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Review Article

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Covid-19 Pandemic and Impact of Orthomolecular Medicine: New Perspectives and Applications

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ABSTRACT

Approximately 3 months subsequent to pandemic, it was further observed for the COVID-19 epidemic. Hence, comprehending remedies for the recurrence of COVID is essential. The use of vaccines, masks, sanitizers, and social stimulants serves as preventive measures; yet, it is plausible that novel variations of COVID-19 may emerge. Nearly 5 years since the onset of the COVID-19 pandemic, a comprehensive resolution remains elusive, with the exception of verified vaccine-related adverse effects. Indeed, inadequate nutrition might possibly have a detrimental impact on the immune system, resulting in an inflammatory reaction. This phenomenon may account for the increased susceptibility to symptoms associated with SARS-CoV-2 infection. Providing the immune system with essential nutrients enhances its capacity to combat viral infections inside the human body. The potential occurrence of comparable pandemic illnesses affects individuals worldwide. This research focuses on the advantages of nutrients such as Vitamin-D, Vitamin-C, and zinc, as well as the influence of weather humidity on COVID-19, in order to proactively enhance preparedness for future instances.

Keywords: COVID-19; Flavonoids; Medicine; Micronutrient; Vitamins; Zinc

INTRODUCTION

In mammals, including both humans and animals, coronaviruses represent a group of viruses that induce respiratory tract ailments.[1] This group of viruses encompasses a wide range of illnesses, spanning from common colds to severe respiratory conditions such as Severe Acute Respiratory Syndrome (SARS),[2] Middle East Respiratory Syndrome (MERS),[3] pneumonia,[4] and the most recent addition, COVID-19. The coronavirus was first identified in 1937 in avian specimens sick with bronchitis, and it is accountable for around 15 to 30 percent of cases of the common cold.[5] Over the course of the last seven decades, researchers have seen a consistent correlation between the coronavirus and several animal species, including rats, dogs, cats, turkeys, horses, pigs, and sheep.[6] These viruses may be transmitted from animals to humans and are characterized as zoonotic.[7] The majority of individuals in this category will impact the respiratory passages in the host organism, resulting in symptoms such as dry cough, dyspnea, myalgia, chills, and hypoxia.[8] Severe instances of the illness are prone to lead to pneumonia, renal failure, and even fatality. COVID-19 is a major respiratory illness that is producing unexpected difficulties globally.[9] SARS-CoV-2 is a coronavirus that is now causing problems. Each kind has distinct genetic variants that set it apart from the others.[10] The Delta (B.1.617.2) variation has been encountered, however, the World Health Organization (WHO) has recently identified the omicron variant (B.1.1.529) **(Figure 1)** with a higher number of modifiable hits as a more significant hazard compared to prior versions.[11]

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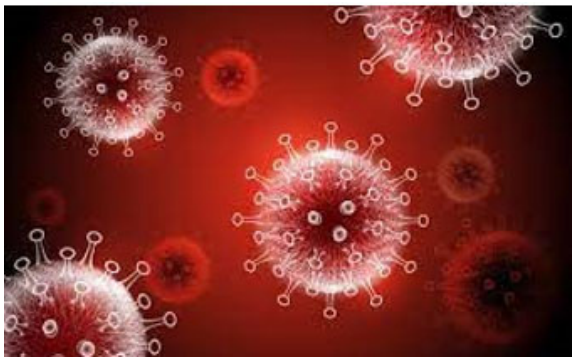

Figure 1: Coronavirus omicron variant (B.1.1.529).

