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MANAGEMENT AGAINST COVID-19 THROUGH NUTRITIONAL SUPPLEMENTATION TO BUILD ADAPTIVE IMMUNITY - A SYSTEMATIC REVIEW

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Keywords:

COVID-19, Adaptive Immunity, Nutrition, Vitamins, Minerals, Immune system

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ABSTRACT: As humanity is progressing, many new borne infections are borne, and the stability and efficiency of the human body are being tested. Today the World is fighting with a deadly Novel infection named Corona Virus Disease. The aim of this systematic review is to find out the efficacy of Nutritional Interventions against the infections caused in the body due to pathogens. Further, the recommendations can be made for further researches based on the evidence collected. To collect the data, electronic databases such as Scopus, Pub Med, NCBI, and web of science have been used. The peer-reviewed journals and newspaper reports are being cited with the English language. The papers were published from 1989 to 2020. Finally, a total of twelve studies were identified, and the pathways of all nutrient metabolisms are included in the study. The studies were mostly carried out in Asian and European countries on human as well as animals. All the studies except one supported the role of Nutrients in preventing and curing the infection caused by pathogens such as Bacteria and Viruses. The Dietary Interventions in any form were proven to have a positive effect on strengthening the Immune system and also curing the disease. The results are supporting that Adaptive immunity can help a person to fight with COVID-19. Mostly the adaptive immunity is built by vaccinations or certain medications. But many researches showed that a diet filled with nutrients and the right choices of food can help to build adaptive immunity.

INTRODUCTION: Coronavirus disease (COVID-19) is an infectious disease caused by a novel coronavirus called SARS-CoV-2 [1]. The symptoms of COVID-19 are respiratory problems and breathing difficulty. The patient experiences flu like symptoms. The sequence analysis showed that the COVID-19 has a distinct genome structure that belonged to the cluster of β-coronaviruses, including SARS-CoV and MERS-CoV[2]. One can protect self by washing hands frequently, avoiding touching face and avoiding close contact (maintaining 1 meter or 3 feet) with people who are infected [1, 2, 3].

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Immunity is basically acquired by the body in two ways; one is the innate immunity, while the other one is adaptive immunity. Innate immunity or the native immunity has its existence from the genes and is not induced artificially through drugs or other external stimulation. It is of two types as (a) Non-Specific innate immunity, which provides resistance to all general infections. Specific innate immunity is the inborn resistance to a particular kind of microorganism. Adaptive immunity is what is acquired through time and contact with a disease-causing agent, by an introduction to deliberate actions such as vaccination [3]. Research Objective To find a Nutritional Cure or Management for COVID-19 through Nutritional supplementation.

MATERIALS AND METHODS:

Role of Nutrients and to strengthen the Adaptive Immunity: The main aim of this review is to impart knowledge to the community about the importance of immune system to fight the diseases.

The present scenario all over the world is to fight with COVID-19 and make different strategies to kill this virus. This review paper is an attempt to help people to manage this disease with their dietary intake. The major limitation is that immunity takes a longer duration of time to be built and we have very less time. But we can try to improve our immune system so that we can efficiently fight with this virus borne disease. But we have to remember that Nutrition supplementation is to be provided to fight the COVID-19.

Tools for Collecting Literature Review: To collect the data electronic databases such as Scopus, Pub Med, NCBI and web of science have been used. The papers were published from 1989 to 2020. Finally, a total of eleven studies were identified and the pathways of all nutrient metabolisms are included in the study. The studies were mostly carried out in Asian and European countries on human as well as animals. The References were checked manually from the reviews and systemic reviews so that they were not identified during the whole search process.

Inclusion and Exclusion Criteria: The studies which correlated the food intake with the building of immunity through nutrients were taken and included.

The studies were also focussed on improving the adaptive immunity by fortification of the nutrients. The studies having gene expressions or drug studies were excluded. Medicinal or herbal studies were also excluded.

Data Extraction: A single-minded approach was used to find out the research being carried out on the role of nutrients to increase immunity.

The country, study design, description of the pathways that how immunity is built was included and then the main results were jotted down.

