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Review Article

Nutrition Section

Nutraceuticals to Support Immunity: COVID-19 Pandemic- A Wake-up Call

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ABSTRACT

The COVID-19 pandemic is spreading throughout the world, infecting thousands of people every day. This public health emergency has got world and regional organisations, governments and health care systems working tirelessly to try to control the spread of the virus and managing the already infected individuals adequately. These events have made everyone realise the policy of "*Prevention is better than cure*", as the best way to fight this pandemic. There are many guidelines for common people, issued by many respected organisations, but most of them are focused on personal hygiene and prevention of the spread the virus. Only minimal focus has been given towards the role of immunity in this scenario and more importantly the role of nutrition in supporting immunity. In this article, it has been attempted to describe the term 'Nutraceuticals' and discuss in detail a few nutraceuticals which are well documented to support immune functions of the body. The article has tried to shed some light on the fact that these nutraceuticals deserve to be promoted amongst the masses, to support the immunity required against infectious diseases.

Keywords: *Echinacea*, Licorice, Mulethi, Nutrition, Supplements, Tulsi, Vitamin C

INTRODUCTION

A cluster of atypical pneumonia cases was reported from Wuhan, China and brought to the notice of the World Health Organisation (WHO)'s Country Office (China) on 31st December 2019. The disease took its natural course and started spreading internationally. But, the severity of this condition was known by the world when WHO announced it a Public Health Emergency of International Concern on 30th January 2020 [1]. The Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), formerly known as 2019-novel Coronavirus (2019-nCoV), is responsible for causing Coronavirus Disease (COVID-19) which is the first and only pandemic to be caused by a Coronavirus [2]. The presentation of this viral infection has a broad spectrum ranging from no symptoms, minimal upper respiratory tract symptoms, pneumonia to Respiratory Failure (RF) and mortality in severe cases [3].

There are several guidelines laid out by experts all around the world to prevent the spread of this virus and in these times of emergency it stands mandatory that we follow them and educate others about them. A few important measures as advised by WHO are highlighted below [4]:

1. Frequent and thorough handwashing with soap and water or an alcohol-based hand sanitiser.
2. Maintaining a social distance of one metre or three feet from anyone sneezing or coughing.
3. Avoiding touching eyes, nose or mouth.
4 Covering mouth and nose with disposable tissues or elbows while coughing or sneezing.
5. Seeking medical care if symptoms of fever, cough and difficulty in breathing develop.

However, two more factors are important for the prevention of infectious diseases, namely, immunity and nutrition. Specific organs, tissues and cells, secreting various protein molecules, including cytokines, chemokines and antibodies, constitute the immune system. This system has developed to defend the human body from an array of microorganisms including bacteria, viruses, fungi, and parasites. The immune system is divided into cellular and humoral components and immunity is of two types- innate and acquired [5]. *"Let food be thy medicine and medicine be thy food"*- so said Hippocrates approximately, 2,500 years ago. These words by the Father of Medicine had turned to the state of being unknown, inconspicuous, or unimportant by the 19th century. Its relevance was realised only in the 20th century when scientists from around the world started re-recognising the importance of nutrition and its role in disease prevention [6]. The 2018 Global Nutrition Report by WHO states that the global burden of nutritional deficiency is very high, unacceptable and now affects every country in the world [7]. To fill in the gaps in nutrition is where dietary supplements come in. Ample and suitable nutrition is required by every part of the body to function optimally, including the immune cells. Consequently, for optimum functioning of the immune system, optimal nutrition is required which allows immune cells to carry out effective responses against pathogens [8]. The word 'nutraceutical' was first used by the Chairman of the Foundation for Innovation in Medicine, Dr. Stephen De Felice in 1989. Although there isn't a worldwide accepted definition for nutraceuticals, but it stands for "any substance that may be considered a food or part of a food which provides medical or health benefits, encompassing, prevention and treatment of diseases." 'Pharmaceuticals' are used to 'treat' a disease, while 'nutraceuticals' are used to 'prevent' them- this is a basic difference between the two. The term 'nutraceuticals' is sometimes also referred to as 'functional foods'. But in this case, the contrast between food and medicine isn't clearly defined. Nutraceuticals and dietary supplements share a very narrow division, in that nutraceuticals not only add nutritional value to the dietary intake but also function in avoiding or treating diseases [9]. India defines 'Nutraceuticals' under Clause 22 of the Food Safety and Standards Act (FSSA), 2006. But due to many unresolved problems under administrations, regulation of these products aren't very strong. This is why there are no widely accepted 'recommended dietary allowances' for some of the below-mentioned substances (Vitamin C, Licorice, *Echinacea*, and Tulsi). This also leads to substandard products compromising the quality in the market. But, many dedicated companies are pioneering and providing the best in class nutraceuticals [9]. The consumer is advised to do the adequate exploration before selecting a product.