Numerous medical, social, and engineering strategies have been suggested to address the COVID-19 pandemic, including therapeutic interventions, preventive measures, detecting techniques, and predictive methodologies.[12] The use of technology has played a significant role in addressing the worldwide COVID-19 epidemic by facilitating the decentralized and on-demand production of various personal protection equipment and medical products.[13] During the COVID-19 pandemic, extensive research has been conducted on various medical equipment and devices.[14]

These advancements have involved the utilization of synthetic and natural polymers, polymer nanocomposites, polymer conjugates, enzymatic modifications and recognition of structure and properties, functionalized nanoparticles, prodrug polymeric nanoconjugates encapsulating gold nanoparticles, biopolymer-based membranes, biosorbents, as well as flexible and portable DNA.[15,16] These materials have become indispensable in the healthcare sector for purposes such as protection, disinfection, and immunization.[17] The use of synthetic polymers has shown to be effective in the development and production of a wide range of face masks, shields, anti-viral coatings, and diagnostic tests.[18] Natural polymers, such as sodium alginate, chitosan, cellulose, and gums, possess desirable characteristics like biodegradability and environmental friendliness.[19] These polymers play a crucial role in the production of personal protective equipment, immunosensors, and anti-viral sprays, which are used to control and combat COVID-19.[20] The current advancements and breakthroughs in research serve as evidence of the benefits in mitigating the transmission of new infectious illnesses, such as COVID-19.[21]

The medication administered to individuals with COVID-19 remains in an experimental phase. The therapy of COVID-19 encompasses three primary aspects: antiviral medications to decrease viral accumulation; administration of steroids to mitigate cytokine syndrome, which has detrimental effects on the lungs, and pharmacological agents to inhibit blood coagulation.[22] Health professionals advise that the number of individuals affected by COVID-19 should not be seen as life threatening, but rather as an escalating issue. Upon the onset of the COVID-19 pandemic, a therapeutic approach including the administration of a combination of many pharmaceuticals is used. There is currently no medicine that is completely effective. Simultaneously, there exist valuable insights to be gleaned from the latter part of this year's experience. These research need to be used in the management of this complex circumstance. Unregulated medicine use that lacks efficacy will yield adverse consequences rather than beneficial outcomes.[23] The administration of medicine and its timing is of utmost importance. Preterm or delayed birth might pose a significant risk. At first, it was hypothesized that the only consequence was a pulmonary infection resulting from an infectious agent. Nevertheless, there have been reports of complications in the lungs and arteries. Pharmaceuticals like heparin are used to prevent this. The administration of this medication should be avoided in individuals who typically do not have COVID-19. Nevertheless, those who have prosthetic heart valves and are suffering from DVT (deep vein thrombosis) may get heparin as necessary, even after the release of COVID. Individuals without autoimmune conditions such as rheumatoid arthritis or other similar ailments should refrain from using corticosteroid medications in the event of recovering from COVID-19.[24]

The consideration of the immune system's participation during pandemics is of utmost importance. Adhering to a balanced diet, taking supplements, and practicing basic cleanliness helps enhance the immune system. WHO advises individuals to embrace a wholesome lifestyle in order to enhance their likelihood of achieving a quick recovery. Efficient diet is essential for the efficient functioning of the immune system. Ensuring a strong immune system necessitates the maintenance of a well-balanced and nutritious diet, since the optimal functioning of the body relies on the presence of essential vitamins and minerals. This study not only presents a concise overview of the data supporting orthomolecular medicines, but also explores their potential applications in the prevention and treatment of COVID-19. Our objective was to collect data on the use of vitamins and Zinc in the treatment of respiratory infections, specifically focusing on COVID-19. Additionally, we aimed to ascertain if the addition of Zinc as a supplement is necessary when vitamins alone are inadequate in addressing these diseases.

Lower temperatures increase the vulnerability of our bodies to the common cold, pneumonia, and other associated illnesses. Numerous health professionals claim that with the increase in temperature, there is a corresponding rise in indoor activity, hence facilitating the transmission of viruses. It is often anticipated that the immune system exhibits somewhat higher efficiency in warmer climates compared to colder climates. A study conducted in 2014 examined the propagation patterns of several viruses under cold and warm temperature conditions, as well as under varying degrees of humidity. Researchers conducted a study on the spread

of the influenza virus by confining guinea pigs in a room and exposing them to a range of environmental conditions. The optimal conditions for infection were found to be a low relative humidity ranging from 20 to 35 percent, whereas transmission was blocked by high humidity levels of 80 percent. Additionally, it was observed that the occurrence of translation awkwardness was more frequent in guinea pigs housed at a temperature of 5°C compared to those maintained at a temperature of 20°C. No transmission is seen at a temperature of 30°C. The propagation of influenza virus is facilitated by low relative humidities resulting from indoor heating and cold temperatures.[25]

