvi<sup>1</sup>

<sup>1,2</sup>Department of Moalejat

<sup>3</sup>Department of Tashreeh ul Badan

<sup>4</sup>Department of Tahaffuzi-wa-Samaji Tibb

School of Unani Medical Education and Research, Jamia Hamdard, New Delhi

*Review Paper*

Received: 20.04.2020

Revised: 25.05.2020

Accepted: 15.06.2020

### ABSTRACT

**Objective:** The aim of this review was to assess the roles of vitamin D in reducing the risk of respiratory tract infections, knowledge about the epidemiology of influenza and COVID-19, and how vitamin D supplementation might be a useful measure to reduce risk and also to outline the research progress and literature available of the epidemiology, pathogenesis, and clinical characteristics of COVID-19 patients information regarding the ongoing pandemic. Unani medicines can play significant role as adjuvant therapy to control the adverse effect of COVID-19 and can also act as a best Immunomodulator.

**Methods:** A literature search was conducted using the databases PubMed, Medline, Scopus and Web of Science. We described overall possible association between COVID-19 and Vitamin D. We have searched by the names corona virus, covid-19 and vitamin D association with COVID-19.

**Result:** Through several mechanisms, vitamin D can reduce the risk of infections by lowering viral rates of replication and also reducing concentrations of pro-inflammatory cytokines that are responsible for the inflammation and injuries in the pleura.

**Conclusion:** It was additionally observed that COVID-19 and vitamin D have a crude substantial relationship and specifically the mortality induced through this infection. The most susceptible crew of the populace for COVID-19, the getting old population, is additionally the one that has the most deficit Vitamin D levels.

**No. of Pages: 11**

**References: 100**

**Keywords:** COVID-19; Coronavirus; SARS CoV; SARS CoV-2; India.

### INTRODUCTION

Since late December 2019, an epidemic of novel coronavirus disease COVID-19 has appeared as a public health emergency worldwide. In December 2019 a cluster of respiratory disease cases, caused by a newly emerged  $\beta$ -coronavirus, appeared in Wuhan, China. Disease caused by this new virus was initially named because of the 2019-novel coronavirus (2019-nCoV) on 12 January 2020 by World Health Organization (WHO)<sup>1</sup>. The International Committee on Taxonomy of Viruses

has officially named SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2)<sup>2,3</sup>. COVID-19 has been declared as a pandemic by the world health organization (WHO) on the 12th of March.<sup>2</sup> Since the beginning of the 21st century, three coronaviruses have developed a huge burden on the health system by causing outbreaks of pneumonia in humans: Severe acute respiratory syndrome (SARS-CoV) in 2002-03 and middle east respiratory syndrome coronavirus in 2012 (MERS-CoV)<sup>4</sup>. Although most coronavirus infections

\*Corresponding author: [rabikhan.rk1195@gmail.co](mailto:rabikhan.rk1195@gmail.co)



are mild, the epidemics of the two beta coronaviruses . Infection caused by the Coronavirus or COVID-19 in 2019 is one the most highly contagious disease which is caused by a new virus though having a lesser mortality rate (average 3.4%) than that of SARS (9.6%) and MERS (35%) respectively <sup>5</sup>. It has spread from a single city of china to the whole of China within a month <sup>6</sup> and has spread to nearly the whole of the world except Antarctica in less than 3 months. <sup>6-8</sup>. The 2019-nCoV is a  $\beta$  CoV of group 2B with at least 70% similarity in genetic sequence to SARS-CoV. It is reported that SARS-CoV-2 has a 79.5% similarity with SARS-CoV and 96.2% structural similarity with a bat coronavirus (CoV RaTG13)<sup>9-11</sup>.

