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## Nutraceuticals antagonists towards COVID-19

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**Abstract**

Nutraceuticals are the blended products containing both nutritional as well as medicinal values. These are specifically processed to satisfy dietary requirements with preventive health benefits. The COVID-19 pandemic outbreak has been very affirmative towards nutraceutical and dietary supplements as boosting the immune system is one of the major challenges for us now. Wide approaches towards therapeutic values led to know us about protective properties of nutraceuticals and functional food as the calories taken in should be less than calories given out. Despite a lack of scientific records, compelling evidence from the literature shows that some nutraceuticals (which include omega-3 enriched supplements, topmost functional foods like gingerols and shogaols in ginger,  $\beta$ -glucans, probiotics, herbs and high intake of vitamin and mineral supplements has shown an excellent effect in reducing the risk of influenza and COVID-19 like infections). Nutraceuticals have poor oral bio availability which lowers the efficiency as health promoting agents. Engineered Nano (EN) particles in this frame of reference have shown stability in food and Gastro Intestinal Therapeutic System (GITs). In the present review article, the benefits of these natural compounds may not only modulate the immunity of a prone population, however may also pave the manner in the direction of the development of drugs which can be used to treat COVID-19. However, here we have discussed various advantages of nutraceuticals in this devastating global pandemic but still the path of attentive clinical trials and experimental studies are required to validate their efficacy, in order to counteract the ongoing increase in the number of cases of COVID-19. The current times have cast a dark shadow yet we strive to continue through strong immunities built by healthy nutraceuticals. So, always keep vigilance on your bite and sip.

**Keywords:** Nutraceuticals, omega-3,  $\beta$ -glucans, Gingerols and Shogaols, COVID-19, Vitamins

**Introduction**

The term "Neutraceutical" refers to medical or nutritious foods. They have also been referred to as designer foods, phytochemicals and nutritional supplements, including daily products such as "bio" yoghurt and fortified breakfast cereals, as well as vitamins, herbs and even genetically modified foods. The COVID-19 epidemic has infected thousands of people not only nationally but also worldwide and the epidemic is growing steadily. Vaccine and effective treatment of COVID-19 have now been taken and more supportive care, social protection, forecasting and segregation will be required to reduce the spread and severity of infection [1]. It is said that patients with COVID-19 increase. Acute Respiratory Distress Syndrome, which is diagnosed using anemia, cardiovascular risk factors and secondary diseases [2]. Intensive treatment with antibiotics (including cephalosporins, azithromycin, vancomycin, quinolones, tigecycline and carbapenems), antivirals (including lopinavir, ritonavir, remdesivir and oseltamivir) and corticosteroids (which include dexamethasone and methylprednisolone for the cause used) in patients with COVID-19 [3]. We had to be careful about the treatment of this deadly disease because we would not waste time on this problem. Therefore, to take a walk-on approach, we suggest considering various nutraceuticals with many properties such as anti-inflammatory, anti-oxidant and anti-viral action [4]. Infection can be prevented only by a healthy diet and maintaining a healthy immune system. The addition of various vitamins A, D, C and Zn and selenium has special benefits in both the prevention and treatment of bacterial infections [5]. DHA and EPA as nutraceutical. Recent studies have found that both EPA and DHA, derived from fish oil, have increased respiration in those with allergies [6]. Oral or intravenous administration of EPA or DHA as a result, may promote recovery in patients with COVID-19 [7]. The added effect of Engineered Nano particles shows a good way to deliver oral doses of nutraceuticals [8]. Did not allow us to adequately prepare the immune system, which now requires the taking of nutraceuticals "desperate maladies, require desperate remedies". In this context the emphasis is on the therapeutic value of some promising herbal products interested in the same viruses, as well as COVID-19 in particular.

### 1.1 Categorization for a grasp on nutraceuticals

Nutraceuticals are made from natural ingredients without any kind of synthetic or minimal ingredients. There is a difference in being natural without any changes and a basic amount of healthy food. Various compounds such as omega-3-fatty acids in fish oil and flax seeds have anti-inflammatory properties. Therefore, there is a lot of proposed use for the future treatment agent. In addition, in the classification of nutraceuticals is mainly focused on its subsequent components.

