

# Role of Immunity Booster to Manage COVID 19 Pandemic

Neha P Singh<sup>1</sup>, Shivani Sharma<sup>1</sup>, Harshit Kumar<sup>\*2</sup>, Amandeep Singh<sup>3</sup>

<sup>1</sup>Assistant Professor, Dev Bhoomi Institute of Pharmacy & Research, Dehradun.

<sup>2</sup>Research Scholars, Dev Bhoomi Institute of Pharmacy & Research, Dehradun

<sup>3</sup> Professor, Dev Bhoomi Institute of Pharmacy & Research, Dehradun

## ABSTRACT:

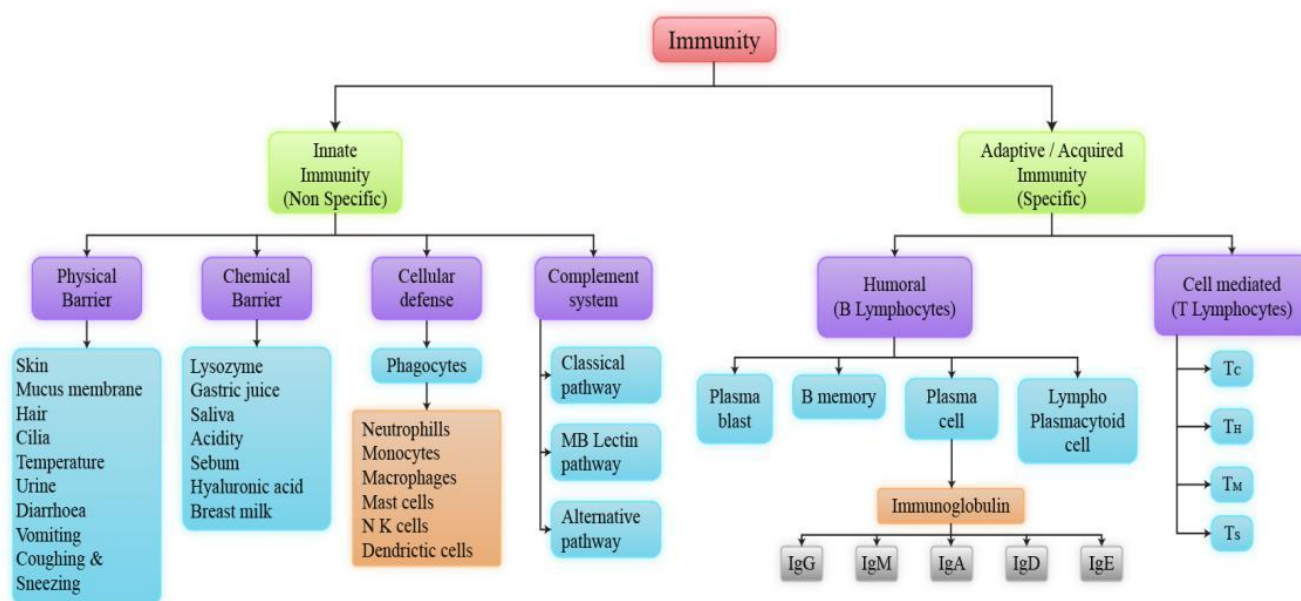
Mankind is at global threat today due to COVID-19 disease caused by a virus known as SARS-CoV-2. WHO has reported this virus as pandemic to be a global public health emergency. As of now, there is no vaccine or curative medicine to stop this COVID-19 virus. Consequently, it is essential for individuals to boost their immunity to fight against the virus. Nutrition enriched diet can help in maintaining immunity, strengthens immune system and to prevent viral infections. In the present review attempts were made to explain the different branches of immune system with the classification tree and strived to evaluate the evidences that has been trailed clinically from the past that analyzed nutrition-based mediations to handle and treat viral diseases. Review summarized possible advantages and immune boosting properties of some essential nutrients of human system such as vitamins, trace elements, probiotics, nutraceuticals, and some healthy practices that enhance immunity against particularly viral infections.

**Keywords:** COVID-19, Immunity, Immune boosting foods, Vitamins, Trace elements, Ayurveda.

## INTRODUCTION

It has been a century back that the world witnessed the pandemic. In 1918 Spanish flu was declared as an influenza pandemic caused by the H1N1 influenza virus. The estimated infection rate was above 500 million and causing about 17-50 million deaths [1]. Now the COVID-19 that is declared as a pandemic by the WHO is spreading rapidly that it has made the world live with it. The first case was confirmed in Wuhan City of Hubei Province in China [2]. The virus was named 2019 nCoV and the causative disease as COVID-19 by the WHO in month of February 2020. A retrospective study that has been done at the starting stage of the COVID-19 pandemic reported that the incubation time for COVID-19 was approximately around 5-14 days, but the new report suggest that the incubation period could be about 24 days [3].