### Coronavirus disease 2019

#### Origin and spread of coronavirus

In late December 2019, few cases of pneumonia with unknown etiology were reported and all those early cases had shared contact history of exposure with the original Huanan seafood market (“wet market”) (a market where dead and live animals are sold) were reported in Wuhan city, China <sup>12</sup>, Later the local health authority of China, broadcasted, and epidemiological alert and the market was shut down on Jan 1, 2020. Meanwhile, there were many suspected cases of dry cough, fever, and other flu-like symptoms that were reported and transferred to the hospital of Wuhan, China. An expert team of medical professionals and government officials was soon informed after the alert <sup>13</sup>. Since the etiology was totally unknown at the onset of these emerging symptoms, the diagnosis of respiratory infections mainly pneumonia was based on clinical characteristics, chest imaging, and the ruling out of common bacterial and viral pathogens that cause pneumonia. The Chinese government passed the order to isolate the suspected patients using airborne precautions in the designated hospital, Jin Yin- tan Hospital (Wuhan, China), and fit-tested N-95 masks and airborne precautions for aerosol-generating procedures were taken. Many local centers for disease control and prevention of China collected blood, respiratory, and feces specimens, then sent them to designated authoritative laboratories to detect the pathogen (NHC Key Laboratory of Systems Biology of Pathogens and Christophe Mérioux Laboratory, Beijing, China) methods <sup>13</sup>. The primers and probe-target to envelope gene of CoV were used and the sequences were as follows: forward primer 5'-ACTTCTTTTCTTGCTTTCGTGGT-3'; reverse

primer 5'-GCAGCAGTACGCACACAATC-3'; and the probe 5'CY5-C TAGTTACACTAGC CATCCTTACTGC-3'BHQ1 <sup>14</sup>. After the laboratory testing, it was reported that the pathogen (Virus) is a  $\beta$  Coronavirus of group 2B with at least 70% similarity in genetic sequence to severe acute respiratory syndrome coronavirus (SARS-CoV) and the World Health Organization (WHO) used the term 2019 novel coronavirus (2019-nCoV) to refer to the coronavirus that was diagnosed from the lower respiratory tract of patients with pneumonia which was originated from the Seafood Market in, Hubei Province, Wuhan, China. The structural analysis suggested that 2019-nCoV might be able to bind to the angiotensin-converting enzyme 2 receptors in humans similar to SARS CoV which was confirmed by Zhou *et al* <sup>9</sup>. The disease caused by this has been christened as COVID-19 (Coronavirus disease 2019) by WHO on 11th Feb 2020 <sup>15</sup>. On January 5 cluster of 59 cases was reported around the South China Seafood Wholesale Market in Wuhan <sup>1,16</sup>. Later So on, it was discovered the secondary source of infection could be human-to-human transmission among close contacts <sup>17</sup>. Presumed hospital-based transmission was also reported in medical staff and admitted patients. In a study by Wang *et al* 57 cases (41.3%) acquired infection in hospitals including 17 (12.3%) patients and 40 (29%) medical staff. <sup>18</sup>. undiagnosed mildly symptomatic or asymptomatic infected cases did not seek health care and thus remain undetectable, continued working, and traveling in crowded places. Thus potentially virus travelled locally and internationally <sup>19</sup>. There was an noticeable increase in the number of infected people with no history of exposure to seafood market or visiting Wuhan, and various cases of infection were reported among health care workers.

#### Microbiology of coronavirus

Coronaviruses are large enveloped non-segmented positive-strand RNA genome ranging from 26 to 32 kb in length belonging to the family Coronaviridae and the order Nidovirales that are responsible to cause respiratory, hepatic, enteric, and neurological diseases. These viruses can be divided into 4 genera: alpha, beta, delta, and gamma, of which alpha and beta CoVs are known to infect humans. A total of Six coronavirus species are known to cause human disease. Four HCoV (HCoV 229E, OC43, and HKU1, NL63) are endemically prevalent and cause the common cold or influenza-like symptoms in immunocompetent individuals globally and account for 10% to 30% of URTIs (upper respiratory tract infections in adults) <sup>5</sup>.

