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REVIEW ARTICLE

FAT SOLUBLE VITAMINS AND MICRONUTRIENTS IN THE PANDEMIC OF COVID-19:EVIDENCE BASED EFFICACY FROM LITERATURE REVIEW

Ms. Snehal S. Gadhave[1], Dr. Aishwaryadevi Deshmukh[2] and Ms. Sayali S. Gadhave[3]

1. Dattakala Shikshan Sanstha's Institute of Pharmaceutical Science and Research (for girls), Swami-Chincholi, Bhigwan, Ta Daund, Dist Pune Pin 413130
2. Sinhgad Technical Education Society's Smt. Kashibai Navale College of Pharmacy. Kondhwa (Bk), Pune 411048.
3. Rajmata Jijau Shikshan Prasarak Mandal's College of Pharmacy, Dudulgaon, Pune 412105.

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Abstract

In the entire world COVID-19 disease has been spread rapidly in December 2019 and now it has been almost 2 years we are facing the trouble of COVID-19 disease condition. Till now we have very less evidence based options for the treatment and prevention. In the COVID -19 Pandemic public health being focused towards the healthy living, hygiene and nutritional dietary routine. COVID-19 patients are at the high risk of nutritional imbalance and thus weak immunity. Due to lack of the specific treatment preventive measures have been focused majorly and here nutrition plays the important role. Since ancient times, nutritional diet, micronutrients and vitamins have been proved best to boost the immunity against viral infections. Deficiency of micronutrients and fat soluble vitamins leads to the weak immunity. Several statistical data and evidences shows that people with weak immunity are being targeted by COVID-19 Virus.Various cross-sectional study, data analysis and clinical trials have been performed to investigate the role of micronutrients in COVID-19 diseased condition. Several recent reports have found the greater risk for the COVID-19 patients associated with other severe diseases like respiratory tract infection, kidney related problems, diabetes, hypertension Etc. Detailed Clinical Trials will be focused more in the future.The various available scientific data, evidences, statistical analysis, reviews, surveys and clinical trials are studied and the collection of these information together forms this effective article. I ensure that, due to the research based evidences presented in this article, this article is being the worthy in all.

Introduction:-

COVID-19 is the deadly respiratory disease first detected in Wuhan, China on December 2019 [1]. As it has been spread (And continues to spread rapidly) worldwide and has become a serious health problem. World Health Organization (WHO) declared it as a global pandemic in 11 March 2020. COVID-19 causes severe damage to the lung tissues, respiratory tissues and to the immune system. In severe cases COVID-19 can cause pneumonia, severe

Corresponding Author:- Ms. Snehal S. Gadhave
Address:- Dattakala Shikshan Sanstha's Institute of Pharmaceutical Science and Research (for girls), Swami-Chincholi, Bhigwan, Ta Daund, Dist Pune Pin 413130.

acute respiratory syndrome, kidney faire, and death [4]. Any person from newborns to people with 65 years and older are affected by COVID-19, it has been shown that the most serious consequences occur in individuals with chronic diseases, Older people and those with weak immune systems [5]. Patients with COVID-19 have a higher nutritional risk [3].

Till now we don't have specific treatment to treat the COVID-19 disease but we are trying to control and or to treat COVID-19 disease by the various complementary ways like antimalarial drugs, antivirals, plasma therapy and so on. Also to prevent the COVID-19 disease, the best supplement is decoction, vitamins and micronutrients. There are many vitamins, micronutrients and trace elements necessary for the normal functioning of the immune system

Fat soluble vitamins and micronutrients are proved best to boost the immune system and their deficiencies can affect the immunity. There are two major types of Immune system, innate immune system and adaptive immune system. Innate immune system is non-specific immune system which provides general defense mechanism whereas Adaptive immune system is the specific immune system which makes the antibodies for fighting against certain germs which body has previously came into contact with, thus this is also called as acquired or learned immune response. Adaptive immunity is specific to T cells and B cells [9].

Proper nutrition will definitely help in the improvement of immune system, with reducing the impact of infections. Adequate nutritional diet is necessary for the development and maintenance of the immune system. Decreased nutritional status increases the severity of the infection.

Micronutrients plays an essential role in supporting the immune system as well as to maintaining the structural and functional integrity of the physical barriers such as skin and the mucous membrane. Supplementation of the micronutrients plays the major role in enhancing resistance to the infection.