#### a) Nutrient

Nutrients are essential for maintaining growth and a healthy lifestyle. They include proteins, carbohydrates, vitamins and minerals. Natural products are beneficial in treating various ailments such as fractures and low hemoglobin<sup>[9]</sup>. Nutrients provide strength to bones and muscles, help with fatty acids, omega-3 PUFAs present in salmon, and contribute to a complete inflammatory response. Lowering cholesterol and lipid-lowering drugs combined with nutraceuticals is an hour-long reduction of cardiovascular function and reducing allergic reactions and the risk of asthma<sup>[10]</sup>.

#### b) Herbals

Nutraceuticals when put under the herbal category show a very good effect in preventing various chronic diseases. The terpenoid herbal class especially menthol, peppermint and bioactive plants especially Aloe Vera, has been shown to cure colds, flu, and its use remains safe in any form and with this epidemic shows the deterioration of the viral envelope.<sup>[11]</sup> One of the most potent compounds responsible for the immune effects of herbal products lies within the structure of complex polysaccharides called  $\beta$ -glucans. B-glucans are ubiquitous in both bacterial and fungal cell partitions and have been implicated in the development of antibacterial effects in both the internal and adaptive immune response. Further in the review, we summarized information about the active role of  $\beta$ -glucans against respiratory problems COVID-19<sup>[12]</sup>.

#### c) Phytochemicals

Antivirus polyphenolic pills can block coronavirus enzymes, which can be important for viral replication and contamination. This circle of natural substances (betulinic acid, indigo, aloemodine, luteolin, and quinomethyl triterpenoids, quercetin or gallates) has the capacity key to design antiviral treatment options to prevent viral proteins<sup>[13]</sup>.

### 1. Immune Booster's Nutraceuticals

It has been observed that decreased immunity in this pandemic is partially responsible for the increase in the rate of morbidity and mortality which is resulting from the infectious agents. In this regard, nutraceuticals encompasses a broad spectrum of dietary supplements like vitamins, minerals, botanicals or probiotics, trace elements and functional foods intend to provide health benefits, including prevention from the disease. So, several nutraceuticals have shown positive effects in the clinical trials. Keeping this in mind, we have discussed below some of the nutraceuticals with their dosage which have shown quite a great potential and positive effects in clinical trials and are proven to increase the immune response against viruses.

### 1.2 Vitamins and Minerals

They serve in almost all the body processes and are obtained from foods and supplements, as our body is unable to make them. According to National Health and Nutrition Examination survey, 52% of adults take dietary supplements<sup>[14]</sup>.

#### a) Vitamin C (The Protector)

Vitamin C or Ascorbic acid is a water-soluble nutrient. Being water soluble, it is not stored in the body and requires daily intake. Vitamin C highly contributes to immune system as well as by supporting various cellular functions of both the innate and adaptive immune system. Vitamin C accumulates in phagocytic cells, such as neutrophils, and can enhance chemotaxis, phagocytosis, generation of reactive oxygen species, and ultimately microbial killing. Supplementation of vitamin C prevents both respiratory and systemic infections<sup>[15]</sup>. In this brutal COVID-19 infection vitamin C is used by many hospital's ICUs to treat the infection wisely. The Food and Nutrition Board of the Institute of Medicine recommend its RDA is 90 mg a day for men and 75 mg a day for women ages 19 years and older<sup>[16,17]</sup>.