## Transmission

### Mode of Transmission

Three main transmission routes have been described by the Chinese health authorities for the 2019-nCoV: 1) direct transmission, 2) aerosol transmission 3) contact transmission. Ingestion or inhalation of respiratory droplets (as produced on coughing or sneezing of the infected person) by a healthy subject nearby in close proximity is reported as direct transmission; Airborne transmission may happen when respiratory droplets blend into the air, creating aerosols thus results in infection when breathed in into the lungs; and surfaces or objects contaminated with the touch of an infected person with the virus may result in contact transmission. According to the literature, individuals can contract the infection at the point when they in this manner contact their mouth, nose, or, eyes<sup>13,14</sup>.

Apart from these three routes, the digestive system could be a possible route of transmission for the same infection since few patients also had diarrhea symptoms abdominal discomfort and study performed by Zhang and his co-researchers showed the found that ACE2 was highly identified in absorptive enterocytes from ileum and colon<sup>20</sup>

### Host

Animals including camels, cattle, cats, and bats, may serve as hosts for coronaviruses<sup>13</sup>. It is considered that,

generally, animal coronaviruses do not spread among human beings<sup>21</sup>. It has been postulated primary spread to humans occurred possibly via transmission from wild animals especially bats illegally sold in the market<sup>12</sup>. In addition to the seafood market, The WHO reported that samples of snakes, birds, and bats including other small mammals were collected from the Marketplace of South China and have found positive for the novel coronavirus, but no specific animal association has been noticed<sup>1,22</sup>.

## Characteristics of COVID-19

### Clinical Features

The complete clinical manifestation is not been known yet, patients can be divided as mild, moderate, and severe but sometimes even resulting fatal<sup>12</sup>. Mild symptomatic patients were noted to be recovered within one week without any complication while severe cases were reported to show progressive alveolar damage which results in Acute Respiratory Distress Syndrome (ARDS) which may lead to death<sup>23</sup>. Viral pneumonia including fever, dry cough, breathing difficulty, myalgia, and lung infection is the main complication induced by the family of these viruses<sup>13</sup>. Patients of COVID-19 followed by death were primarily elderly patients pre-existing diseases (diabetes, cirrhosis, coronary heart disease, hypertension tumor surgery and Parkinson's disease) (Table 1)<sup>12,14,24</sup>.

**Table1: Symptoms of COVID-19**

Common symptoms	Less common symptoms	Severe symptoms
Fever	Headache	Difficult breathing and shortness of breath
Cough	Diarrhoea	Chest pain
Myalgia (fatigue)	Hemoptysis	Loss of speech or movement
Pneumonia	Loss of taste or smell	
Dyspnoea (shortness of breath)	A rash on the skin, or discoloration of fingers and toes	

### Incubation Period

The time elapsing between the moment of exposure to a pathogen and the appearance of symptoms of the disease plays an important role in epidemiology because it helps in the decision regarding the length of quarantine for prevention and control of the disease. According to Li et al and Jing et al, it can be estimated that mean of the studies is 2-14 days. Precisely the incubation period of the COVID-19 virus is 14 days with most of the cases

occurs within the 4 to 5 days after the exposure with the virus.<sup>12,25,26</sup>

### Pathological features

The pathological features of COVID-19 closely resemble with coronavirus infections of SARS and MERS.<sup>27,28</sup>. Research conducted by Zhe Xu et al suggested that the biopsy of the liver specimen of the COVID-19 showed moderate vesicular steatosis and

mild lobular portal activity, signifying cause could be due to injury either SARS-COV-2 OR drug-induced liver injury. Few interstitial mononuclear inflammatories infiltrate were also found but no other substantial heart damage. In peripheral blood reduced counts and hyperactivated CD4 and CD8 T cells were reported with high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. In addition, there was an increased concentration of cytotoxic granules in which 31.6% and, 64.2% of cells were positive respectively for perforin and granulysin. Rapid progression of pneumonia and some differences between left and right lungs were also reported in X-ray images. No obvious histological changes were seen in cardiac tissues suggesting that SARS-COV-2 might not directly damage the heart<sup>29</sup>.