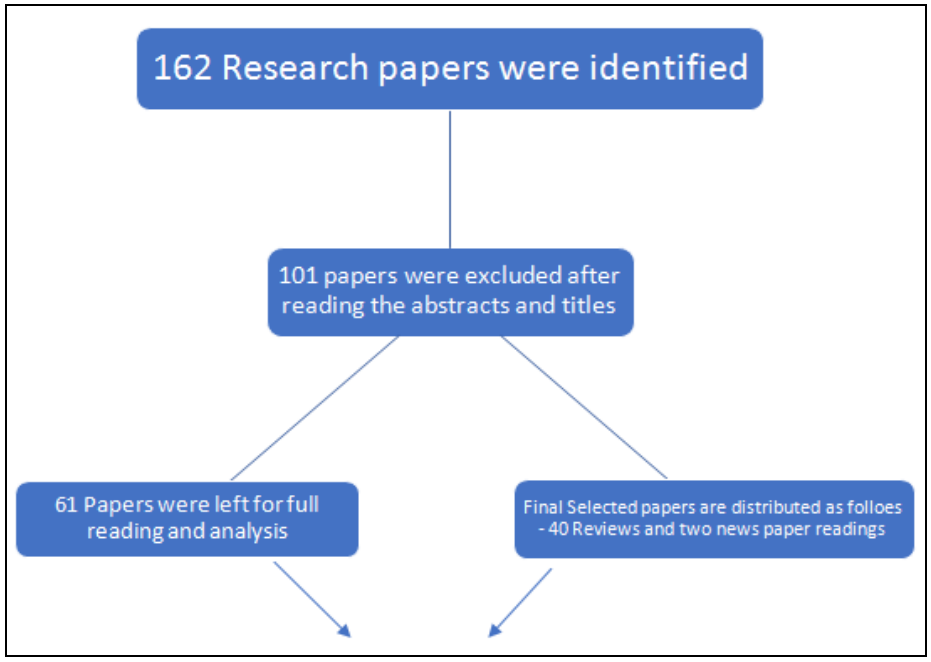
Data Analysis: A narrative synthesis was taken because no uniformity in the case studies was found in terms of the population, gender, or ethnicity. And Metanalysis was not possible in this paper.

RESULTS:

Nutrients: Their pathways and Case Studies in Strengthening Immune System.

Vitamin A:

Nutritional Recommendations to Increase Immunity: Nutrition acts as a modifiable factor in impacting immune system function, and researches in this field are called as Nutritional Immunology. Below are some of the major nutrients that qualify to maintain our Adaptive immunity [41].



Twelve Studies were finally included in the paper. Studies not supporting or with no results shown were excluded. One case study is from recent newspaper reading and rests eleven are from the review papers

FIG. 1: PRISMA DIAGRAM SHOWING THE SCREENING PROCESS

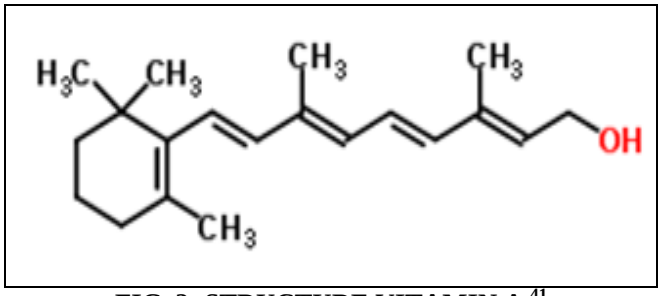


FIG. 2: STRUCTURE VITAMIN A [41]

Vitamin A is a type of fat-soluble vitamin. It is a group of unsaturated monohydric alcohols containing an alicyclic ring [4]. Vitamin A is the most popular nutrient which is studied and recommended to improve immunity. An obser-vation was made that there is a strong link between vitamin A and immunity, even before the structure of vitamin A was deduced [5]. Vitamin A is called as the "anti-inflammation vitamin". It has ability to boost the body's system against the possible attack of pathogens and activate the anti-inflammatory response of the body. Both the innate and adaptive immunity system is affected by the role of vitamin A as it promotes and regulates immune system; thus, enhancing the functions of the immune system and increases the capability of the body to fight against a number of infectious diseases [6] Vitamin A can be obtained from the diet in the form of all-trans-retinol, retinyl esters or β-carotene.

The food products rich in Vitamin A are all yellow food products such as Pumpkin, Carrots, Broccoli, Spinach, Squash, Sweet potato, Mangoes, Papaya, Cantaloupes, Apricots, and fortified Breakfast cereals. Antibody production by B cells is central to humoral homeostatic maintenance. Antibodies represent a specific class of immunoglobulins [36, 37].