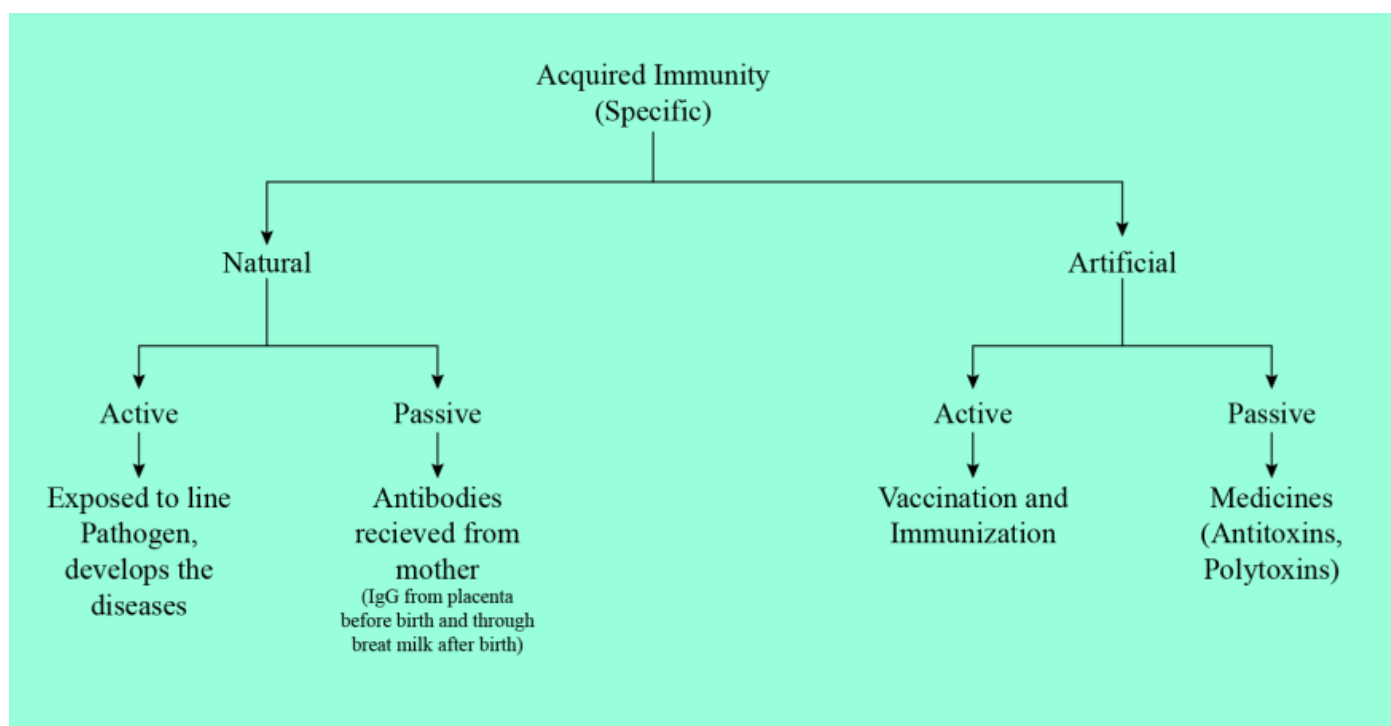
Although in the presence of many anti-viral drugs like remdesivir safety and efficiency are still unclear and they are also in clinical valuation. COVID-19 has no vaccine and curative medicine as of now, it is important to enhance the immune system to fight against the viral infection. Strong immunity will serve as our multi-level defense network against the harmful pathogens, bacteria, and viruses. This increases the demand for several nutrients due to its significant effects on the immune system. The present review gives readers a brief idea about immunity and their types and mainly concentrate on the supplements that boost immunity naturally viz Vitamins, Trace elements, Probiotic supplements, Nutraceuticals, Yoga, and Ayurvedic approach. This insight may help to enhance the immune system naturally.



**Fig.1:Immune system and its branches (Innate and adaptive)**

## Background

Immunity is the capability of multicellular organisms to fight against harmful microorganisms, toxins, and unwanted biological invasions that cause infections and disease. The immune system is mainly made up of cells, special organs, and chemicals that fight against microorganisms. The major parts of the immune system are leukocytes, phagocytes, lymphocytes - T cells and B cells, complement system.