### Management

No specific antiviral treatment is recommended or available for the infections caused by nCoV. along with respiratory and contact isolation for an infected individual to stop the further spread and Symptomatic and supportive care is recommended<sup>30,31</sup>. Chinese Centre for disease control and prevention showed increased mortality in people with already existing diseases specifically diabetes<sup>6</sup>. Diabetic patients may need special attention and clinical care<sup>32</sup>.

### Role of Vitamin D

In the time of the current COVID-19 pandemic, and given the importance of diet to overall health and well-being, macro and micronutrients deserve special importance<sup>33</sup>. As an essential micronutrient, vitamin D deserves particular focus not as a 'wonder drug' to beat COVID-19 but rather to maintain the "status of well being" and also to ensure that populations are in best possible nutritional status<sup>34</sup>. Vitamin D is a prohormone which is produced in the skin during exposure to sunlight in UVB radiation at 290–315 nm, usually, trace amounts of Vitamin D can be obtained from food<sup>35</sup>. Circulating metabolite 25-hydroxyvitamin D (25OHD) is the level for the determination of the status of Vitamin D, which is produced after hepatic hydroxylation<sup>36</sup>. If the Normal concentration of 25OHD is as defined in the UK by a 25OHD concentration of <25 nmol/L<sup>7</sup> and in the USA and some other countries by a 25OHD concentration of <30 nmol/L<sup>37</sup>.

Many studies suggested vitamin D reduces the risk of viral infections<sup>38-46</sup>. Vitamin D has many mechanisms by which it reduces the risk of microbial infection and death. A recent study regarding the role of vitamin D in lowering the risk of the common cold divided those

mechanisms into three categories: physical barrier, cellular natural immunity, and adaptive immunity<sup>45</sup>. The induction of antimicrobial peptides, including human cathelicidin, LL-37, by 1,25-dihydroxy vitamin D<sup>47-49</sup>, and defensins through Vitamin D enhances the cellular innate immunity<sup>49,50</sup>. Inflammatory and anti-inflammatory markers such as Th1 cytokines, tumor necrosis factor  $\alpha$ , and interferon  $\gamma$  produced in response to viral and bacterial infections by the innate immune system were observed to reduce with the help of Vitamin D, noticed in in COVID-19 patients<sup>51,52</sup>. Vitamin D is a modulator of adaptive immunity<sup>45,52</sup>. 1,25(OH)2D3 suppresses responses mediated by the T helper cell type 1 (Th1), by primarily repressing production of inflammatory cytokines IL-2 and interferon-gamma (INF $\gamma$ )<sup>53</sup>. Additionally, 1,25(OH)2D3 promotes cytokine production by the T helper type 2 (Th2) cells, which helps enhance the indirect suppression of Th1 cells by complementing this with actions mediated by a multitude of cell types<sup>54</sup>. Vitamin D helps maintain tight junctions, gap junctions, and adherens junctions (e.g., by E-cadherin)<sup>55</sup>. Several articles discussed how viruses disturb junction integrity, increasing infection by the virus and other microorganisms<sup>56-58</sup>.