Animal experiments have demonstrated that the addition of carotenoid-rich foods to rabbit diets can increase their serum levels of IgG, IgM and IgA, thereby enhancing humoral immunity [7] Vitamin A metabolites affect the adaptive immunity in human body in the most positive way. The Retinoic acid enhances the B and T cell activation, which are responsible for increasing immunity in Human Body. The pathways go as suppose an inflammatory factor is present in body, then the stored Retinoic Acid enhances DC maturation with further increment of IL-2, which activates the B and T cells and the adaptive response is activated [8].

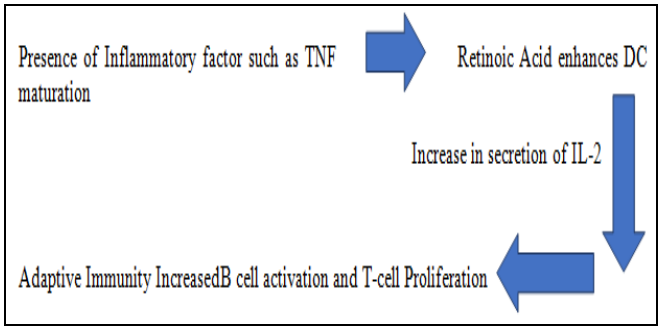


FIG. 3: PATHWAY OF THE ACTION OF VITAMIN A AND ADAPTIVE IMMUNITY

Vitamin C:

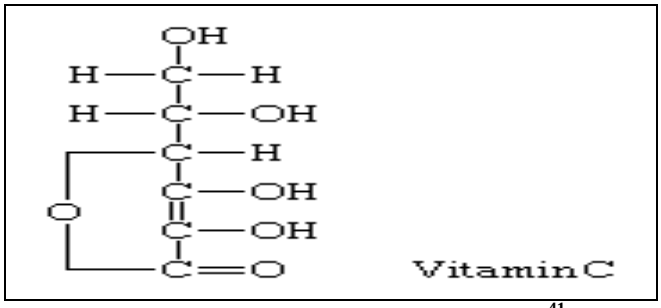


FIG. 4: STRUCTURE OF VITAMIN C[41]

Vitamin C or ascorbic acid is a water-soluble vitamin. The immune system of the body is supported by vitamin C. Vitamin C supplementation has been able to both prevent and treat respiratory and systemic infections and improves activities of the immune system such as antimicrobial and natural killer cell activities, lymphocyte proliferation, chemotaxis and delayed-type hypersensitivity [9.] Vitamin C helps to strengthen the immune system in the following ways: 1). by enhancing the synthesis and stabilization of collagen, 2). providing protection against damages induced by ROS, 3). aiding the process of wound healing, 4). acting as an antioxidant, 5). enhancing phagocytosis & microbial killing and decreasing necrosis, 6). enhancement of levels of antibodies & 7). Through modulating cytokines production *etc.* [9, 10, 11]. The food products rich in Vitamin C are Amla, Lemon, Guava, Oranges, Fruit juices, and tomatoes. According to a Newspaper report, Vitamin C supplementation in high doses of about 1500 mg intravenously was effective for the recovery of Patients suffering from COVID-19. This line of treatment is being used in New York as well as China [12]. The immune mediator Histamine is given birth by Eosinophils, Basophils and mast cells. The Histamines are produced at greater levels when the body is in stress and results in the increased

symptoms of allergy like flu and others. Histamine increases in body, and Vitamin C is depleted in the body. A study was carried on guinea pigs, they were provided with Vitamin C supplementation, and it showed a decrease in Histamine levels, thus reducing the allergy symptoms [13, 14]. The intervention of oral Vitamin C 125 mg per day has helped to decrease histamine levels in patients having allergy symptoms [15].