#### b) Vitamin D

The 'sunshine vitamin' has its several important functions. It is found in fatty fishes, eggs and fortified foods like milk, cereals, etc. Getting a Sunlight exposure between 11am to 1 pm, for 20-30 minutes is a way to ensure its good availability. Vitamin D with both antiviral and antibacterial effect gives a decrement of the viral replication and also prevents respiratory infections. Vitamin D3 or oral vitamin D is converted to 25(OH) D in the liver and then to the hormonal metabolite, 1,25(OH)<sub>2</sub> D (calcitriol) and calcitriol participate genetically and epigenetically in modifying transcriptional output<sup>[18]</sup>. Vitamin D also helps in enhancing cellular immunity, by reducing the cytokine storm induced by the innate immune system. In COVID-19 patients anti-inflammatory cytokines observed in response to viral and bacterial infections as observed in clinical trials with the supplementation of 4000 IU/d helps in decreasing dengue virus infection as well<sup>[19]</sup>. Vitamin-D3 also acts as a model lipophilic-bioactive, re-assembled casein micelles (RCM) which is a protein-based and with 0% fat yoghurt as a considered as a nonfat food<sup>[20]</sup>. For good results, In COVID-19 Patients it is recommended that higher vitamin D3 concentrations should be raised above 40-60 mg/mL (100-150 mol/L) further large population studies are suggested to evaluate and confirm the results<sup>[21]</sup>.

#### c) Zinc

Zinc is one of the essential mineral available in natural sources such as flax seeds, pumpkin seeds, whole legumes, dark chocolates, nuts etc. Zinc helps to suppress viral attachment and replication with this property it is also seen that zinc deficiency if found to be common in coronavirus patients and also cause gastrointestinal diseases<sup>[22]</sup>. So, 30-60mg of dose of zinc is recommended in daily diet contributes to immune defense by supporting functions of both the innate and adaptive immune system. In human intestines there is absorption and reabsorption of zinc which states the bioavailability of zinc<sup>[23]</sup>.

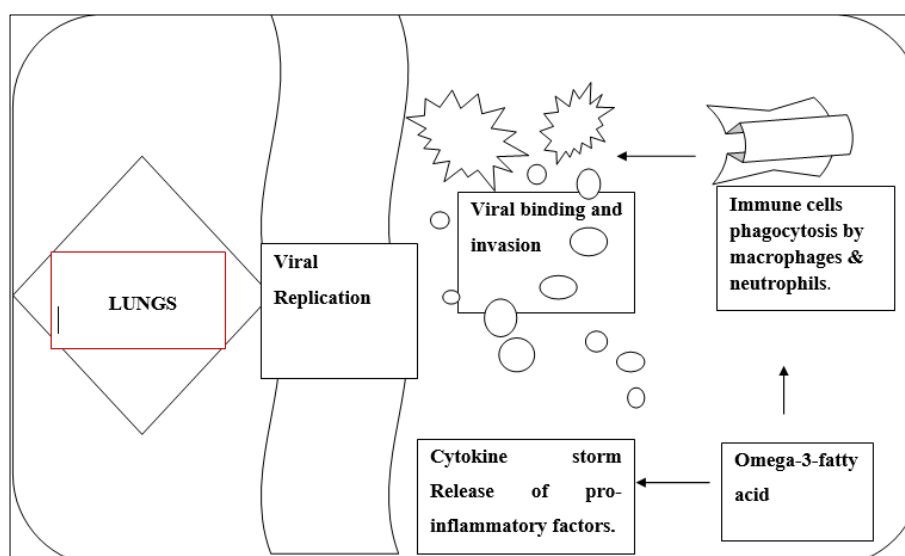
## 2.2 Functional Therapeutics/foods of nutraceuticals leading to an optimistic approach towards respiratory problems

Functional foods in combination with nutraceuticals provides a good opportunity to improve the human health and also reducing the health care cost. The phrase “Let food be the medicine and medicine be the food” coined by Hippocrates is so relatable to realize consumers the many health benefits in certain foods and completing the ultimate goal of foodies around the world [24]. As food is always been fun but it should also be functional and it's high time we should discuss about the sustainable food approach regarding many food products as given below.