### Vitamin D, Respiratory Health and COVID-19

It has been hypothesized that there's an association between seasonal URTI's and low vitamin D standing as a result of each occur within the winter months. vitamin D inhibits pulmonary inflammatory responses by enriching innate defense mechanisms against respiratory pathogens<sup>59,60</sup>. URTIs (Upper Respiratory Tract Infections), or 'common colds', are the foremost widespread of infectious diseases, with quite 200 viruses contributing to the clinical symptoms. Epidemiological studies in children have found a robust association between URTI and rickets<sup>60</sup>. There is evidence that lower vitamin D status is associated with acute respiratory tract infections (ARTIs)<sup>50</sup>. Exposure to sunlight has been known for quite 100 years to assist with the treatment of tuberculosis<sup>61</sup>. A recent study found that low Vitamin D is associated with a higher risk of active tuberculosis<sup>62</sup>. Moreover, a recent study of young Finnish working on a military base noticed a link between low vitamin D status and days of absence from his work due to physician-diagnosed acute respiratory tract infections<sup>50</sup>.

Viral or bacterial infections often exacerbate COPD, the ability of vitamin D to enhance cathelicidin expression, might reduce viral load, and the frequency of these exacerbations. in winter peaks when serum 25(OH)D levels are at their lowest exacerbations of COPD are

quite often<sup>63</sup>. Influenza virus affects the respiratory tract through two ways first by direct viral infection secondly by damaging the immune system response. A comprehensive review regarding the role of vitamin D and influenza<sup>44</sup> concluded that the evidence of vitamin D's effects on the immune system reduces the risk of influenza. Numerous studies suggest that high serum levels of 25(OH)D through vitamin D supplementation during winter lowers the risk of developing influenza or other respiratory tract infections. Moreover, the peak of influenza also coincides with cold weather it has been observed influenza virus survives longer outside the body than at high temperatures<sup>64-66</sup>. Epidemiological and clinical relation between 25(OH)D concentrations and COVID-19 has been extracted from the observed fact that COVID-19 infection is linked with the high production of pro-inflammatory cytokines, C-reactive protein<sup>51</sup>, increased risk of pneumonia<sup>67</sup>, sepsis, acute respiratory distress syndrome, and heart failure<sup>68</sup>. A recent review stated that intake of multiple micronutrients such as vitamins D, C, and zinc having immune-supporting roles may boost up the immunity and reduce the risk of COVID-19 infection. Another recent review suggested using vitamin D loading doses of 200,000–300,000 IU in 50,000-IU capsules to reduce the risk and severity of COVID-19<sup>69</sup>. Although it is evident that the protective effect of vitamin D against COVID-19 is related to the role vitamin D in the suppression of pro-inflammatory and inflammatory markers and reduce severity/risk for ARDS (acute respiratory distress syndrome)<sup>70</sup>. However, more and higher design or layouts of human clinical studies addressing quantity and combinations of micronutrients in different groups of people are required to be studied also regarding the beneficial functions and properties of micronutrient against COVID-19<sup>46</sup>.

#### Plan of action in the light of Modern Medicine for Vitamin D deficiency

Supplementation with vitamin D according to Government guidelines should be followed, the UK SACN, US IOM, and EU European Food Safety Agency recommend that vitamin D intake including total from both foods and dietary supplements should be up to 4000 IU/day (100 µg/day) for adult. Consumption of a nutritionally balanced diet, for example,<sup>71,72</sup> vitamin D rich foods, that is, oily fish, red meat, egg yolk and fortified foods, breakfast portions of cereal, as well as fortified milk.<sup>73,74</sup> Safe sunlight exposure to boost up or maintain the required vitamin D status. Safe sunlight exposure for vitamin D production in the skin through the dermal synthesis of vitamin D is most efficient<sup>75</sup>.

Accordingly, it should be necessary to measure serum 25(OH)D levels in all patients with COVID-19 and at different stages of the disease to study the role and importance of circulating levels of 25(OH)D<sup>76</sup>.

#### Suggested Plan of action for COVID-19 in the light of Unani medicine

Unani system of medicine is known for holistic and gentle ways of treatment with less known side effects since ages. Unani drugs can be given in two forms single and compound formulations. At this tender and crucial time of pandemic Unani drugs can be potentially beneficial as prophylactic and also for the management of COVID-19. AYUSH has suggested best possible plan of action for the same. Ismail Jurjani (1041-1136 CE) mentioned that use of Tiryqaq during epidemics strengthens the heart and keeps the body faculties strong<sup>77</sup>. Single and compound Unani drugs mentioned hereunder, may prove to be beneficial and can be used under the supervision of qualified Unani physicians for possible immune-boosting / symptomatic relief in upper respiratory tract infections and other associated symptoms.