SARS-CoV-2 infection mainly manifests are acute respiratory illness with pneumonia, but may also involve various organs, namely, heart, kidneys, digestive system, blood and nervous system [10]. Whereas at one end SARS-CoV-2 infection can be asymptomatic, there are upto 5% of patients who might develop serious respiratory complications, such as Acute Respiratory

Distress Syndrome (ARDS) and RF. Other complications include septic shock, Multiple Organ Dysfunction (MOD), or Multiple Organ Failure (MOF) [11]. There are also reports of neurological complications of this infection, including encephalopathy [12]. Other than the hurdles during an ongoing infection, a patient with SARS-CoV-2 infection has long-term complications of the cardiovascular system; especially if Cardiovascular Disease (CVD) is a pre-existing condition [13]. There is limited data regarding the exact epidemiological features of this infection and the picture will become clearer as research progresses. However, it has also been observed that the overall secondary attack rate of SARS-CoV-2 is around 35% among the exposed population [14] and the crude mortality rate of 3-4% is significantly higher than influenza [15]. There is a risk of infection to every member of society exposed to the virus, but there are certain individuals who have a notably higher risk of severe illness than others. These include: (i) individuals aged 65 years and above; (ii) people with chronic lung disease or asthma; (iii) individuals with pre-existing CVD; (iv) immunocompromised individuals; (v) severely obese individuals; (vi) diabetics; (vii) Chronic Kidney Disease (CKD) patients undergoing dialysis; and (viii) individuals with liver diseases [16].

Despite the cumulative efforts of researchers, organisations and governments from around the world to find a medical solution and improve the condition of infected patients, it remains the personal responsibility of every individual to take appropriate measures for the prevention and transmission of this viral infection. Revisiting the famous and age-old quote by a Dutch philosopher Desiderius Erasmus: *"Prevention is better than cure"*- the COVID-19 pandemic calls to attention the important role played by immunity and nutrition in prevention in this context. This article has focused on several dietary supplements/nutraceuticals that could play a role in strengthening the immune system to fight-off infectious diseases, including the current COVID-19.

VITAMIN C

"A vitamin is a substance that makes you ill if you don't eat it." -Albert Szent-Gyorgyi, Nobel Laureate in Physiology or Medicine for 1937.

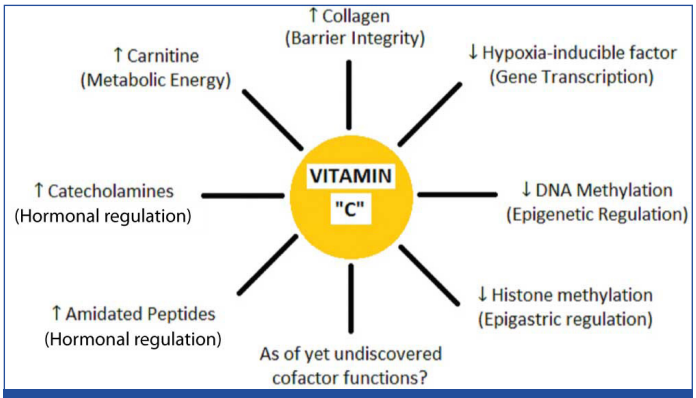
Vitamin C has established its position as a vital component in many parts of the immune system, especially in immune cell functions and this is a statement supported by 50+ years of studies [17,18]. In turn, infections cause markedly reduced levels of vitamin C in the body because of increased inflammatory processes and requirements in metabolism [19]. As essential as it is, vitamin C is not produced in our body because of the absence of an important enzyme in the biogenesis pathway [20].

Being a water-soluble vitamin, there is a low storage scope for vitamin C. Hence, a regular and ample quantity of the vitamin is required in dietary intake to avoid hypovitaminosis C. A dietary intake of 100-200 mg/day is adequate in saturating plasma concentrations in healthy individuals [21]. At moderate intakes of oral ascorbic acid (30-180 mg/day), the absorption occurs at the highest (70-90%). Increasing the oral intake of vitamin C (>1 g/day), decreases the absorption to around 50% and the rest is excreted in the urine. The body stores around 300 mg vitamin C (at near scurvy) to about 2 g. The highest levels of vitamin C are found in leucocytes, eyes, adrenals, and pituitary, while the lowest levels are present in extracellular fluids, Red Blood Cells (RBCs) and saliva [Table/Fig-1] [22,23].