Individuals may have rhinorrhea without contracting a cold in the winter season. Consequently, if they have a cold and a runny nose, the transmission of infections via nasal secretions may be accelerated. Occasionally, individuals engage in the act of rubbing their noses without cleansing them, shaking others, or touching things, resulting in more contact with others. This provides an additional rationale for the accelerated propagation of viruses throughout the winter season. Rhinoviruses account for 40% of those who get infectious colds.[26] The COVID-19 virus is the second most prevalent causative agent of the common cold. This literary work Coronavirus, or SARS-CoV-2, is distinct from all other coronavirus viruses. Research has shown that rhinoviruses exhibit accelerated replication in cooler environments, suggesting that individuals might get a cold more quickly while they are outside. This is certainly applicable to the coronavirus as well. There is a potential for individuals to allocate a greater amount of time inside during the winter season due to a combination of factors mentioned above, including lower temperatures and reduced humidity levels. Low temperatures induce rhinorrhea and enhance the maturation of our immune system. The combination of these conditions likely accounts for the increased susceptibility of Kohl's and COVID-19 to infections during the colder winter season.

Currently, there is no authorized medication for the treatment of coronavirus infection in humans. Numerous treatment regimens are globally accessible; nevertheless, none of them have shown efficacy in completely eliminating the coronavirus. The investigation of prospective therapeutic interventions and a number of antiviral medications are now being used. While the process of creating entirely new pharmaceuticals or vaccines may take many years, a significant number of the drugs now under testing have already received approval as indications for further research of other antiviral medications. The currently under investigation antiviral agents include chloroquine, darunavir, galidezivir, interferon beta, LIG, and several other compounds. The production of viral RNA in human cells is attributed to Dependent RNA polymerase, also known as non-structural protein-nsp12. Consequently, Remdesivir, an antiviral medication that inhibits this chemical reaction, is now used in the management of COVID-19. There is a growing apprehension over the potential incapacity or delayed response to future pandemics due to a lack of knowledge acquisition from the present occurrence, namely the COVID-19 pandemic. As previously said, COVID-19 may be effectively managed by the use of preventive measures such as vaccinations, masks, sanitizers, and social stimulants. The acceleration and expansion of novel pharmaceuticals play a crucial role in enhancing the resilience of vital healthcare systems, enabling them to effectively anticipate and respond to any future shocks or a potential resurgence of the current epidemic. This study specifically examines the benefits of vitamins and the impact of weather humidity on COVID-19, with the aim of preparing for future instances.

BIOLOGICAL PROPERTIES

Genomics and proteomics

The enveloped size of the SARS-CoV-2 virus is 100 nm; its mass is around one femtogram, and its positive-sense linear single-strand RNA is composed of roughly 29,800 base pairs. Roughly, 66% of the genome is comprised of nonstructural proteins, while structural proteins account for roughly 33%. The viral structure has four primary proteins, including the membrane (M), envelope (E), nucleocapsid (N), and spike (S) proteins. The major antigen present on the surface of the virus is the spike protein, including two subunits referred to as S1 and S2. As the level of species diversity grows, the role of S1 becomes more significant. The S2 subunit has heightened protective properties and assumes a pivotal function in the process of viral membrane fusion. The major and specific target for the virus in the development of diagnostic tests and therapies is the receptor-binding domain (RBD) sequence of the spike S1 subunit. This motif enables the virus to bind to the receptor. The current body of literature includes over 5000 publications that investigate the whole genomes and mutations of the virus. According to the available data, a cumulative count of 1100 nucleoids has experienced point mutations. According to reports, mutations have taken place in various parts of the viral gene, leading to an augmentation in the quantity of amino acid residues to around 12 nucleotides. The virus in question exhibits a mutation rate of around 10^6 per site each cycle, a very modest figure when juxtaposed with the mutation rate seen in closely related viruses such as influenza, which stands at $3x10^6$. The mutations in question are mostly influenced by the presence of proofreading enzymes, namely endonuclease and exonuclease, together with the RNA-dependent RNA polymerase enzyme (RdRp). The genomic layouts of the Bat coronavirus (RATG13) and Penguin coronavirus are 96 percent and 91 percent similar to SARS-CoV-2.23 and 24, respectively. A number of newly identified strains have