**Fig.2:Acquired Immune system and types.**

### **Nutrition and hydration: Key weapons in the fight against COVID-19:-**

The body is composed of about 70% water. Water is normally lost in urine and stool and from our skin and respiratory tract. When ill with a fever, the body loses water rapidly. For an adult with a fever of 39°C, sweating results in the loss of about 30 ounces of fluid every 24 hours with an additional 3 ounces lost during coughing and breathing. Hydration and nutrition play an important role in your body's response to and recovery from the COVID-19 virus and are an essential part of your medical treatment.[4]

### **Nutritional requirements**

- 1.) Fluid: About 3 quarts (3 liters) of fluid per day<sup>2</sup> Calories: 2000-2500 calories per day?
- 2.) Protein: 75-100 grams per day
- 3.) The optimal fluids to drink are clear liquid beverages with calories and protein and oral rehydration solutions.

### **Fluids**

- 1.) Even though you may not be thirsty or hungry, it is important that you continue to eat and drink fluids to support your body's ability to fight the virus and support your body's immune function.
- 2.) Drink water or clear liquid fluids every hour. At a minimum, you should drink 2-4 ounces of fluid every 15 minutes.
- 3.) Increase your fluid intake as needed to ensure that you are passing light yellow urine every 3-4 hours.
- 4.) If you are vomiting or have diarrhea, make sure that you are taking an oral hydration solution in addition to water.
- 5.) The optimal fluids to drink are clear liquid beverages with calories and protein, oral rehydration solutions.

### **Eat a high calorie, high protein diet**

- 1.) Protein and calories are important to protect against muscle loss while fighting COVID-19, especially if you are bedridden or inactive.
- 2.) Try eating 6 times a day, every 2-3 hours. Eat even if you are not hungry.
- 3.) Calories are important to protect against breakdown of muscle for energy. Due to the increased stress

from COVID-19. you need more calories than your normal diet.

- 4.) Try to eat 75-100 grams of protein per day which is 10-14 ounces of a protein source. Good protein sources are: peanut or nut butters, milk, eggs, yogurt, cheese, meat/fish/poultry, protein shakes.
- 5.) Due to decreased appetite, now is not the time to restrict calories. Eat nutrient dense foods. Drink fruit juice, milk, or other calorie containing beverages.

### **COVID-19 and thermoregulation-related problems: Practical recommendations**

THE COVID-19 pandemic started in the cold months of the year 2020 in the Northern hemisphere Concerns were raised that the hot season may lead to additional problems as some typical interventions to prevent heat-related illness could potentially conflict with precautions to reduce coronavirus transmission Therefore, an international research team organized by the Global Health Heat Information Network (GHHIN) generated an inventory of the specific concerns about this nexus and began to address the issues. Three key thermal and COVID-19 related topics were highlighted:[5]

- 1.) Heat strain in medical personnel caused by wearing personal protective equipment (PPE)
- 2.) Conflicting behavioral recommendations for the general public on how to cope with heat and how to cope with COVID-19
- 3.) Distinguishing heat strain from fever when monitoring body core temperature

### **Preventive measures for heat strain and the relation with COVID-19**

Common preventive measures against heat-related mortality and morbidity in the heat health action plans include drinking enough fluids and limiting exercise to cooler parts of the day. It is recommended to cool down, hydrate, and recover between shifts, as heat stress can increase with consecutive days of exposure.

### **Heat strain reduction during heat exposure and the relation with COVID-19**

Working in protective clothing not only reduces a person's endurance and physical performance, the increase in body core temperature can also reduce cognitive performance. The combination of workload, heat, and PPE can result in heat stress. To minimize heat strain, it is recommended to minimize the clothing insulation and water vapor resistance. Drinking cold fluids attenuates heat storage during work/rest cycles. A progressive attenuation in body core temperature responses is reported with increasing levels of fluid replacement during work.

### **Recommendations of the GHHIN group**

- 1.) Use PPE that is less likely to lead to heat stress
- 2.) Identify symptoms of heat-related illness

- 3.) Cool down, hydrate, and recover between shifts, as heat stress can increase with consecutive days of exposure
- 4.) Stay hydrated and eat regularly. In case of heavy or prolonged sweating ensure electrolyte balance is maintained
- 5.) Maintain or improve your aerobic fitness where possible Similar to medical personnel, the general public is advised to drink sufficient fluids in order to maintain the required hydration level so that sweating is not compromised. Drinking cold fluids. help to lower the body heat storage and resulting body core temperature.