Several vitamins and trace elements supports the cells of immune system [2]. As per the research study, it has been found that due to the early administration of nutritional support mortality rate and poor clinical outcomes such as admission to Intensive Care Unit (ICU), readmission to the hospitals, impaired functional status and major complications has been reduced up to 35 % [3].

Several clinical trials have been performed on the micronutrients for identifying the key function of micronutrients against the COVID-19. Many experiments, investigations and clinical trials have been performed whereas some micronutrients are still being focused for their great role against COVID-19 and other infectious diseases.

Micronutrients, Immunology and COVID-19

Nutrition must be always at the higher priority. Immune system functions as the first line defense and thus adequate amount of nutrients are mandatory. Impaired nutritional status enhances the severity of the infectious disease. Low amount of micronutrients can cause deficiency whereas high amount of micronutrients can be toxic to the health. Depletion or higher consumption of micronutrients can prove risky for the weak immune people as well as

unhealthy people. Thus it is necessary to maintain the optimum balance of each micronutrients and to avoid the infectious diseases.

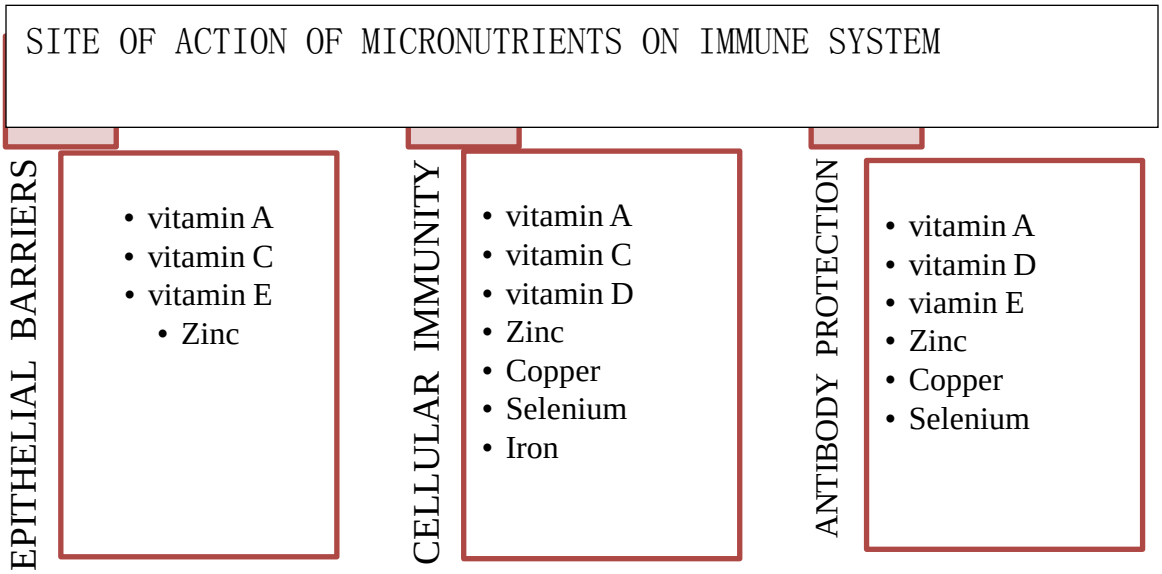

Fig 2:- Role of Micronutrients in Improving the Immune System.

(Referred from: Sunita Mishra, Monika Patel, "Role of Nutrition on Immune System During Covid-19 Pandemic" Food, Nutrition & Health, Accepted on September 01, 2020; 02

Nutritional diet plays an important role for the normal daily routine and especially in the sick and infectious conditions. There are two types of nutrients as macronutrients and micronutrients. Macronutrients are specially proteins whereas micronutrients can include fat soluble vitamins such as vitamin A, vitamin K, Vitamin D and vitamin E and several trace elements like copper, selenium, magnesium and zinc.

Various evidences have suggested that micronutrients has key role in maintaining and enhancing the immune functions by the various mechanisms.