emerged since the onset of the pandemic and are associated with heritable alterations in the SARS-CoV-2.25 virus.

Viropathology

Cell fusion involves the virus entering the cell by surface phospholipids. The incubation period of the virus typically spans around 10 hours, after which a further assembly process occurs for a duration of 10-12 hours. Subsequently, the 10^3/cell virus further causes cell lysis, leading to infection. Compared to other viruses in the same family, SARS-CoV-2 has a much higher affinity for human cellular receptors. The establishment of a protease cleavage site entails the incorporation of 12 nucleotides that are positioned at regular intervals between the sequences of S1 and S2. The cleavage location of the SARS-CoV-2 virus is unique and has a substantial impact on its pathogenicity.

Virus receptors

The ACE2 cell receptor, situated inside the cellular membrane, has a hemostatic role by mitigating the effects of ACE on the cardiovascular system. Endocytosis occurs when a virus attaches to ACE2, resulting in a reduction in the amount of surface ACE2 seen on endothelial cells. The perturbation of the metabolic balance between ACE and ACE2 results in an increase in the concentration of angiotensin II. The compound known as angiotensin-II has vasoconstrictive effects and induces inflammatory responses via the activation of enzymes, including disintegrin and metalloprotease 17 (ADAM17). Several receptors, such as ACE2, which encompasses the coronavirus-like NL-63, have been identified for the entrance of SARS-CoV-2. CD209L, also known as L-SIGN and CLEC4M, and CD209, generally referred to as DC-SIGN, are two proteins belonging to the immunoglobulin family that function as cell adhesion receptors. The expression of CD209L is notably increased in Type-II alveolar cells and lung endothelial cells, while CD209 is elevated in dendritic cells (DCs) and tissue-dwelling macrophages. Basigin, also known as CD147 or EMMPRIN, is a viral receptor that functions as an inducer of extracellular matrix metalloproteinase. The membrane-bound glycoprotein, which has resemblance to immunoglobulins, serves as a ligand for viral spikes. Inhibitory medicines also referred to as anti-receptors, rely on the spatial epitopes present on surface glycoproteins to effectively block receptors.

Virus immunopathology

The similarities between the SARS-CoV-2 virus and other viruses in its family suggest that the immune response elicited by the interaction between the host and the infection would be similar. Regarding the fight against SARS-CoV-2, the lack of an appropriate immune response has the capacity to alter the intensity of the disease. Acute respiratory distress syndrome, lung organ loss, respiration, and shock are seen in a minority of patients, namely less than 20%, and are associated with a death rate of less than 2.4 percent. The immune system's limited capacity to adequately prevent and regulate the immunological response might potentially contribute to the onset of many illnesses. Cytokine storms are a phenomena characterized by the overproduction of pro-inflammatory cytokines by immune cells, including interleukin-1 (IL-1), IL-2, IL-6, IL-8, IL-17, and tumor necrosis factor-alpha (TNF-alpha), as well as chemokines such as CXCL10 and CCL2. Another mechanism seen in these patients, similar to MERS, is lymphopenia, especially a decrease in T-lymphocytes, which may occur under several circumstances. Key factors that contribute significantly include the virus's source, its age, the immune system's functionality, and the existence of chronic diseases caused by an imbalance in pro-inflammatory and anti-inflammatory cytokines. Viral proteins directly and indirectly trigger the production of cytokines and the activation of signaling pathways, especially those involving S- and N-proteins. Comprehending the process by which a disease affects the immune system might help identify possible targets for improving the immunological response.