### **Enhancing immunity in viral infections, with special emphasis on COVID-19**

**Introduction and background** Considering the current pandemic of COVID-19 where no effective preventive and curative medicine is available, a healthy immune system is one of the most important weapons. There are several vitamins and trace elements which are essential for the normal functioning of the immune system. Furthermore, supplementation of these have shown positive impact on enhancing immunity in viral infections. Vitamins A and D supplementation has increased the humoral immunity of pediatric patients following influenza vaccination. High dose zinc supplementation has shown immune enhancement in patients with torque teno virus (TTV). Similarly, selenium supplementation has shown a positive response after an influenza vaccination challenge. These data suggest that balanced nutrition can help in maintaining immunity and is essential for prevention and management of viral infections. While data regarding nutrition in coronavirus infection (COVID-19) are not available, Jayawardena, et al evaluated the evidence from previous clinical trials that studied nutrition-based interventions for viral diseases (with special emphasis on respiratory infections). A systematic search strategy was employed using keywords to search the literature in 3 key medical databases: PubMed Web of Science and SciVerse Scopus. Studies were considered eligible if they were controlled trials in humans. measuring immunological parameters, on viral and respiratory infections. Clinical trials on vitamins, minerals, nutraceuticals and probiotics were included.[9]

### **Clinical highlights**

**A)** Among vitamins, A and D showed a potential benefit, especially in deficient populations.

#### **B) Vitamin A**

1.) Vitamin A supplementation to infants has shown the potential to improve antibody response after some vaccines, including measles and anti-rabies vaccination (2.1 times).

2.) In addition, an enhanced immune response to influenza virus vaccination has also been observed in children (2-8 years) who were Vitamins A and D-insufficient at baseline, after supplementation with Vitamins A and D.

#### **C) Vitamin D**

1.) Observational studies predominantly report statistically significant associations between low

Vitamin D status and increased risk of both upper and lower respiratory tract infections.

- 2.) Supplementation of Vitamin D reduced the incidence of acute respiratory infections in older long-term care residents.
- 3.) Vitamin D promotes a higher transforming growth factor beta (TGF- $\beta$ ) plasma level without improving antibody production and suggested that supplementation seems to direct the lymphocyte polarization toward a tolerogenic immune response.

#### **D) Selenium**

- 1.) Low selenium status has been associated with an increased risk of mortality, poor immune function, and cognitive decline, while a higher selenium concentration or selenium supplementation has shown antiviral effects.
- 2.) Selenium supplementation resulted in a dose-dependent increase in T-cell proliferation, IL-8 and IL-10.

#### **E) Zinc**

- 1.) Zinc deficiency has been associated with an increased susceptibility to infectious diseases, including viral infections.
- 2.) In children with pneumonia, zinc supplement showed a statistically significant clinical improvement (duration of illness, respiratory rate and oxygen saturation).

### **Potential inhibitors for SARS-CoV-2 and functional foods to boost immune system**

The severe acute respiratory syndrome is a viral respiratory infection and commonly called as COVID-19, caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). It is widely transmitted through direct or indirect contact. Currently, no specific treatment against SARS-CoV-2 are available; only prevention and supportive strategies are the preventive measures. Recent interest in SARS-CoV-2 has focused on transmission, symptoms, structure, and its structural proteins that exhibit promising therapeutic targets for rapid identification of potential inhibitors. The quick identification of potential inhibitors and immune-boosting functional food ingredients are crucial to combat this pandemic disease.[12]

### **Synthetic inhibitors for the management of COVID -19**

The antiviral drugs that the previous clinical experience of managing this severe acute respiratory syndrome and other virus infection have been used against the confirmed patients of COVID-19. Several possible treatment therapies, including supportive intervention, antiviral drug, anti-malarial drugs, anticoagulants, immune-modulatory agents, nutritional supportive care and convalescent plasma transfusion, have been tentatively applied in the clinical therapy. However, a number of these therapies have provided significant therapeutic benefits in the management of SARS-CoV-2 infection.[15]

## Functional foods to boost the immune system

Functional foods are defined as "the dietary items that are modulated to perform one or more targeted functions in the body", so besides providing nutrients and energy, they also provide their benefits in the diet during effective treatment in the diseases by enhancing the physiological response and/or reducing the risk of disease. Functional food components, including the probiotics and micronutrient supplement, helps to maintain the gut healthy by maintaining the microflora and bacterial colonies, claim to immune-boosting properties (Table 2)

**Table 1. Possible synthetic inhibitors for the management of COVID-19**

Vaccine platform	How it work	example
Affenuated live virus	Live virus that is weakemed to not cause disease	Measles,rubella
Whole inactivated virus	Inactivated dead virus	Influenza,rabies,
Protein subunit	Antigenic viral protein subunit derived from a pathogen is presented to stimulated immunity	Influenza
recombinant	Recombinant cells are engineered and use to produce antigenic viral protein	Hepatitis B
peptides	Synthetically produced fragment of a viral protein antigen	Novel Platform
Replication or non replication viral vector	Viral protein expressed on a safe virus that do not cause disease	Dengu