Sr no.	**Vitamins and Micronutrients**	**Dietary Sources**	**Role in COVID-19**
1)	Vitamin A	Milk, Cheeze, Fruits, Green Vegetables, Carrots, Amaranthus, Etc.	Core targets of vitamin A used for management of COVID-19. Inhibits viral Replication and reduces morbidity and mortality rate of COVID-19.
2)	Vitamin C	Citrus fruits, Guava, Green vegetables, Potatoes, ?Tomatoes, Milk	Improves the resistance against viral infection. Decreases severity of RTI and thus risk of COVID-19 infection.
3)	Vitamin D	Fatty fish, Fish liver oils, Egg yolk, Natural foods, Irradiating foods like yeast, Fortification foods like milk, butter and from sunlight.	Vitamin D decreases viral docking by reducing ACE 2 receptors. Vitamin D functions as protective against respiratory infection and reduces the risk of COVID-19.
4)	Vitamin E	Nuts, Seeds, Fortified cereals, Green Leafy Vegetables, Spinach, Mango, Sunflower oil.	In the COVID-19 patients, vitamin E helps immune cells to defense oxidative damage. It boosts immune system.

5)	Vitamin K	Cabbage, Tomatoes, Green vegetables, Spinach, Egg yolk, Meat, Dairy products.	Vitamin K administration decreases the D-dimer protein level and it reduces the severity in COVID-19 patients.
6)	Zinc	Meat, Dark chocolates, Shellfish, Pumpkin seeds, Dairy products, Eggs, Poultry, Cheese.	Reduces severe respiratory illness. Zinc supplementation in COVID-19 patients targets the ACE2 receptors and reduces the risk of COVID-19 diseases.
7)	Omega-3-Fatty Acids	Walnuts, Canola oil, Soybeans, Marine fish, Spinach.	Improves acute lung injury and acute respiratory distress syndrome and reduces severity of COVID-19 infection.
8)	Iron	Dried beans, Dried fruits, Liver, Eggs, Lean Red Meat, Poultry, Fortified cereals, Oysters	Iron supplementation plays vital role in host-defense mechanism and declines the risk of COVID-19 disease.
9)	Selenium	Nuts, organ meats, Cereals, Grains, Dairy products.	Selenium produces and develops the antibodies, improves the immune response against viruses and reduces the risk of COVID-19 infection.
10)	Copper	Shellfish, Beans, Nuts, Potatoes, Dark leafy green vegetables, Black pepper, Yeast, Dried fruits Whole grains.	Copper is used for the production of antibodies and it functions as a self-protective of immune cells. Copper shows the preventive effects against COVID-19.

Fig:- Fat Soluble Vitamins and Micronutrients with Their Sources and Role in COVID-19 Infection.

Vitamin A

Vitamin A is also called as "Anti-inflammatory Vitamins" It is fat soluble vitamin which is present in the body in three different forms as retinal, retinol and retinoic acid [13]. Vitamin A has an importat role in regulation of the immunity and metabolism. It has been considered as 'anti-infective agent' because of its effectiveness in infection [14]. Also it reduces the morbidity and mortality rate causing due to infectious disease. Multiple studies have proved that Retinoid consists of Interferon-1 (IFN-1) i.e. robust immune modulating channel possess antiviral activity. In the recent study, seven core targets of vitamin A have been investigated against COVID-19. Those core targets are MAPK1 (Mitogen Activated Protein Kinase), IL10 (Interleukin 10), EGFR (Epidermal Protein Growth Factor Receptor), ICAM (Intercellular Adhesion Molecule), MAPK14 Mitogen Activated Protein Kinase 14), CAT (Catalase), PRKCB (Protein Kinase C β).

The various studies proved that Vitamin A has beneficial potential role in the management of COVID-19. Vitamin A plays the main role in development and differentiation of B cells and regulates the natural killer (NK) cells, neutrophils and macrophages which regulates the cell mediated immunity and it ultimately regulates the innate immune system [6]. Viral replication is inhibited by Vitamin A thus morbidity and mortality rate is inhibited and it promotes the immune response [7].

Vitamin C

Vitamin C is also known as an ascorbic acid, which is water soluble vitamin but beneficial micronutrient. It functions as protective against various viral infections, mainly it functions as an anti-oxidant. Vitamin C improves the resistance against the viral infections.

Human clinical trials reported that it reduces the flu-like symptoms like cold, sneezing, runny nose as well as it decreases the severity and duration of the respiratory tract infections. It increases the immune system by enhancing the development and maturation of lymphocytes [11]. Vitamin C is the cofactor for various enzymes which are involved in biosynthesis and gene regulation process. Also it has the potential to regenerate the vitamin E [8]. It decreases the potential damage of the infected tissue [13]. Due to deficiency of Vitamin C, it causes impairment of immunity which has highest susceptibility to the infection which increases risk of pneumonia and it increases the severity of diseases leads to morbidity in patients with COVID-19.(10) Vitamin C supports the differentiation and proliferation of lymphocytes, B cells and T cells, and promotes the function, production and migration of immune

cells it ultimately enhances chemotaxis, supports the production of antibodies, IFN production and reversible cell death which may helpful in reducing the mortality rate of COVID-19 patients [12, 16].
Clinical trials and several experimental study suggests that vitamin C inhibits pro-inflammatory cytokines and it exerts antiviral immune response [15].