Host immune response

There are two main categories in which host immune responses may be characterized. The role of the innate immune response is crucial in either safeguarding against or impeding viral responses within the first category. Neutrophils and monocytes-macrophages, constituents of the innate immune system, recognize single-stranded RNA (ssRNA) or double-stranded RNA derived from viruses as molecular entities linked to infections. The recognition of these patterns is achieved via the use of the cytosolic RNA sensor (RIG-I/MDA5) and intracellular or endosomal RNA receptors (TLR3 and TLR7). The immunological response of a host may be categorized into two separate classifications. The innate immune response plays a crucial role in either safeguarding against or hindering viral responses within the first categorization. Neutrophils and monocytes-macrophages, constituents of the innate immune system, recognize single-stranded RNA (ssRNA) or double-stranded RNA (dsRNA) derived from viruses as molecular fingerprints linked to infections. The cytosolic RNA sensor (RIG-I/MDA5) and intracellular or endosomal RNA receptors (TLR3 and TLR7) are used to identify these patterns.

Pathogen immune evasion strategies

A multitude of viral proteins, namely M, N, and S, have the capacity to impede the host's intrinsic antiviral response by inhibiting the type-I interferon signaling pathway. Conversely, the virus may evade the adaptive immune response by the downregulation of MHC-I and -II (major

histocompatibility complex-I and complex-II), therefore limiting the presentation of antigens. Other methods of evading the immune system include immunological fatigue, viral changes, and immune deviation.

Prevention and treatment with micronutrients: Orthomolecular medicine

Orthomolecular medicine **(Figure 2)**, also known as important drugs, nutrition, or micronutrient medicine, is a kind of alternative medicine that uses nutritional supplements to maintain human health. In 1968, Linus Polling, a renowned American biochemist and recipient of the Nobel Prize for Chemistry, selected the word because to its ability to effectively encapsulate the fundamental notion of essential pharmaceuticals. The judicious administration and amalgamation of essential nutrients serve to safeguard and sustain the organism against ailments, while concurrently mitigating age-related complications. It preserves health by regulating the optimal levels of chemicals commonly found in the human body and is crucial for overall well-being. Orthomolecular medicine is founded on the recognition that the human body necessitates many micronutrients (essential elements) in the appropriate proportions to ensure the optimal and efficient operation of all cellular processes and organs.[27] Micronutrients are essential compounds present in the human body that play a crucial role in preserving vitality and overall health[1]. These substances can be synthesized by the body, but they must be ingested by food. These vital compounds, known as micronutrients, include vitamins, minerals, trace elements, necessary fatty acids, essential amino acids, secondary plant nutrients, and other essential chemicals. Hence, the presence of sufficient micronutrients guarantees appropriate healthcare when all the components in the body are in sufficient amounts. Conversely, an insufficient supply of key nutrients, such as substandard food quality and nutrition, may result in deficiencies in macro or micronutrients owing to an individual's excess need for these critical nutrients. A deficiency in macro and micronutrients may be identified by clinical laboratory analysis.

Figure 2: Orthomolecular medicine.

Another method involves doing a thorough nutritional analysis. This assessment aids in the identification of an individual's specific macro or micro-nutrient needs, taking into account several factors such as dietary patterns, stimulant use, physical activity levels, prior medical issues, and prolonged prescription usage. Ensuring adequate intake of vitamins and minerals is crucial for maintaining optimal health and maybe decreasing the risk of diseases. This is because micronutrients have a role in almost every physiological activity in the body. In addition, several vitamins and minerals may act as antioxidants. Antioxidants provide the potential to combat cellular damage associated with several illnesses, such as cancer, Alzheimer's disease, and heart disease, while also strengthening the immune system. The alternative medicine branch of the National Research Centre has developed dietary recommendations for the use of natural micronutrient supplementation in individuals with COVID-19.