There may be many properties that make vitamin C important for the immune system. It is a strong antioxidant because of its property of easily donating electrons, thus helps in protecting various biomolecules from the oxidative stress of normal metabolism and also from toxins and pollutants [24]. Vitamin C also acts as a cofactor for a group of monooxygenase and dioxygenase enzymes, which have biosynthetic and gene regulatory actions [Table/Fig-2] [25].

Age	Male	Female	Pregnancy	Lactation
0 to 1 y	Cannot be fixed*		-	-
1 to 3 y	400 mg		-	-
4 to 8 y	650 mg		-	-
9 to 13 y	1200 mg		-	-
14 to 18 y	1800 mg		1800 mg	
19 y and above	2000 mg		2000 mg	

[Table/Fig-1]: Allowable upper limit of vitamin C intake [23].
*The food consumed and formula feed should be the only source of vitamin C for infants



[Table/Fig-2]: Functions of vitamin C as a cofactor [25].

Vitamin C has a critical part in all facets of the human immune system. Below mentioned [Table/Fig-3] shows it's various contributions in various parts of the immune system.

Part of immunity	Mechanism of action
Surface barrier	• Increases collagen formation • Antioxidant property against Reactive Oxygen Species (ROS) • Helps keratinocytes to differentiate and become functional • Lipid formation • Fibroblast synthesis and movement • Reduces wound healing duration
Phagocytosis	• Antioxidant property • Increases chemotaxis • Increases phagocytosis • Increases ROS formation • Aids in apoptosis
B-cells and T-cells	• Increases formation and development to functional state • Increases antibody formation
Inflammation mediation	• Facilitates cytokine formation • Reduces histamine secretion

[Table/Fig-3]: Various mechanisms by which vitamin C helps the immune system [26].

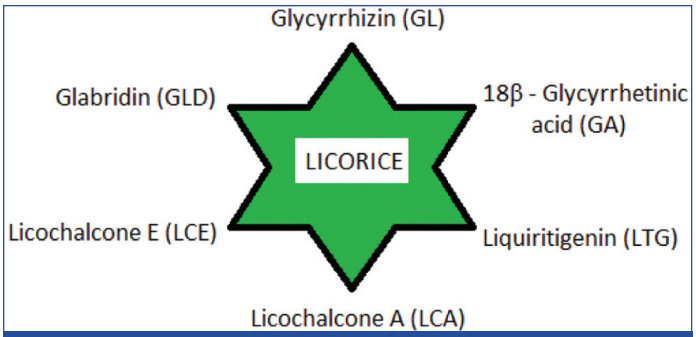
Overall, vitamin C exhibits numerous favourable holdings on the functioning of the specific and non-specific immune cells. The various biosynthetic and gene regulatory enzyme functions add to its immunomodulatory properties. Vitamin C has shown the ability to prevent as well as treat respiratory and systemic illnesses. Prevention of illness can be done at a prophylactic dosage of 100-200 mg/day [26].

LICORICE (MULETHI)

Licorice (*Glycyrrhiza glabra*) is a well-known herb being utilised for its antimicrobial and antiviral properties for centuries. Licorice is known as 'gancao', which means 'sweet grass' in Chinese. Its first mention in texts was in 2100 BC in Shennong's Classic of Materia Medica, a part of traditional Chinese medicine [27]. It is also mentioned in Ayurveda's book Amarkosha (5th century AD) compiled by Amar Singh [28]. This plant, belonging to the genus *Glycyrrhiza* has various species having medicinal use.

Various studies have shown licorice to have anti-viral [27,29], anti-bacterial [30,31], anti-inflammatory [32,33] and even anti-tumour [34,35] properties. Amongst all, the properties of licorice that are well documented are against bacteria and viruses. Viral and bacterial infections can put substantial load on health care systems,

especially in high prevalence countries. Hence, effective and affordable anti-virals and anti-microbials are necessary to tackle the problem. Licorice contains greater than 20 triterpenoids and nearly 300 flavonoids [Table/Fig-4,5] [27,29,30].



[Table/Fig-4]: Important active ingredients of licorice [27].