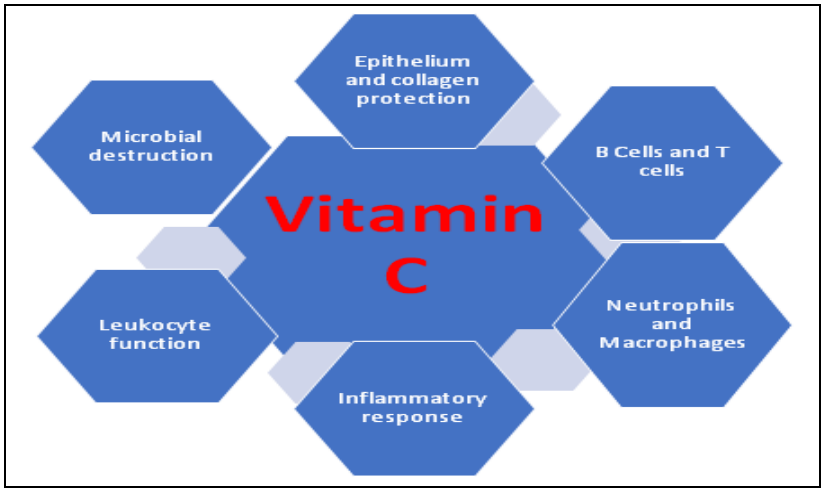


FIG. 5: FUNCTIONS OF VITAMIN C IN HUMAN BODY

Vitamin C has a role in phagocytosis; it increases Neutrophil migration whenever there is chemotaxis and enhances the engulfment of microbes. The Oxidative species of reactive oxygen is increased and it results in killing of microorganisms [13, 39]. The animals who were deficient of Vitamin C showed the microbial invasion, and infection resulted. The generation of reactive oxygen species with the help of neutrophils is enhanced by the supplementation of Vitamin C by 20 percent. A study showed that patients with recurrent infections had impaired Microbial deaths in the body so, with the supplementation of Vitamin C through diet or intravenously, resulted in the killing of infection and condition of the patients improved significantly [40, 41]. This supports the improvement in the condition of COVID-19 patients with Vitamin C supplementation [16].

Vitamin E: Vitamin E is a fat-soluble antioxidant vitamin. It is also one of the most important vitamins needed for the proper functioning of the immune system. Even a minor deficiency of this vitamin can affect the efficiency of the immune response [41]. Supplementation of vitamin E has shown to have various advantages on the immune system, such as increased levels of immune-globulin, lymphocyte proliferation, anti-body responses, natural killer (NK) cell activity and interleukin (IL)-2 productions, enhanced resistance to some specific pathogens and infections [17]. All the vegetable oils and Nuts and oilseeds contain Vitamin E [41]. A case study carried out has shown that Vitamin E supplementation has enhanced immunity in old aged people. The Healthy elderly population was administered with 800 mg 2-ambo-α-tocopherol or placebo/d for 30 days. The results showed increased DTH levels, which is an indicator of cell-mediated immunity. Further, it was found that Vitamin E is related to increased plasma Vitamin E, DTH score, Mitogenic response. These all factors are related to the immunity build up in the body [17]. Vitamin E supplementation of1500 IU d-α-tocopheryl acetate/day for 16 weeks in allergic asthmatic patients resulted in the oppression of alveolar macrophage nuclear factor (erythroid-derived 2)-like 2 (NRF2) activity. This study has positively correlated the role of Vitamin E in managing and preventing the respiratory disorders **Fig. 6** [18]

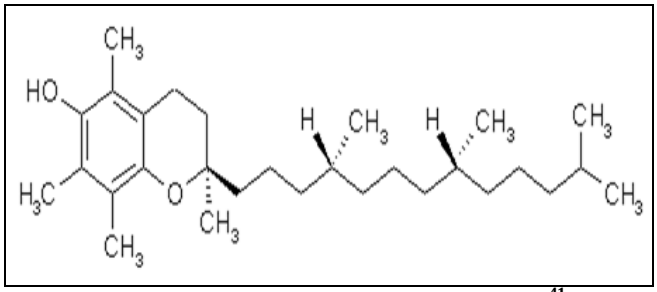


FIG. 6: STRUCTURE OF VITAMIN E [41]