### a) Omega-3-Fatty Acids

Omega-3 FAs is a safe and comparatively inexpensive prophylactic technique for folks who are at excessive threat. For a problem that has arisen from nature, we may also go back to nature for the therapy. The major supply of omega-

three FAs in the human weight loss plan comes from ingesting fresh fish, specifically oily fish, together with mackerel, salmon, herring, cod and flounder. This takes place because most fish ingredients consisting of microalgae and different invertebrates are wealthy in Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Quantities present in non-marine meals include cereals, seeds, nuts, and a few culmination of fruits and vegetables. Besides this, maximum microorganisms such as marine protists and dinoflagellates, Omega-3 fatty acids, through their anti-inflammatory mechanism, inhibit the production of pro-inflammatory mediators like interleukin (IL)-1 $\beta$ , IL-6, tumor necrosis issue (TNF)- $\alpha$  and save us from cytokine storm. Some research also endorse that they dampen the inflammatory response through regulatory T cells (Treg) differentiation. They additionally exert an anti-viral impact by means of enhancing the phagocytic venture of cells of the innate immune machine- Neutrophils and Macrophages. Shown in the image given below.



**Image 1:** Depiction of Omega-3 fatty acid performing on distinctive factors of the immune response [25].

### b) $\beta$ -glucans

$\beta$ -glucans, are powerful activators of immune cells, including neutrophils, natural killer cells and macrophages, exert a positive effect at the host protection system. In addition to the immunomodulatory effects,  $\beta$ -glucans have additionally been proven to show off antiviral interest in opposition to HSV-1 and influenza virus. More recently, it became cautioned that  $\beta$ -glucans can assist to lessen morbidity and mortality associated with COVID-19 [26]. Long-lasting immunity is presently a big assignment in COVID-19-affected patients.  $\beta$ -Glucans can produce long-lasting TRIM (Trained Immunity) in opposition to a huge range of pathogens. Furthermore,  $\beta$ -glucans are safe for intake at every age, and they fall under the FDA's generally diagnosed as safe class.  $\beta$ -Glucans are strong and can be ate up continuously as a meals supplement. Many kinds of  $\beta$ -glucans exist, but yeast- and mushroom-derived  $\beta$ -glucans exert stronger immunomodulatory results than do other forms of  $\beta$ -glucans. Oral  $\beta$ -glucans have been thoroughly described as prophylactic dietary supplements to enhance immune responses and to abrogate COVID-19 symptoms through their TRIM actions. Though SARS-CoV-2 is predominantly taken into consideration an epidemic that affects the respiratory gadget, the viral host receptor ACE2 appears within the cytoplasm of gastrointestinal epithelial cells, with the viral nucleocapsid protein performing within

the cytoplasm of rectal, duodenal, and gastric epithelial cells, suggesting that the gut can be applicable inside the pathogenesis of COVID-19 and perhaps a possible direction of contamination.  $\beta$ -Glucans with immune results at the intestine might also therefore be an tremendous supplementation strategy for COVID-19 remedy [27].

### c) Probiotics

Treatment with probiotics bacteria have been shown to reduce both upper and lower respiratory tracts infections. In the gastrointestinal tract (GIT), referred to as one of the maximum microbiologically active ecosystems playing a essential position inside the operating of the mucosal immune system, probiotics stimulate the immune system and result in a network of signals mediated via the whole bacteria or their wall shape. Many probiotic consequences are mediated in particular, stability management of pro-inflammatory and anti-inflammatory cytokines. Another vital effect exerted by probiotics is to implement and maintain the integrity of junction between enterocytes, in this manner front of SARS-CoV2 is reduced, in addition to the hazard to expand COVID-19. In latest years, the connection among intestine microbiota and standard health were confirmed. Diet can modulate the capability of the intestinal microbiome which uses nutrients from ingested ingredients, releases dangerous or useful

metabolites and regulates the immune system. The gut mucosal surface is an important web page of entry of pathogens into the human body however in wholesome topics, intestinal epithelium and its microbiota offer an efficient barrier to invading microorganisms. Probiotic moves inclusive of an effect on cytokines manufacturing by means of intestinal epithelial cells, IgA secretion stimulation to improve mucosal immunity, activation of phagocytosis and macrophage manufacturing, modulation of degrees and function of regulatory cells, and induction of dendritic cells maturation, likely have an effect on systemic inflammation [28].