## Role of micronutrients in boosting immunity to reduce or prevent pregnancy complications in COVID-19 infected women

Pregnancy is a state of physiological changes and partial immune suppression of the body predisposes pregnant women to viral infections. These changes can put pregnancy at higher risk and may increase the risk of pregnancy complications through respiratory viral infection. COVID-19 infection may have adverse effects on pregnancy outcomes, causing problems such as fetal distress, premature birth, newborn respiratory distress syndrome, and even neonatal death. Moreover, Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and Middle East Respiratory Syndrome Coronavirus (MERS-CoV) are also known to be responsible for adverse pregnancy outcomes. Successful pregnancy outcomes and healthy maternal immune systems rely on adequate intake of micronutrients. Micronutrients including vitamins (A, C, D, E.) and minerals (Fe, Se, Zn) have a vital role in sustaining immune competency and preventing adverse pregnancy outcomes.[20]

## **Viral infection and immunity in pregnancy**

- 1.) Immune cells such as natural killer (NK) cells and monocytes respond more strongly to viral infection, however, some immune cells function (T and B cells) are downregulated during pregnancy.
- 2.) Based on the recent literature, COVID-19 infection is associated with cytokine-storm, lymphopenia and inflammation. Pregnant women in their first and third trimester are produced pro-inflammatory state and the cytokine-storm because of COVID-19 infection that may induce more severe inflammation and leads to pregnancy complications.

## **Role of micronutrients in immunity and pregnancy outcomes**

**Vitamin A:** Vitamin A is one of the fat-soluble vitamins known as "anti-inflammatory vitamin". It contributes in the production, regulation, maturation, and functions of the immune cells including macrophages, neutrophils, natural killer T cells, dendritic cells (DCs), innate lymphoid cells (ILC), T cells (Thymus cell), and B cells (bone marrow cells). Vitamin A supplementation has shown a significant reduction in morbidity and mortality in different infectious diseases such as diarrheal disease, measles-related pneumonia, and human immunodeficiency virus (HIV) infection.

**Vitamin C:** Vitamin C in plasma decreases with advancing in gestational age and its deficiency is associated with various pregnancy complications, especially in the third trimester. Its supplementation found to reduce the risk of oxidative stress and may be important to prevent pregnancy complications, including preeclampsia, gestational hypertension, gestational diabetes, IUGR, and endothelial dysfunction.

**Vitamin D:** Vitamin D has various kinds of actions in pregnancy, including its effect on angiogenesis, placental implantation, oxidative stress and endothelial functions. Deficiency of maternal Vitamin D is common in pregnancy due to insufficient dietary intake and less exposure to sun that associated with preeclampsia, preterm birth, low birth weight (LBW), and later in life associated with autoimmune diseases, asthma and type 1 diabetes. Moreover, many observational and randomized clinical trials found that its supplementation is beneficial to both mother and developing fetus.

**Vitamin E:** Vitamin E regulates macrophages which serve as antigen presenting cells (APC) and regulate NK cells and T cells by producing cytokines, while reduces reactive oxygen species (ROS), reactive nitrogen species (RNS), and prostaglandins. It expedites activities of NK cells, regulates the maturation and functions of dendritic cells (DCs), increases interleukin-2 (IL-2) producing capacity of T cells, and enhances the humoral response of immune system.

**Iron:** Iron (Fe) promotes normal growth and development of fetus. Its deficiency affects more than 50% of all pregnant women in both developed and developing countries and may lead to anemia, IUGR. SGA, perinatal morbidity and mortality, induces maternal-neonatal stress, and can damage fetal erythrocytes. Furthermore, Fe deficiency can cause long-term cognitive and behavioral problems in childhood. Iron supplementation in pregnancy showed significantly higher mean birth weight and lower incidence of LBW.

**Selenium:** Sufficient intake of selenium (Se) above the recommended levels has been shown to enhance



immune competence and resistance against influenza infections. During pregnancy, Se levels in maternal blood reduces significantly and causes miscarriage, pre-eclampsia, and IUGR. Its supplementation has a positive effect on hypertension.

**Zinc:** Zinc (Zn) is essential for embryogenesis and normal fetal growth and its requirement in third trimester of pregnancy is two times higher than non-pregnant women. Its supplementation reduces preterm birth, increases neonatal birth weight, reduces incidence of gestational hypertension and increases neonatal head circumference.

### **Fight COVID-19 depression with immunity boosters**

Beyond infection, the COVID-19 pandemic has affected individuals through associated anxiety and stress and caused a collateral damage. Real and perceived fear of infection and distorted daily activities invites psychiatric illness including depression. Void for specific therapeutic measures also contributed to this psychotic illness. A tsunami of psychiatric illnesses will follow as predicted by various organizations and imminent experts. Therefore, attention towards this mental health crisis approaching worldwide is necessary. Along with preventive measures, incorporating immunity boosters', including established food ingredients/herbs, are advised. Recently, uncovering the potential of Ayurveda was exigencies to combat COVID-19 outbreaks through modulation of psychoneuroimmune (PNI) response.[22]

### **Curcumin for psychoneuroimmunomodulation**

Curcumin is the bioactive component of turmeric, one of the key ingredients of prescribed ayurvedic interventions and spices used in meal preparation in South-East Asia. The inter dependent nature of immunity and psychological state is established and decides the outcome of disorders. An immune response can be largely affected by mental well-being, and depression can negatively affect its outcome. Targeting either one of depression or immunity may face insufficiency, dual-acting drug hold promise to improve health amid COVID-19 pandemic. Known for immunoboosting aptitude, curcumin can alleviate the COVID-19 associated ill-effects including cytokine storm. Alleviating psychological stress by curcumin will also adjunct its immunoboosting potential.