Immunonutrition refers to the manipulation of the immune system via the modification of dietary components. The potential benefits of increasing the levels of antioxidant molecules in the body have been widely acknowledged due to the pro-inflammatory nature of ARDS. In addition, the administration of nutrients such as glutamine has been shown to have benefits in enhancing the activity of lymphocytes, macrophages, and neutrophils. The administration of nutrient supplements has had a positive impact on the clinical outcome in a range of patients; including those who are in a critical condition.[28] There are many commercially available formulae that include a combination of immunonutrients, both orally and parenterally. The most prevalent vitamins include antioxidants, trace minerals, essential amino acids, fatty acids, and gamma-linolenic acid.

The available evidence on the beneficial impacts of immunonutrition in cases of acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) exhibits inconsistencies and is often distorted. Clinical studies have shown that individuals with ARDS have reduced levels of beta-carotene, retinol, alpha-tocopherol, and total radical antioxidant capacity in their baseline plasma. After four days of feeding with eicosapentaenoic acid, gamma-linolenic acid, and antioxidants, this issue might be rectified in comparison to a control group that did not get any supplementation. Nevertheless, no clinical ramifications were recorded. The effects of eicosapentaenoic acid, gamma-linolenic acid, and antioxidants were examined in patients suffering from severe sepsis and septic shock. The study revealed a substantial decrease in mortality, ventilator-free days, and intensive care unit-free days. However, the results obtained from the systematic reviews and meta-analyses of those researches are not very promising. The pooled analysis of the six controlled studies included in a comprehensive review of enteral immunomodulatory diets in patients with ALI and

ARDS did not find any significant decrease in all-cause mortality or an increase in the number of ventilator-free or intensive care-free days. Nevertheless, the two studies indicated that those with the greatest mortality risk get the most benefits. A 2019 Cochrane review identified ten trials that included 1015 patients with acute respiratory distress syndrome (ARDS). These patients were randomly allocated to receive either omega-3 fatty acid or antioxidant therapy. There was no observed reduction in the overall mortality rate. According to suggestions, there has been a reduction in the duration of time spent on ventilators and in critical care units. The significance of immunonutrition in the ongoing SARS-CoV-2 pandemic has been acknowledged by several individuals, leading to the formulation of recommendations for the prompt administration of nutritional supplements to those who have contracted the virus.[29] There has been a scarcity of documented research conducted on this topic among the epidemic. The 'immunonutrition diet' exhibits heterogeneity in various dietary supplement studies, including a multitude of vitamins, minerals, and fatty acids administered together, hence posing challenges in assessing the individual efficacy of each vitamin.

CONCLUSION

Considerable debate has arisen on the efficacy of various vitamins and nutritional supplements in combating the virus or reducing the risk of contracting COVID-19 since the onset of the epidemic. Joan Driggs, vice president of content and thought leadership at IRI, asserts that vitamins and supplements are now seen as a limited means of exerting control over one's life during a very unpredictable period. The provision of micronutrients, which are necessary nutrients, plays a crucial role in preventing micronutrient deficits and enhancing the immune system's ability to defend against many illnesses. Furthermore, it mitigates the risk factors and accompanying symptoms of the ageing process. Based on the findings of the meta-analysis and retrospective investigations, there seems to be a potential association between reduced micronutrient levels and an increased susceptibility to COVID-19 infection. Further investigation is required in order to ascertain the impact of these micronutrients and the imperative nature of supplementation on the outcome of the condition. This might potentially lead to enhancements in illness outcomes and prognosis. The current analysis elucidates the significance of adhering to a nutritionally balanced diet in order to enhance general well-being, fortify the immune system, and mitigate the likelihood of contracting infectious and chronic ailments in humans, hence mitigating the potential for future pandemics.

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CONFLICT OF INTEREST

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