**Table 1:** List of some specific compounds and the benefits they provide on targeted viruses

Compound	Source	Recommended daily intake	Food Concentration/100g	Target Virus
Quercetin	Eg-onions, Capers, chives	50-800mg	up to 234mg	Influenza A virus, SARS
Curcumin	Turmeric	3mg/kg body weight	3000mg	Influenza virus, hepatitis C virus, Zika virus (ZIKV), human immunodeficiency virus (HIV), herpes simplex virus 2 (HSV-2), human papillomavirus (HPV), chikungunya virus (CHIKV)
Epigallocatechin gallate (ECGC)	Green tea	130mg	7380mg	Herpes simplex virus, adenovirus, human papillomavirus, hepatitis B and C virus, Zika virus (ZIKV), dengue virus, chikungunya virus (CHIKV), human immunodeficiency virus (HIV), West Nile viruses ZIKV (MR766 and PRVABC59 Influenza (H1N1), chikungunya virus.
Phloretin	Eg-Apples, pears	40mg	0.65mg	
Berberine	Strawberries Barberry, Turmeric	<1500mg	1.6-4.3mg	

### Melatonin

Melatonin's multiple actions as an anti-inflammatory, anti-oxidant, and anti-viral (against other viruses) make it a reasonable choice for use with its readily availability, can be easily synthesized in large quantities and is inexpensive with a very high safety profile and can be easily self-administered [30].

In olive oil melatonin is present at higher levels in extra virgin olive oil than in refined olive or sunflower oil samples. So, it gives us a view that melatonin is the phytochemical agent in olive oil particularly; extra virgin olive oil had almost double the melatonin contents of the other refined oils analyzed. Thus, melatonin may account for the health effects of the Mediterranean diet in which olive oil is the main source of fat [31]. Dilly-Dally of time is not we can afford in this period of crisis. Thus, to use currently-available and safe molecules to slow or treat COVID-19 disease. Suggestion of melatonin is also considered as a best to use for prophylactic use or treatment alone or in combination with other drugs [32].

### e) Gingerols and Shogaols

Ginger being a conventional food are generally considered as a health food as well. Ginger is also recognized as an anti-inflammatory food that helps relieve arthritis pain as it holds antioxidant and cancer fighting properties. Gingerol is an active anti-inflammatory compound present in the rhizomes of ginger [33]. It is stronger and fresh in raw ginger than in dried products. Gingerols, however, are thermally labile due to the presence of a  $\beta$ -hydroxyketo group in the structure, and undergo dehydration readily to form the corresponding shogaols. Shogaols are the important bio-markers; they are used as the quality control of many ginger-containing products. Both of them being ginger extracts have biological activities which allow them to provide a valuable protection against diabetes, cardiac and hepatic disorders [34]. One of the most widely used home remedies for coughs and colds, ginger

### d) Quercetin, Curcumin, Epigallocatechin gallate (ECGC), Phloretin, Berberine and Melatonin

These are all our senolytic drugs which selectively induce death of senescent cells which accumulates in many tissues causing aging and many other multiple chronic diseases so to improve health in humans there introduction is recommended as a good functional foods. Nutraceuticals and functional foods have broad potential for preventing the mechanism of viral infection and modulating the immune responses. Here is a table showing plant extracts, plant sources, recommended daily intake, targeting the type of viruses [29].

is known for its anti-inflammatory properties, which help detoxify the respiratory tract. It contains many vitamins and minerals including potassium, magnesium, beta-carotene and zinc. As with several studies, certain ginger extracts are also known to kill lung cancer cells. The best way to strengthen the immune system and fight off seasonal colds and illnesses is to make homemade kadha or simply by eating healthy ginger tea. Ginger also modulates genetic pathway, acts on tumor suppression of genes [35].

### 2.3 Herbs

Some of the immunity-boosting herbs are garlic, black cumin, and liquorices'. Include them in the food regimen of the aged inside the form for tea or by using including them of their meals. This will now not only beautify their immunity however improve their intestine as well. Herbal treatment is very widely recognized in Traditional Chinese Medicine (TCM).