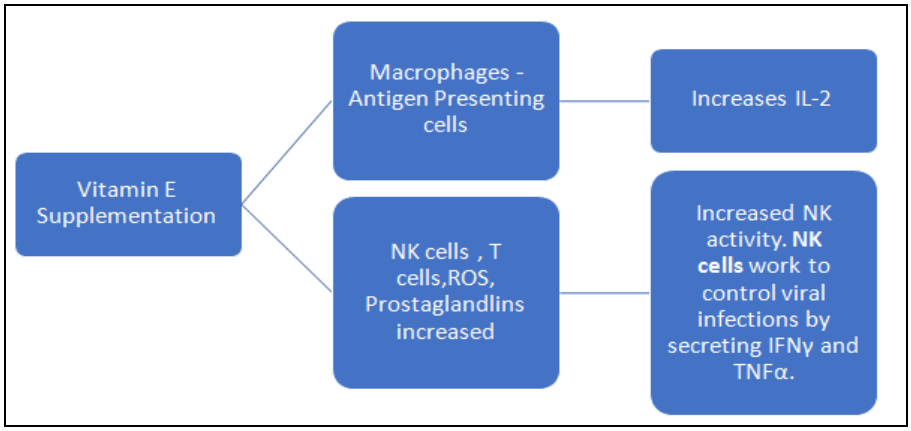


FIG. 7: ROLE OF VITAMIN E IN INFECTIOUS DISEASES IN HUMANS

Vitamin B_9: Also known as folate, it is an essential vitamin for the synthesis of DNA and protein in the body. It is an essential vitamin as it is not synthesized by the body and hence needs to be supplemented through food and drugs. Deficiency of folate affects the immune system adversely since it limits the activities of growth and cell division and also interferes with the production of red blood cells (erythropoiesis) [19, 20]. The vitamin B9 rich foods are green leafy vegetables and nuts [41]. Vitamin B9 is required for the survival of $Foxp3^+$ Treg cells. Studies have shown that Vitamin B9 is responsible for increased levels of Foxp [3-20]. Dietary vitamin B9 maintains $Foxp3^+$ Treg cells in the small intestine, A study was carried out in mice, and it showed that Mice maintained with vitamin B9(-) diet showed less vitamin B9 in the small-intestinal wash than controls. In contrast, the amounts of vitamin B9 in the large-intestinal wash and serum were not different in those mice presumably due to vitamin B9 production from commensal bacteria [19]. Vitamin B9 or Folate is mandatory for the production of protein synthesis. So, Folate deficiency can result in a compromised immune system. The activity of $CD8^+$ T cells and NK cells can be declined due to folate insufficiency, and this declination can result in low resistance of the body to infectious diseases [21].

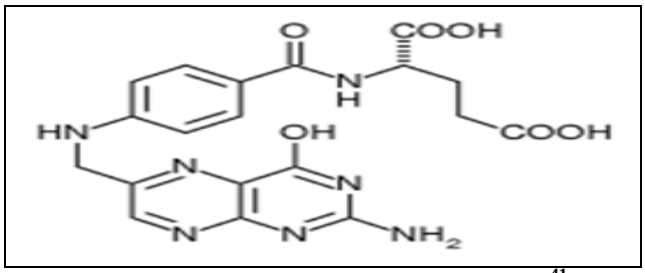


FIG. 8: STRUCTURE OF VITAMIN B9 [41]

Zinc: Zinc is a very important micronutrient needed by the human body when it comes to the immunity. It helps in normal functioning and development of the human cells, which arbitrate the working of innate immunity, killer cells, macrophages and neutrophils [41].

Zinc not only aids the function of the immune system by supporting it to act as a barrier to infection but also affects the gene regulation within lymphocytes. The deficiency of zinc increases the chances of infection and makes the person more prone to a variety of pathogens.

Activities of the human body such as phagocytosis, intracellular killing, and cytokine production are also affected in the state of zinc deficiency [22]. The food products rich in Zinc are Red Meat and Oysters.

The fair sources are grains, peanuts, fruits, and green leafy vegetables. Zinc has a mechanism of getting absorbed through intestines by specific zinc transporting and bound proteins such as albumin, α_2-macroglobulin (A2M), and transferring [23].

Studies show that Patients suffering from Viral Infections such as HIV, Common cold, Chronic Diarrhea or Chronic Hepatitis OR some bacterial infections such as *Helicobacter* pylori or any disease of autoimmune disorders benefit from Zinc Supplementation.

Though Zinc deficiency is hard to diagnose but it is a major nutrient that regulates our immunity. Zinc Homeostasis is essential for haematopoiesis, cell differentiation, and maturation, *etc*. Whenever our body has inflammatory disorders adequate zinc supplementation improves condition [24].