### **Mechanism of action of curcumin**

#### **Curcumin**

- 1.) Can avert the anxiety and the stress-driven manifestation of depression through modulation of the monoaminergic troupe (dopamine, glutamate, serotonin, and noradrenaline).
- 2.) Through nuclear factor erythroid-2-related factor 2 (Nrf2), can prevent such stress and improve antioxidant Glutathione (GSH) production. GSH prevents the physiological damage to brain cells during stress. Nrf2 also balances the tone of the immune response.
- 3.) Can correct the HPA disturbances and avert elevated glucocorticoids, their receptor as well as inducers (cortisone and adrenocorticotrophic hormone).

- 4.) Along with evident immunomodulator, turmeric component, especially curcumin exhibit antidepressant activity, and improve cognitive/mood function.
- 5.) Can alleviate the overt inflammatory consequences, even those associated with COVID-19, and thus will improve physical well-being.
- 6.) Ameliorates inflammation and its regulators like STAT3 in a variety of disorders including COVID-19; thus, may improve major depressive disorder through PNI modulation.
- 7.) Can improve the hematopoietic differentiation of immune cells and thus can mitigate its effects even through reinstating immune cells number. Moreover, curcumin improves neurogenesis and hippocampus functioning.

### **Dietary recommendations in the COVID-19 era**

#### **Introduction and background**

Optimal nutrition is one of the main determinants of health that can improve well-being. Nutritional modulation of the immune system is also important across the age spectrum. In individuals infected with SARS-CoV-2, nutritional status is a crucial factor for optimal prognosis and can determine the clinical severity of COVID-19. Dietary supplementation with selected vitamins (eg. A, B, C, and D), minerals (eg, selenium, zinc, and iron), and omega-3 fatty acids has been suggested by some researchers as a treatment option for COVID-19 patients and as preventive therapy against lung infection, although this remains controversial.[25]

#### **Clinical highlights**

- 1.) Consumption of fruits, vegetables, and whole grain foods is recommended as they contain adequate amounts of vitamins and minerals, including Vitamins A, C, D, E, and B complex, as well as zinc and selenium, which are important modulators of the immune system.
- 2.) Micronutrients contribute to immune function through a variety of pathways in both innate and adaptive immune responses.
- 3.) Vitamins A, C, D, E, B6, and B12 and zinc are important for the maintenance of structural and functional integrity of physical barriers (eg, skin, gastrointestinal lining, respiratory tract, and others) as well as for the differentiation, proliferation, function, and migration of innate immune cells.
- 4.) Vitamins C and E, along with zinc and selenium, protect against free radical damage during increased oxidative stress.
- 5.) Vitamins A, C, D, E, B6, and B12 and zinc and selenium support the adaptive immune response by influencing the differentiation, proliferation, and normal function of T and B cells. These nutrients also affect antibody production and function, contribute to cell mediated immunity, and support the recognition and destruction of pathogens. These nutrients have antimicrobial activity

and regulate the inflammatory response.

- 6.) Omega-3 polyunsaturated fatty acids support the immune system by activating cells from both the innate and the adaptive immune systems Omega-9 monounsaturated fatty acids have antioxidant, antimicrobial and antiviral effects.
- 7.) For adult males and nonpregnant/nonlactating adult females, the recommended dosage of omega-3 polyunsaturated fatty acids (eicosapentaenoic acid plus docosahexaenoic acid) is 250 mg/d.
- 8.) Drinking water or maintaining adequate hydration is important as water is essential for cellular homeostasis, kidney function, body temperature control, mood regulation, cognitive function, gastrointestinal and heart function, and headache prevention.
- 9.) Adults with moderate levels of physical activity who consume approximately 2200 kcal/d can meet water recommendations by drinking 12 cups of water and beverages daily, while children require 4 to 5 cups per day, adolescents (9 to 18 years) 7 to 11 cups per day, and older adults 9 to 13 cups per day.
- 10.) Vitamin C supplementation may be useful for individuals at risk of respiratory viral infections. Vitamin C is a recognized antioxidant nutrient that can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and, ultimately, microbial killing.
- 11.) Vitamin D is an antioxidant that has been associated with a reduction infections.in pulmonary
- 12.) Zinc and selenium are antioxidant micronutrients often considered for supplementation. Zinc supplementation (ie, elemental zinc, 30 mg/d) might be adequate to improve immune function and to reduce the risk of infections in the elderly.
- 13.) Selenium has been found to increase the activity of glutathione peroxidase, another antioxidant enzyme, and to augment several host immune responses, including interferon  $\gamma$  production, T-cell proliferation, antigen stimulation, and natural killer cell activity.