#### Single Unani drugs

**Behi dana (Cydonia oblonga):** Antioxidant, immunomodulator, antiallergic<sup>78</sup> and anti-influenza<sup>79</sup> (Dose is 3-5 gm)

**Unnab (Zizyphus jujuba):** Anti-influenza<sup>80</sup>, immunomodulator and antioxidant.<sup>81</sup> (Dose is 5 pcs.)

**Sapistan (Cordia myxa):** Immunomodulator<sup>82,83</sup>, tracheal smooth muscle relaxant<sup>7</sup> and anti-oxidant.<sup>8</sup> (Dose is 9 pcs.)

**Karanjwa (Caesalpinia bonducella):** Antipyretic<sup>84</sup>, antimicrobial, anti-inflammatory and immunomodulator.<sup>85</sup> (Dose is 3 to 5 gm)

**Tiryqaq-e-Arba** has Dafaee Sumoom (antidote) and Dafaee Tashannuj (anti-spasmodic) properties and used in the dose of 3-5 gm with **lukewarm water**<sup>86</sup> (Not recommended for diabetics).

#### In case of respiratory discomfort local application of

**Roghan-e-Babuna Sada** on chest is advocated (in quantity sufficient).<sup>87,88</sup>

#### Inhalation

**Arq-e-Ajeeb** 2-5 drops<sup>88</sup>



### Antivirals

Below mentioned Unani herbs have shown few leads to possess certain antiviral activities. They may be used under the supervision of a qualified Unani physician.

1. **Kalonji (Nigella sativa):** 1-2 gm <sup>8889</sup>
2. **Seer (Allium sativum):** 2-3 gm <sup>8890</sup>
3. **Zanjabeel (Zingiber officinale):** 5 gm <sup>9188</sup>
4. **Aslassus (Glycyrrhiza glabra):** 5-10 gm <sup>92</sup>
5. **Afsanteen (Artemisia absinthium):** 3-5 gm <sup>93</sup>
6. **Tukhm-e-Kasoos (Cuscuta reflexa):** 15 gm (seeds) <sup>94</sup>
7. **Khayarshamber (Cassia fistula):** 10-20 gm (pulp) for gargle <sup>8895</sup>
8. **Gilo (Tinospora cordifolia):** 5-10 gm <sup>8896</sup>

### Immunity Enhancers

**Khameera Marwareed:** 3-5 g <sup>9788</sup> (Not recommended for diabetics)

**Asgandh (Safoof):** 5 g <sup>98</sup>

### CONCLUSION

The outbreak of COVID-19 swept across China rapidly and has almost spread to the whole world in less than three months <sup>7,8</sup>. High infectivity implies that it has more possibilities of catching the susceptible and immune-compromised population and causing higher mortality. Many studies have speculated that close to two-thirds of COVID-19 cases from China may have gone unnoticed <sup>99</sup>. Going by the present trends, the cases are likely to increase in the near future <sup>11</sup>. In conclusion, it was additionally observed that COVID-19 and vitamin D have a crude substantial relationship and specifically the mortality induced through this infection. The most susceptible crew of the populace for COVID-19, the getting old population, is additionally the one that has the most deficit Vitamin D levels. whereas, The spread of COVID-19 infection can be reduced by minimizing the human-to-human transmissions for that Infection prevention and control guidelines by WHO and MOHFW are to be followed <sup>15,100</sup>. Research work is still needed to fight with the COVID-19 disease. We really hope to overcome the epidemic as fast as possible.

### Funding

None.

### Acknowledgments

None.

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