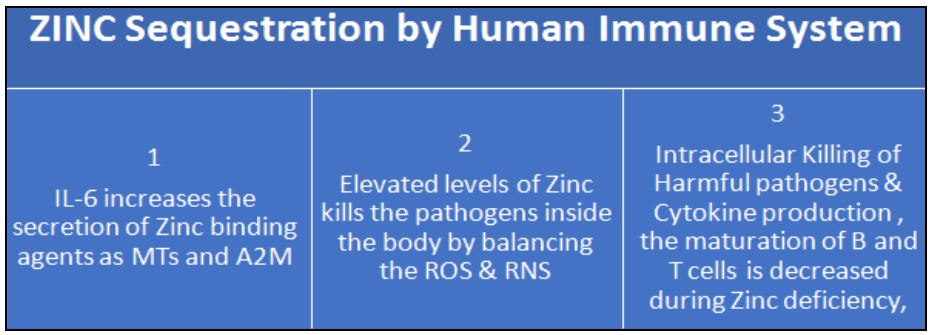


FIG. 9: PATHWAY OF ZINC IN BUILDING ADAPTIVE IMMUNITY

Copper: Copper is also an essential trace micronutrient for the human body for survival. It is a necessity for proper growth, metabolism of iron, functioning of neuroendocrine, elasticity of lungs, cardiovascular integrity and neovascularisation. Deficiency of copper leads to decreased levels of IL-2, T cell proliferation and also reduces the ability to generate superoxide anion and kill ingested microorganisms [25]. The food products which are good sources of copper are oysters, nuts, seeds, shitake mushrooms, lobster, liver, leafy greens , and dark chocolate [41].

Iron: Iron is a much-needed nutrient for normal functioning of immune and non-immune cells biochemical reactions. The effect of the iron homeostasis on the immune function and risk of infection has been recognized in the 1970s [26] Iron is an important nutrient for proliferation and maturation of immune cells, especially lympho-cytes. Not only the deficiency but also the excess of iron can affect the normal functioning of the innate and adaptive parts of the immune system. Excess of iron assists in the development of infections and invasion of diseases [27]. The foods rich in Iron are red meats, nuts, garden cress seeds, fruits rich in vitamin C will enhace iron absorption and liver of chicken and lamb [41].

Iron and Adaptive Immunity: Antigen-specific B and T lymphocytes proliferation starts as the body is being attacked by any foreign material. So, a number of studies were carried out and was found that Iron deficiency can result in impaired phyto-hemagglutin in induced lymphocyte proliferation and delayed-type hypersensitivity responses with relative preservation of humoral immunity [28]. Therefore it is being correlated that Iron is important for lymphocyte working in the body in times of infection [41].

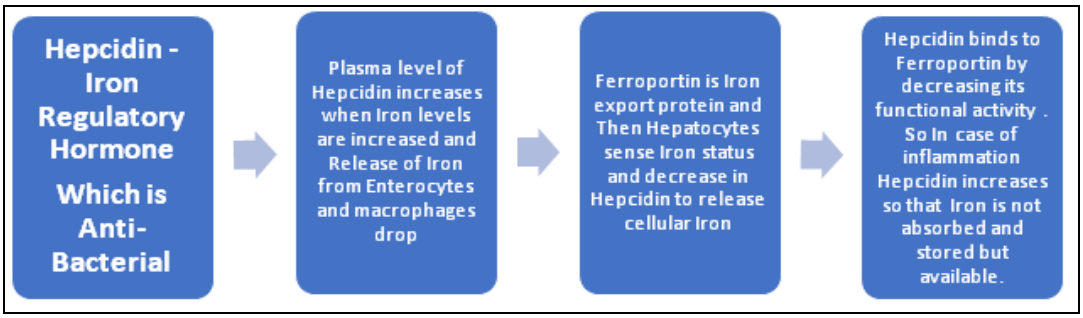


FIG. 10: ROLE OF IRON REGULATORY HORMONE HEPCIDIN IN RESPONSE TO INFECTIONS [26]

The anti-pathogen response of Human body is related to the status of Iron in the system. The infections such as Malaria and Tuberculosis are treated with supplementation of Iron and the success rate is also excellent. The status of the Iron in the body is associated with chronic infections. The link between the non-functional immunity and Iron homeostasis has shown that the transcription factor HIF-1α, which has well-known functions in the immune response, Iron-dependent modulation of NF-κB activation and TLR4 signalling. Iron is being linked positively with combating the infections in the body [29].