According to several investigations, vitamin C at high doses kills the viruses as well as supplementation of vitamin C in COVID-19 patients shows the reduction in severity of respiratory tract infections which may reduce the risk of COVID-19 infection [17, 18].

A Cochrane review analyses that administration of vitamin C decreases the frequency of infections [19].

Meta-analysis performed for vitamin C shows that, intravenous administration of vitamin C as a regular treatment, COVID-19 patients showed the improvement in the clinical outcomes. (20) Hence new controlled trials focuses on the results of intravenous administration of vitamin C in the COVID-19 patients [21].

The phase II clinical trial was being conducted at Virginia, USA, study has been completed in May 2021 and it has proved as efficacious.

Recently, Diao et al. did retrospective review in 499 COVID-19 patients and he found reduction of count of T cells in his study. This investigation could enhance the recognition of role of Vitamin C in the prevention and treatment of COVID-19 [9].

Conclusion of recent reviews states the supplementation of vitamin C reduces symptoms of acute respiratory and lung viral infections additionally it reduces the incidence and duration of hospital stays [21].

Vitamin D
Vitamin D is the fat soluble vitamin synthesized in skin with the exposure of ultra-violet sunlight as well as it is derived from the diet. Daily vitamin D supplementation is advised by British Food Safety Authority [22].

Vitamin D promotes monocyte precursor's differentiation, prevents tissue damage and decreases the inflammatory response [23].

Vitamin D has potential antiviral activity also it enhances recovery and being protective against respiratory infection. Activity of ACE 2 is directly linked with Vitamin D. Vitamin D acts by reducing the viral docking potential by reducing the activity of ACE 2 receptors [24]. Thus Vitamin D plays an essential role for immune system by various mechanisms, it induces the production of antimicrobial peptides like Cathelicidine, human B defensing from the immune system cells [25, 26]. Vitamin D enhances TLR and CD14 expression which increases the antimicrobial activity [27].

According to reports of several meta-analysis administration of vitamin D results in the reduction in the incidence of respiratory tract infections [26]. Recently various reviews and meta-analysis of 25 randomized clinical trials have been performed and observed reports shows the decrease in the incidence of acute respiratory tract infections due to daily or weekly administration of vitamin D [28]. As per Cohort data, insufficiency of vitamin D increases the chances of respiratory mortality [29]. According to recent systematic reviews and meta-analysis of 28 publications concluded severity of COVID-19 patients due to inadequacy of vitamin D [30].

Cohort study on 57 patients in the French states that enhanced clinical improvements of COVID-19 patients were associated with supplementation of vitamin D [30].

According to study of Ilie and colleagues, there is correlation between mean Vitamin D level, COVID-19 cases and deaths in each country.

In New Orleans, Lau et al. described the higher insufficiency of Vitamin D in the COVID-19 hospitalized patients (admitted to Intensive Care Unit). According to study performed in Wuhan, China on 2013-2016, supplementation of vitamin D is associated with decrease in the respiratory tract infections [31].

Recently, Pilot study shows that administration of high dose of 25-hydroxyvitamin D reduces need of ICU for the COVID-19 patients [2].
Several researches shows that administration of vitamin D reduces the hazards for viral infections and thus can be beneficial for the effect of immunoregulation.

Several large scale clinical trials for detection of vitamin D in COVID-19 are being studied for the outcomes of better results [32].

Vitamin E
Vitamin E is the fat soluble vitamin which has high metabolic activity also they can protect the Polyunsaturated Fatty Acids (PUFAs).

Vitamin E supports and increases the integrity of epithelial membranes and it increases activity of the NK cells, IL-2 production, function of T cells as well as proliferation of lymphocytes also vitamin E prevents the oxidative damage of the cells and collectively it boosts the immune system [33].

Several studies suggests that due to the presence of high concentration of Vitamin E in the immune cells of COVID-19 patients, it defends them from oxidative damage. Vitamin E increases the chances of infection resistance.

According to several studies, onset of severe lungs injury in COVID-19 patients is due to activation of oxidative stress mechanism. There are little evidences of antiviral activities of Vitamin E whereas they have direct and indirect effect on immune cells especially T cells. Investigational study of Vitamin E is still ongoing although it shows immune-regulatory and preventive function from oxidative disruption.