Active ingredient	Mechanism of action	Virus
Glycyrrhizin	• Hampers virus release during cell-to-cell transmission • Prevents viral genetic material expression	Hepatitis C
	• Decreases adhesive property between Cerebral Capillary vessel Endothelial Cells (CCECs) and Polymorphonuclear (PMN) leukocytes	Herpes simplex
	• Prevents the breakdown of nuclear factor inhibitor	Cocksackie virus B3
	• Aids in T-cell formation	Duck hepatitis virus
	• Reduces the virus-induced synthesis of C-X-C-L-10, interleukin-6, C-C-L-5 • Reduces cell death caused by virus	H5N1
	• Decreases HMGB1 attachment to DNA • Hinders viral polymerase enzyme functions	Influenza
	• Inactivates the virus itself	Coxsackie virus A16
	• Prevents virus replication	Herpes simplex 1
Glycyrrhetinic acid	• Decreases viral protein load	Rotavirus
	• Counters virus attachment to cells and internalisation • Induces interferon synthesis	Human orthopnuemovirus

[Table/Fig-5]: Antiviral activities of major active components of licorice and their mechanism of action against various viruses [29,30].

Increasing antibiotic resistance in bacteria urges modern medical science to find alternatives. The anti-microbial property of licorice can be harvested for the same. Recent studies have shown the potency of licorice extracts against both Gram-positive and Gram-negative bacteria. It is also under investigation as a potential fungicidal agent [Table/Fig-6] [27].

Active ingredient	Mechanism of action	Microbe
GA	• Inhibits expression of viral genes (*Sae*R and *Hla*)	*Staphylococcus aureus* (Bacteria)
	• Aids T-helper cells	*Candida albicans* (Fungi)
LCA	• Prevents development of biofilm • Stops transition of hyphae	*Candida albicans*
LCE	• Decreases α-toxin synthesis	*Staphylococcus aureus*
GLD	• Stops transition of hyphae	*Candida albicans*
LTG	• Decreases α-toxin synthesis	*Staphylococcus aureus*

[Table/Fig-6]: Licorice's active compounds and their mechanism of action for preventing bacterial and fungal infections [27].
GA: Glycyrrhetinic acid; LCA: Licochalcone A; LCE: Licochalcone E; GLD: Glabridin; LTG: Liquiritigenin

Out of the six compounds listed, only Glycyrrhizin has been refined as a drug. But licorice is widely used as a nutraceutical around the world, for the prevention and management of many infectious conditions. Because of its anti-viral, anti-microbial, and anti-inflammatory properties, licorice supports the respiratory system strongly, and hence is considered to be an essential nutraceutical.

ECHINACEA

Echinacea or 'purple coneflower' is a herb belonging to the genus *Echinacea* and having 10 species. It was originally from North America and have been used by the natives for its medicinal value for a long time. As compared to other medicinal plants, *Echinacea* is a relatively new addition to the list, with its first archaeological evidence dating back to the 18th century [36].

The most well-known pharmacological function of *Echinacea* is its support in the management of common cold and Upper Respiratory Tract Infections (URTIs), in which it decreases the severity and/or duration of the complaints [37,38]. The herb is also known for its palliative effect on wound complications [39], inflammation [39,40] and carcinogenic growth [41].

The majority of the studies suggest that *Echinacea* acts as non-specific immunomodulator by acting on the innate immune cells [42]. Mentioned below are a few mechanisms by which *Echinacea* aids and hence supports the immune system:

1. Enhancement of cells of the immune system [43]
2. Migration of certain WBCs [44]
3. Phagocytic action of macrophages [45]
4. Cytotoxic action of Natural Killer (NK) cells [46]
5. Pro-inflammatory cytokine production [43]
6. Stimulation of pathways of the complement system [47]

A few animal model studies also suggest *Echinacea* spp. role in the modulation of the adaptive immune response [48].

The pharmacologically functional components of this plant are lipophilic alkamides and caffeic acid derivatives [49]. But, it is noted that the immunological function of an isolated phytochemical does not match that of the whole plant extract. This means that the immunological action of *Echinacea* is due to the aggregation of many active components and not any individual active ingredient [50].

Against viral infections, NK cells play an important role due to their cytotoxic properties and production of cytokines like Interferon (IFN)-γ. *Echinacea* increases the cytotoxic action of NK cells in healthy individuals as well as in immunodeficient patients [51]. In response to complex antigens, helper T (Th) cells are activated. Th cells and cytotoxic T (Tc) cells multiply and produce cytokines in response to viral infection and Tc cells kill the viral-infected cells. Th1 cells in turn activate macrophages, which play an important role against microbial invasions [52].