Selenium: Selenium, in combination with seleno-proteins, plays a very crucial role in the maintenance of human health. The deficiency of selenium has been associated with increased susceptibility to diseases caused due to oxidative stress, while supplementation of selenium showed

increased resistance to diseases and viral infections [30]. Selenium influenced both the components of the immune system- innate, the non-adaptive one, and acquired the adaptive one. It can also be called as an immunity booster; selenoproteins play a very important part in oxidative stress reduction and redox balancing in tissues and cell types [32]. The food products rich in selenium are Pork, beef, turkey, chicken, fish, shellfish, and eggs [41].

Selenium and Viral Infections: The studies conducted at Beck Laboratory on mice showed that Selenium deficiency alters the immune system under the attack of viral infections.

It was studied that the mice suffering from influenza were having inflammation due to higher levels of oxidative stress. It was found in early stages of the infection that macrophages were present at larger levels with selenium deficiency, and later, the levels of macrophages, $CD8^+$, and $CD4^+$ T cells were lower in Se-deficient mice. This showed that Se-deficiency affects cell-mediated immunity to a greater extent than humoral immunity for anti-influenza viral responses in this model [30, 31]. Selenium is said to increase the general immunity but the mechanism or the pathway that selenium takes to increase immunity is still not very clear [32].

TABLE 1: RECOMMENDED DIETARY ALLOWANCES FOR INDIANS TO INCREASE IMMUNITY

Nutrient	Recommended Dietary Allowances	Recommended Dietary Allowances
	Male (Adult)	Female(Adult)
Vitamin A(Retinol)	600 (Micrograms/day)	600 (Micrograms/day)
Vitamin C	40 (mg/day)	40(mg/day)
Vitamin E	15 (mg/day)	15 (mg/day)
Vitamin B9	200 (Micrograms/day)	200 (Micrograms/day)
Selenium	400 (Micrograms/day)	400 (Micrograms/day)
Copper	900 (Micrograms/day)	900 (Micrograms/day)
Iron	17 (mg/day)	21 (mg/day
Selenium	400 (Micrograms/day)	400 (Micrograms/day)
Zinc	12	10

Source – ICMR, 1989, 2007 40, mg - milli grams

CONCLUSION: Nutrition and Infection works as a good nutritional status leads to less infections and vice versa. The deficiency prevailing in body could be improved by supplementation of Nutrients in accordance to recommended dietary allowances, which could strengthen the immune system in return. Adaptive Immunity is the system that our body designs to fight any foreign body, which is new to the human system. So this theory itself explains the people recovering from corona attack are young people with strong immunity, Old age people have weakened immunity and same is with the children. According to World Health Organization (WHO) 55 years is the beginning of old age and also WHO says that the old age is the start of losing active life, loss of previous roles, or inability to make active contributions to society. The ageing results from the destruction of cells at molecular levels and then there is slow reduction in the physical and mental capability and then old people become prone to diseases and untimely death [5]. One of the most important factors adding up to the competency of the immune system is the nutritional status.

If a person is undernourished, he/she is more susceptible to infection and diseases since the activities of the immune system get suppressed due to lack of energy and important nutrients intake. The other reason can be specific nutrient or of more than one nutrient deficiency Essential nutrients needed for the efficient functioning of the immune system include Vitamin A, Vitamin C, Vitamin E, Essential amino acids, Essential fatty acid, Linoleic acid, Folic acid, Zinc, Copper, Iron and Selenium [39]. The infections prevail according to life cycle like the infants and geriatrics population has weak immunity. And it can be altered with interventions easily. The intervention features can be a vaccine or drugs or the dietary intake with lifestyle changes. The dietary supplementation should be tailormade in accordance to the age, gender, ethnicity and heredity as well [33, 34].

The present review encapsulates that micronutrients in diet or in form of fortification can result in recovery from the disease. The deficiency of micronutrients may lead to the development of many infections due to pathogens and also decrease

the body's ability to fight with life threatening infection such as COVID -19. We are not claiming the treatment of the COVID-19, but the life-threatening diseases could be managed well through the sufficient supply of micro and macronutrients; therefore a balanced diet can increase the chances to fight back with the infections.

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CONFLICTS OF INTEREST: Nil

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