Traditional Chinese Medicine, focused on an overall major cause of COVID-19 pneumonia patients, may have beneficial prescriptions.

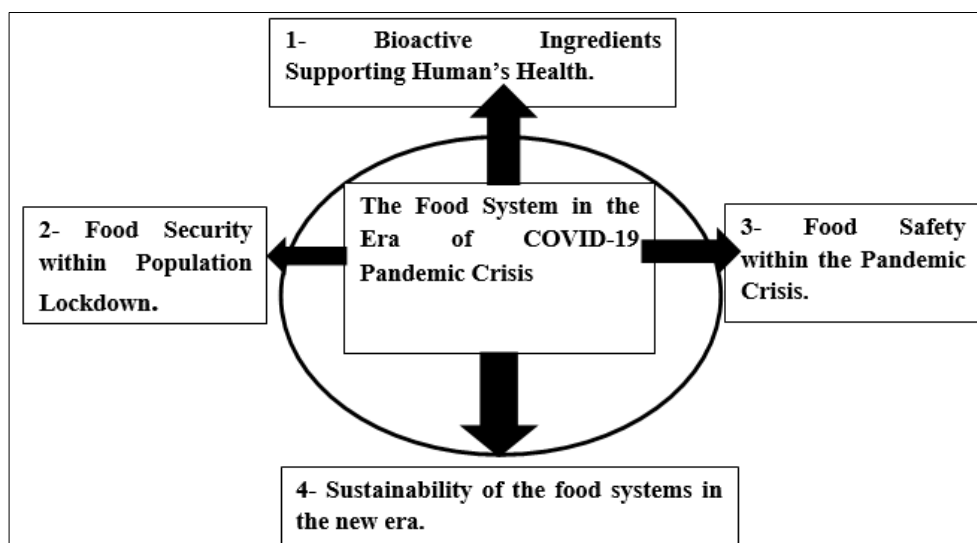
In COVID-19's remedy and prevention, the benefits of TCM in differentiating syndrome and reduces health issues and mortality rate. Furthermore, clinical research at the TCM with clean healing efficacy of COVID-19 ought to also be surpassed out for us to absolutely evaluate its mechanism of action and deep understanding of COVID-19 [36].

### 3. Sustainable approach towards food system in this era of pandemic crisis

Human health is always affected by food systems. So, It's a need of the hour to reconsider the food systems and design their future, i.e., it is essential to increase their resilience. The current food systems are highly dependent on animal-based protein sources that are not sustainable from an environmental point of view. For example, meat consumption is proportional

to the amount of greenhouse gas (GHGs) emissions, whereas the consumption of red meat has been associated with chronic diseases like cancer [37]. The increasing demands for proteins, in the every age group people are leading to tremendous depletion in the resources, which made researchers to

investigate more sustainable and safer food sources in order to feed the world and meet markets' need. According to researchers there are four significant issues that food supply chain should address in the new era are described in the figure given below [38].



**Fig 1:** Issues addressed by food supply chain in the present era

**4. Bioavailability and delivery of nutraceuticals:** The therapeutically active component that reaches the body's circulation and at a particular site of action is what we consider the extent of bioavailability. Carotenoids having protection ability from UV-radiations, oxidative stress etc, but the drug delivery does kind of challenging task owe to its poor bioavailability due to its poor solubility and instability in gastrointestinal region. So, researchers have included novel approaches like microencapsulation, nano-encapsulation, nano-emulsions [39]. Nano-emulsions can be prepared through high and low energy emulsifications. Scientists revealed that the improved oral bioavailability through nano-emulsion route has been confirmed by dibenzoylmethane (DBM) nano-emulsion. DBM is found as a minor constituent in the root of licorice, being a natural phytochemical with anti-cancer activities. It is a beta-diketone analog of curcumin. Thus, its structure is similar to curcumin [40]. Poor bioavailability is shown by many nutraceuticals which lowers our most important health promoting agents efficiency. In this regard, Engineered Nano-particles (ENs) are used to construct delivery systems that improve bioavailability in a manner that stability in food and gastrointestinal tract (GIT) facilitates absorption of nutraceuticals [41]. Hydrogel beads ("microgels") are assembled from proteins helps in improving nutraceutical performance by protecting them from chemical degradation. Hydrophilic nutraceuticals are mixed directly with the biopolymer solution prior to formation of the hydrogel beads, whereas hydrophobic nutraceuticals are typically incorporated into lipid droplets (emulsions or nano-emulsions) prior to mixing with the biopolymer solution. Hydrogel beads show prominent potential for improving nutraceutical bioavailability [42].