Vitamin E is an important nutrient in COVID-19 still there is no recommend dosage estimate is available while 15 mg per day is recommended dose for healthy individuals [34].

Some investigations proved the effective role of vitamin E in defense mechanism against few infectious diseases [34].

In-vitro study have been suggested that deficiency of vitamin E causes the increase in viral pathogenicity whereas administration of vitamin E activates the immune system by enhancing the antibody response [36].

Vitamin K
Vitamin K is beneficial for synthesizing the several proteins. Sources for vitamin K are green leafy vegetables and fermented foods like animal liver, cheese and curd.

Vitamin K and vitamin K dependent proteins have main role in the calcification, energy metabolism and inflammation [37, 38]. Vitamin K modulates the Anti-inflammatory activity through the NF-kB signaling [39]. Vitamin K acts as potent oxidant and it used in the reduction of lipid peroxidation in the cells [40, 41].

Recently researchers have found the link between vitamin K status of the patients and COVID-19 status. Decreased level of vitamin K is reported in the COVID-19 patients, [42] Also, one of the most common laboratory findings suggests that D-dimer level is elevated in the COVID-19 patients. COVID-19 Patients which are hospitalized in ICU are having the great risk of vitamin K deficiency with elevated D-dimer protein level [36]. It is postulated that Vitamin K deficiency may be associated with severity in COVID-19 patients [43, 44] Furthermore detailed study is required to investigate whether administration of vitamin K improves the severity of COVID-19 patients.

Zinc
Zinc is the essential micronutrient which is found in fruits and vegetables. Normally all cells in our body contains zinc. Zinc functions for maintaining and enhancing the innate and adoptive Immune system Also, it plays major role in preventing the lower respiratory tract infection as well as in the host-virus interaction. Zinc deficiency occurs due to stress or inflammation [45]. And its deficiency leads to higher risk of respiratory tract diseases as well as enhances the pro-inflammation cytokines, reduces the activity of lytic NK cells which may weakens the immune system [46]. Zinc supplements are proven to reduce the morbidity and mortality rate. Immune system dysfunction

may be majorly due to zinc deficiency which impairs the NK cell activity, T cell mediated antibody response and macrophage / neutrophil phagocytosis activity that weakens the immunity [47].
Zinc has shown the antiviral activity by effectively impairing the replication of corona virus, inhibiting activity of RNA polymerase and by inhibiting protease activity [48].

Recent study shows that, zinc is used in COVID-19 essentially for targeting the ACE 2 receptors which enters the host cells [13].

Speeth et al. is the scientist who found that with the help of Zinc, activity of ACE2 receptors in the lungs of rats were reduced. Recent case study was done on COVID-19 confirmed patients, study shows significant improvement with the high dose of zinc salt [49].

Several clinical trials suggests that zinc supplement improves the reduction of viral infection by the immunotherapy [49].

Recently reviewed scientific proofs proves that optimal intake of Zn is works as the main strategy to reduce COVID-19 [51]. Much evidences focuses the strong review of zinc in the immune system and wound healing [52]. Currently, clinical trials of zinc treatment is being performed for identifying its role in COVID-19 patients [53)].

Omega 3 fatty acids
Omega 3 fatty acids are the poly unsaturated fatty acids (PUFA) with presence of double bond at omega 3 carbon atom. Omega 3 fatty acid plays an essential role in the body by forming the structure of cell membrane. Also omega 3 fatty acids provides energy to the body and having immune regulatory function in the body. Although, it is not formed in the body, they must be obtained from diet. Omega 3 fatty acids has a crucial role in the interferon induced inflammation in the respiratory tract [54].

Recent investigation on COVID -19 shows that omega 3 fatty acids reduces the risk of infection to lower respiratory tract and gives the modulatory effect on systemic inflammation [2]. More detailed study is required to detect the role of omega-3-fatty acids in reducing the COVID-19 infection as well as other infectious diseases.

Iron
Iron is the effective micronutrient which is obtained from red meat, fish, poultry, shellfish, eggs, legumes, grains and dried fruits.

Iron plays an important role in development of immunity. Error can be seen in host defense mechanism or host immunity due to iron deficiency whereas higher dose of iron can cause viral mutation. Iron is seen to be useful in case of acute respiratory tract infection as well as in the upregulation of immune response. Iron metabolism is controlled by innate immune response [55]. Ability of immune system is reduced due to iron deficiency while overload of iron weakens the immune response to the viruses and it can cause higher risk of COVID-19 [56, 57, 58].