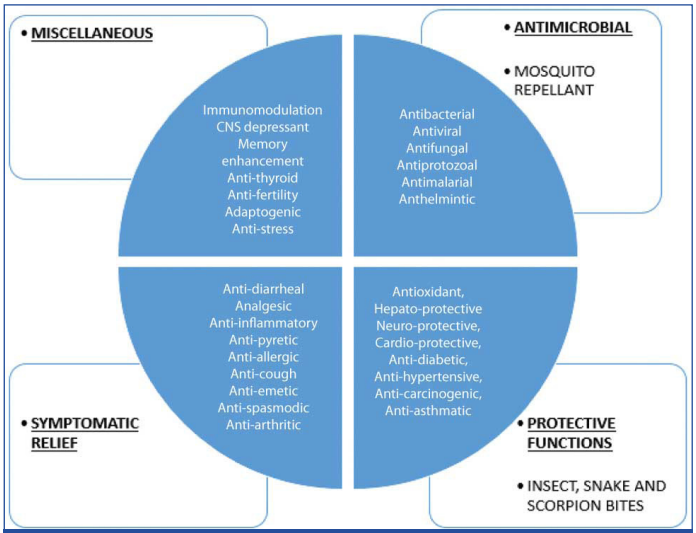
Echinacea is therefore effective in augmenting innate as well as adaptive immunity. Due to these strong immunomodulatory effects of *Echinacea*, it can most definitely be used to support the immune functions of the body.

TULSI

Ayurveda (The Science of Life) provides a holistic approach to health and diseases, maintaining and aiding good health and healthy lifestyle practices to prevent diseases. Being 5000-year-old, Ayurveda is one of the most ancient health sciences, and it mentions tulsi (*Ocimum tenuiflorum*) in conjunction with the prevention and management of several diseases [53]. Tulsi is worshipped by Hindus as a sacred plant in India and parts of South-East Asia and rightly so, because even though Ayurveda includes numerous medicinal herbs, having diversity which is unequaled by any other medicinal system, still none of these plants are even at par with tulsi. Tulsi is a fragrant plant belonging to the family *Lamiaceae* and is believed to have originated in north-central India, but is now widely found in the tropical countries of the eastern world [54].

It is believed to be a potent 'adaptogen'. Tulsi provides wellbeing and resilience. Adaptogen means any substance which helps to deal with stress and promote homeostasis in the body [55].

There are hundreds of studies, including in vitro, animal and human experiments, supporting the various medicinal uses of tulsi. These studies reveal numerous uses of tulsi [Table/Fig-7] [56-60].



[Table/Fig-7]: Various beneficial effects of tulsi [56-60].

The anti-microbial and anti-viral properties of tulsi have been studied in depth. The cytokines IFN-γ (Th1) and Interleukin (IL) 4 (Th2) were found to be significantly raised after regular oral tulsi preparation ingestion, and after a washout period of stopping the supplementation, the cytokine levels were found to decrease back [61]. IFN-γ is produced at the time of infection by any intracellular microbe and has potent action against viruses, bacteria, tumour cells and allergies [62]. It is also documented that tulsi leads to the proliferation of Th and NK cells in the body [61], which are particularly helpful against viral infections. The pharmacological and immunomodulatory effects of tulsi are due to flavonoids in the plant [63].

Tulsi is called "The Incomparable One," "Mother Medicine of Nature" and "The Queen of Herbs," in Ayurveda [56] and its great number of beneficial pharmacological effects proves that it deserves all the above titles. Hence, tulsi deserves a spot in the list of nutraceuticals that may be used to support immunity.

CONCLUSION(S)

Eating habits and lifestyle pattern changes in modern human society have contributed to the development of illnesses such as diabetes, CVD, respiratory illnesses, among other conditions. These comorbidities makes one susceptible to severe illness during this COVID-19 pandemic.

Nutraceuticals provide many advantages with fewer side effects and have enough literature to support its claims. In times where the world faces a health crisis worsened by the shortage of modern medical science facilities, be it medicines, protective wears, or hospitals and equipment, there stands no harm in including alternative or traditional medicines as a support.

Vitamin C, Licorice, *Echinacea* and Tulsi are only a few names in the long list of nutraceuticals that may be used to support immunity. It is necessary to fulfill the requirement of essential nutrients like protein, carbohydrates, lipids, micro- and macro-nutrients to be healthy. These nutraceuticals are additions to the diet, suggested to support the immune system and not a replacement for the essential nutrients. There is a wide field of research still called upon to discover new nutraceuticals, consolidate the knowledge about the existing in-use ones and formulate an effective and economical way to extract and deliver these products for future use.

This public health emergency having international concern is a wake-up call for us to realise the importance of immunity and nutrition and it calls upon us to educate the masses about it.

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