## 5. Conclusion

Neutraceuticals show considerable interest and potential to improve immune health, delay the aging process, as immunity boosters, being functional foods, prevention of various chronic diseases and increasing the life expectancy and function of the human body. Recent studies have shown

promising results for nutraceuticals. In the present review much effort has been devoted to provide their herbal remedies and categorization of nutraceuticals and its viral related mechanisms, especially SARS-Cov-19 related infections, which gives some hope of plant-derived regimens facilitating pre-interventions or combinations with pharmaceutically derived medication gives us a better understanding of the interactions with the diseases and also boosting the development of functional foods for immune-senescence and healthy aging [43]. The COVID-19 pandemic crisis has created a new era. We are still trying to figure out the consequences for humanity, economy and subsequently food systems. Ensuring food safety as well as identifying alternative and safe protein sources that meet the nutritional expectations of consumers. Keeping in mind there is undoubtedly a need to avoid "business as usual" practices, to think out of the box and accelerate efforts to develop sustainable and modern food systems, e.g., to reduce the cost of aseptic lab-grown meat, reutilization in the food chain, and develop new and large food supply chains based on insects' and microalgae proteins, etc. [44]. Neutraceuticals are food supplements and have nutritional value. All the nutrients discussed in this review have exhibited significant clinical & pharmacological activity. The potency of herbal drugs is significant & they have negligible side effects than the synthetic drugs. Nano-emulsions-based delivery systems have been proved to be one of the best platforms to enhance the oral bioavailability and biological efficacies i.e., anti-inflammation, anti-cancer, and so on. They are especially appealing to the food industry because there are many food-grade lipids and emulsifiers available. They are simpler and easier to prepare compared with other lipid-based delivery systems, such as multiple emulsions and solid lipid nanoparticles. In addition, the human body has different lipases ready to digest these lipids, therefore, the potential toxicity of these phytochemical nano-emulsions may be minimal [45]. Fruits like oranges, papaya, kiwi, and guava are wealthy in diet C, even as greens like eggplant, bell peppers, beetroots, spinach, and cauliflower are known to be pretty wealthy in vitamin C and are appropriate

for immunity. Vitamin D improves cell resistance, in part by means of elevating the cytokine hurricane that the innate immune system causes. Green vegetables like broccoli, mushrooms, or even kale are some immunity boosters that enhance the immune system of older humans pretty hastily. Moreover, a few herb combination in TCM is likewise known to play important position inside the prevention of COVID-19<sup>[46]</sup>. The outbreaks of COVID-19 has highlighted the situation where consumer awareness and consumer engagement will be a key to succeed and it can be done with the help of social media. As well as knowledge sharing can be used as a tool to engage and retain customer. Nutraceuticals have proven their health benefits and disease prevention capabilities, which should be taken according to their acceptable recommended intake. But, still at last the success of nutraceuticals depends on maintaining their quality, safety and efficacy by emerging the clinical practices for further research<sup>[47]</sup>. The aim of this review is to aid better understanding and benefits of popular nutraceuticals. Regardless of the established infective immune pathways in COVID-19<sup>[48]</sup>, this narrative review has highlighted some of the possible treatments to be done by the intakes of nutraceuticals. We hope the collective approach towards nutraceuticals in this review paper would definitely enlighten the nutritionist, health workers, professionals, policy makers and consumers as well to enhance their knowledge.

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