The retrospective analysis of COVID-19 hospitalized patients indicates prolonged hospital stay and or progressive inflammation is linked with functional Iron deficiency [13]. Research have recommended that low iron level affects the ability of sufficient immune response [59].

According to retrospective study performed on hospitalized COVID-19 patients demonstrated that it shows the decreased serum iron concentration and it causes the severity of diseases [53].

Selenium
Selenium is crucial trace element functions as antioxidant and involved in the processes like differentiation, proliferation, production and development of antibodies as well as normal functioning of innate immune system [60].

Viral genome mutation is occurred due to weakened immune system which is observed due to selenium deficiency, eventually it increases the viral infection [61]. Decreased cytotoxicity of NK cells, antibodies and imbalanced cellular immunity are the main reasons for selenium deficiency. Selenium deficiency causes the mutation of RNA

virus [62]. Reduction of selenium status decreases the recovery rate and simultaneously increases the death rate of COVID-19 [63, 64].
Supplementation of selenium improves the cellular immunity and it improves the immune response against viruses [45].

Recent study performed in China detects the significant correlation between selenium status and outcomes of COVID-19 cases [60].

Results of retrospective studies performed on 18 February 2020 shows the positive correlation for the COVID-19 recovered patients. Data for the selenium is not much conclusive. Logically it is assumed that strategy for the prevention of viral infection has been represented with optimum amount of selenium [66]. Various proofs of selenium have been found that it plays a key role about the immune system function [67]. As per the evidences it has been concluded that lack of selenium in the body is connected with occurrence and severity of viral infectious diseases [67, 68].

Several clinical trials revealed that selenium administration is used for increasing the proliferation of lymphocytes, activity of NK cells and increase in the expression of IL-2 receptors [69]. The evidences shows that selenium alone or in combination with other nutrients exert the great immune response for the antivirals also it shows the resistance for the different viruses [70]. According to recent study, 64.7% inadequacy of selenium found in COVID-19 patients [71].

Copper
Copper is proved to be an essential nutrient for the development and maintaining of the immune system. Copper play main role in production of IL-2, antibodies production, balancing of the intracellular anti-oxidant for the adoptive immune cells as well as self-protection of immune cells [72, 73]. Reduction of phagocytic ability, proliferation of T cells and reduction of IL-2 level as well as enhancement in the viral virulence can be seen due to depletion level of copper [74].

Potent anti-viral activity is exhibited by the optimum supplementation of copper [75]. Copper plays vital role in the control of pulmonary infection [76]. Due to the administration of copper by the intravenous route, it results I the greater concentration of copper in the lungs [77]. It has been suggested that copper irreversibly alters the viral morphology and demolishes the viral genome and thus it shows the effectiveness as an antiviral [78].

Several in-vitro study shows that fundamental protein replication is blocked by Copper ions [79].

As per the various evidences it has been hypothesized that optimum quantity of copper level increases the immune and adoptive immunity as well as it exerts the preventive and therapeutic effect against COVID-19 [80]. Recent review identifies that copper is the main candidate to study its combination with other drugs for the strategic treatment of COVID-19 [81].

Discussion and Conclusion:-

Healthy diet and great nutrition is needed to improve the immune system for achieving the protection and to defend the infectious diseases. From the ancient study it has been proved that fat soluble vitamins and micronutrients plays the vital role to boost the immune system whereas recently it has been studies with the various ways such as reviews, surveys, meta-analysis, clinical trials and in-silico approaches to identify its role in COVID-19 disease. By considering these evidences it has been concluded that due to unavailability of specific treatment for COVID-19, preventive measures should be followed to avoid the disease and thus nowadays globe has focused towards the use of vitamins and micronutrients. Also special attention should be given to the vitamins and micronutrients for nutritional and healthy diet to enhance the immune system and to prevent the infectious disease.

Nowadays, researchers started to observe and link the vitamins and micronutrients with the COVID-19 outcomes. Diagnosis of deficiency of vitamins and micronutrients will help to increase the preventive strategy to minimize the severity of diseases and enhance the immune response. Currently published data confirmed the role of the micronutrients in the immune system whereas some clinical trials are being studied in support to COVID-19 diseases. However further detailed studies and more evidences should be required to investigate role of micronutrients in accordance to COVID-19 disease.

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