## CONCLUSION:-

People with low immunity are more prone for this world pandemic named as COVID-19. To help or boost the immunity, the plant-based foods play vital role by promoting beneficial bacteria in the body. Various vitamins like C, D, and E are investigated to provide important aspects for improving immunity. Fruits like oranges, papaya, kiwi, and guava are rich in vitamin C, while vegetables like eggplant, bell peppers, beetroots, spinach, and cauliflower are known to be quite rich in vitamin C and are good for immunity. A very crucial micronutrient is used in DNA synthesis and cell proliferation, which regulate innate and adaptive immune responses. Vitamin D improves cellular resistance, partially by raising the cytokine storm that the innate immune system causes. Green vegetables like broccoli, mushrooms, and even kale are a few immunity boosters that improve the immune system of older people quite rapidly. Moreover, some herb combination in TCM is also known to play crucial role in the prevention COVID-19. Future aspects of this account for more

research which is needed significantly on physical behaviors or exercises and their role in immunity-related issue thus preventing COVID-19 aspects. More research is needed to know about the behavior of coronavirus and the role of food in its prevention. Immunity-boosting food combinations should be studied which, in combination, provide one and one makes eleven roles. In nutshell, green foods are vital against novel coronavirus by improving the immunity of all aged groups.

## **REFERENCE:-**

1. .Roy A, Patwardhan B, Chaguturu R. Reigniting pharmaceutical innovation through holistic drug targeting. *Drug Discov World*. 2016;17: 45–55.
2. .Bhushan Patwardhan RC. Innovative Approaches in Drug Discovery: Ethnopharmacology, Systems Biology and Holistic Targeting. *Acad Press*. 2016.
3. .Patwardhan B, Vaidya ADB. Natural products drug discovery: Accelerating the clinical candidate development using reverse pharmacology approaches. *NISCAIR Online Period Repos*. 2010; 220–227. pmid:21046974
4. .Patwardhan B, Gautam M. Botanical immunodrugs: scope and opportunities *REVIEWS*. 2005;10.
5. .Saggam A, Tillu G, Dixit S, Chavan-Gautam P, Borse S, Joshi K, et al. *Withania somnifera* (L.) Dunal: A potential therapeutic adjuvant in cancer. *J Ethnopharmacol*. 2020;255: 112759. pmid:32173425
6. .Balkrishna A., Pokhrel S., Singh J., Varshney A. Withanone from *Withania somnifera* May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor. *Virol J*. 2020.
7. .Balkrishna A, Pokhrel S, Singh J, Varshney A. Withanone from *Withania somnifera* May Inhibit Novel Coronavirus (COVID-19) Entry by Disrupting Interactions between Viral S-Protein Receptor Binding Domain and Host ACE2 Receptor. *Virol J*. 2020.
8. .Ghosh S, Saha S. *Tinospora cordifolia*: One plant, many roles. *Anc Sci Life*. 2012;31: 151. pmid:23661861
9. Girme A, Saste G, Pawar S, Balasubramaniam AK, Musande K, Darji B, et al. Investigating 11 Withanosides and Withanolides by UHPLC-PDA and Mass Fragmentation Studies from *Ashwagandha* (*Withania somnifera*). *ACS omega*. 2020;5: 27933–27943. pmid:33163776
- a. \
10. .Ahmed SM, Manhas LR, Verma V, Khajuria RK. Quantitative determination of four constituents of *Tinospora* sps. by a reversed-phase HPLC-UV-DAD method. Broad-based studies revealing variation in content of four secondary metabolites in the plant from different eco-geographical regions of India. *J Chromatogr Sci*. 2006;44: 504–509. pmid:16959127
11. .Patil D, Gautam M, Gairola S, Jadhav S, Patwardhan B. HPLC/Tandem mass spectrometric studies on steroidal saponins: An example of quantitative determination of shatavarin IV from dietary supplements containing *Asparagus racemosus*. *J AOAC Int*. 2014;97: 1497–1502. pmid:25632427
12. Kim S, Chen J, Cheng T, Gindulyte A, He J, He S, et al. PubChem 2019 update: Improved access to chemical data. *Nucleic Acids Res*. 2019;47: D1102–D1109. pmid:30371825
13. Liu T, Lin Y, Wen X, Jorissen RN, Gilson MK. BindingDB: A web-accessible database of experimentally determined protein-ligand binding affinities. *Nucleic Acids Res*. 2007;35: D198–D201. pmid:17145705
14. .The UniProt Consortium. UniProt: the universal protein knowledgebase. *Nucleic Acids Res*. 2016. pmid:27899622
15. Kanehisa M, Furumichi M, Tanabe M, Sato Y, Morishima K. KEGG: new perspectives on genomes, pathways, diseases and drugs. *Nucleic Acids Res*. 2017;45: D353–D361. pmid:27899662
16. .Shannon P, Markiel A, Ozier O, Baliga NS, Wang JT, Ramage D, et al. Cytoscape: A software Environment for integrated models of biomolecular interaction networks. *Genome Res*. 2003;13: 2498–2504. pmid:14597658
17. .Morris GM, Huey R, Lindstrom W, Sanner MF, Belew RK, Goodsell DS OA. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J Comput Chem*. 2009;30:

2785–91. pmid:19399780

18. Dallakyan S OA. Small-molecule library screening by docking with PyRx. *In*Chemical Biol. 2015; 243–250. pmid:25618350
19. Gao Y, Yan L, Huang Y, Liu F, Zhao Y, Cao L, et al. Structure of the RNA-dependent RNA polymerase from COVID-19 virus. *Science* (80-). 2020. pmid:32277040
20. Yan R, Zhang Y, Li Y, Xia L, Guo Y, Zhou Q. Structural basis for the recognition of SARS-CoV-2 by full-length human ACE2. *Science* (80-). 2020;367: 1444–1448. pmid:32132184
21. O’Boyle NM, Banck M, James CA, Morley C, Vandermeersch T, Hutchison GR. Open Babel. *J Cheminform.* 2011;3: 1–14. pmid:21214931
22. Pronk S, Páll S, Schulz R, Larsson P, Bjelkmar P, Apostolov R, et al. GROMACS 4.5: a high-throughput and highly parallel open source molecular simulation toolkit. *Bioinformatics.* 2013;29: 845–854. pmid:23407358
23. Jo S, Kim T, Iyer VG, Im W. CHARMM-GUI: a web-based graphical user interface for CHARMM. *Journal of computational chemistry.* United States; 2008. pp. 1859–1865. pmid:18351591
24. Huang J, MacKerell ADJ. CHARMM36 all-atom additive protein force field: validation based on comparison to NMR data. *J Comput Chem.* 2013;34: 2135–2145. pmid:23832629
25. Borse S, Singh D, Nivsarkar M. Understanding the relevance of herb–drug interaction studies with special focus on interplays: a prerequisite for integrative medicine. *Porto Biomed J.* 2019;4: e15. pmid:31595257
26. Daina A, Michielin O, Zoete V. SwissADME: A free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci Rep.* 2017;7: 1–13. pmid:28127051
27. Girme A, Saste G, Balasubramaniam AK, Pawar S, Ghule C, Hingorani L. Assessment of Curcuma longa extract for adulteration with synthetic curcumin by analytical investigations. *J Pharm Biomed Anal.* 2020;191: 113603. pmid:32957065
28. Patwardhan B, Chandran U. Network Ethnopharmacology Approaches for Formulation discovery. *NISCAIR Online Period Repos.* 2015.
29. Chandran U, Patwardhan B. Network ethnopharmacological evaluation of the immunomodulatory activity of Withania somnifera. *J Ethnopharmacol.* 2017;197: 250–256. pmid:27487266
30. Tillu G, Chaturvedi S, Chopra A, Patwardhan B. Public Health Approach of Ayurveda. 2020;X: 1–5. pmid:32310670
31. Mukherjee PK, Banerjee S, Kar A. Exploring synergy in ayurveda and traditional Indian systems of medicine. *Synergy.* Elsevier GmbH; 2018. pp. 30–33.
32. Nandal, N., & Nandal, N. (2019). BSCQUAL: A Measuring Instrument of Service Quality for the B-Schools . *International Journal of Psychosocial Rehabilitation*, Vol. 23, Issue 04, 1574-1589
33. Yuan H, Ma Q, Cui H, Liu G, Zhao X, Li W, et al. How can synergism of traditional medicines benefit from network pharmacology? *Molecules.* MDPI AG; 2017. pmid:28686181
34. Joshi M, Rajpathak SN, Narwade SC, Deobagkar D. Ensemble-Based Virtual Screening and Experimental Validation of Inhibitors Targeting a Novel Site of Human DNMT1. *Chem Biol Drug Des.* 2016; 5–16. pmid:26850820
35. Hopkins AL, Keserü GM, Leeson PD, Rees DC, Reynolds CH. The role of ligand efficiency metrics in drug discovery. *Nat Rev Drug Discov.* 2014;13: 105–121. pmid:24481311