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A Comprehensive Evaluation on Immuno Modulatory Activities of Some Consumables in Viral Infections with Special Emphasis on COVID-19

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Abstract
The global pandemic COVID-19 has led human race to concentrate seriously on global health in the absence of standard treatment against it. Despite of the tremendous advances in modern science and medicine, viruses if left unchecked spread exponentially in human body and can be a serious threat. Various respiratory disorders known till today are expected to be caused due to viral infections, severe acute respiratory syndrome coronavirus 2 (SARS-CoV2, the COVID-19 virus), is one most severe of them. Thus, analysing the present situation, it is important to realize that we must prepare our body to fight against such infections by boosting our immune system. A healthy immune system is the most powerful weapon against such viral infections. Natural immunity boosters include foods, fruits, vegetables, few herbs, spices etc. While artificially designed supplements are also immune boosters that help us increase our ability to fight against illnesses. Micronutrients are crucial for an adequate functioning of the immune system and in promoting health and nutritional well-being. In addition to micronutrients, several herbal products, nutraceutical, and probiotics have also shown their effectiveness in enhancing immune response and in treatment and prevention of viral infections. The objective of this review is to investigate various immunity-boosting bioactive components present in food items and supplements along with few factors which affect the immune system. This investigation is expected to develop an understanding regarding various immunity boosting consumables and their importance.

Keywords
Micronutrients, bioactive component, nutraceuticals & probiotics

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INTRODUCTION
The case of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) or COVID- 19 was reported first time in Wuhan, of Hubei province in China in December 2019 (**1**). Later it was confirmed by Chinese scientists that the zoonotic transmission events associated with a large seafood market has led to the disease outbreak and then soon it also transferred from person to person and took the face of "Pandemic" all over the world. However, the case in India was first reported in Kerala. Inspire of tremendous work done in medicinal field, COVID 19 still lacks in standard treatment and only a few antiviral agents, some antibiotics and anti-inflammatory agents are being used for the treatment (**2,3**).

As known antivirals are small molecules that function as inhibitors of one or more stages of a virus lifecycle. Because of similarities between different virus replication mechanisms, some antivirals can be repurposed against various viral infections. Currently, most of the available antiviral drugs tested against SARS-CoV-2 are small molecules previously developed against SARS-CoV-1, MERS-CoV, or other RNA and DNA viruses (**4, 5**). In this context the investigation done by Bukreyeva et.al have shown the IMPDH inhibitor merimepodib suppresses SARS CoV2 replication invitro while M. Milewska et al. have studied HTCC as a highly effective polymeric inhibition of SARS CoV2 and MERS-C0V (**6,7**). Immunity is our bodies ability to provide resistance or protection against diseases and infections caused by pathogens such as viruses, bacteria, parasites, and other harmful microorganisms All the parts of our body that help us fight against diseases and help improve our immunity are collectively named as the immune system. Our immune system has the ability to detect harmful bacteria and viruses that enter our body-these cells, also known as antigens, attack them by producing antibodies.

There are several vitamins and trace elements which are essential for the normal functioning of the immune system. The top ten micronutrients (**8**) included in new immune-boosting products in the five-year period were:

Vitamin C (38 percent), Vitamin D (31 percent), Vitamin B6 (27 percent), Vitamin A (26 percent), Zinc (25 percent), Vitamin E (24 percent), Calcium (24 percent), Folic acid (23 percent), Niacin (23 percent), Vitamin B1 (22 percent).

In addition to micronutrients, several herbs, and probiotics (**9**) also have shown effectiveness for treatment and prevention of viral infections. As known protein-energy malnutrition or even subclinical deficiencies of one micronutrient may impair one's immune responses. The importance of optimal nutritional status to protect against a viral infection and nutritional advice to reduce damages to the lungs from corona virus and other lung infections are also being studied in detail. Still much more work, investigations and trials are required for further studies.

The clinical potential of vitamin A and D metabolites for modulating tissue-specific immune responses and for preventing and/or treating inflammation and autoimmunity is also known. Vitamin D_3 (VD_3), the most physiologically relevant form of vitamin D, is synthesized in the skin from 7-dehydrocholesterol (**10**). Vitamins modulate a broad range of immune processes (**11**), such as lymphocyte activation and proliferation, T-helper-cell differentiation, tissue-specific lymphocyte homing, the production of specific antibody isotypes and regulation of the immune response.

There is some evidence that various micronutrient deficiencies — for example, deficiencies of zinc, selenium, iron, copper, folic acid, and vitamins A, B6, C, and E — alter immune responses in human being however, the matter is still being assessed. The studies conducted by separate research groups namely Carr et al, Hojya et al, & Spritzler et al **(12-14**) have shown the importance of vitamin C, Mg & Zn respectively in building immune system defense however much more investigation and trials are still required.
In this brief review, we will try to discuss few factors which affect the immunity along with immunity boosters which are having immense potential to prepare our body to fight against diseases.

Factors Affecting immunity

Effect of aging on immune function

There is a clear verdict on the relation of immunity and age therefore elderly people are more liable to catch disease as our immune response capability gets reduced. With age the number of immune cells also lessens, the communication among these cells gets hampered and therefore they take longer to react to harmful bacteria and cannot defend the body efficiently.
The role of T-cells in the immune system is of 'retaining in memory' the harmful antigens to be able to fight against them better in the future. With growing age, the production of T-cells decreases and in turn defense mechanism of body is adversely affected (**15**).

Effect of stress on immune function

Modern medicine has come to appreciate the closely linked relationship of mind and body. A wide variety of maladies, including stomach upset, hives, and even heart disease, are linked to the effects of emotional stress.
Most scientists studying the relationship of stress and immune function, however, do not study a sudden, short-lived stressor; rather, they try to study more constant and frequent stressors known as chronic stress, such as that caused by relationships with family, friends, and co-workers, or sustained challenges to perform well at one's work. Some

scientists are investigating whether ongoing stress takes a toll on the immune system.

IMMUNITY BOOSTERS: FRUITS & VEGATABLES (16, 17)

1. **CITRUS FRUITS:** They are rich source of Vitamin C, expected to increase the production of white blood cells, key to fight infections. As human body doesn't produce or store it, one needs daily consumption of vitamin C for continued health. The recommended daily amount for most adults is 75mg for women and 90 mg for men.
   Popular citrus fruits include:
   a) Grapefruit
   b) Oranges
   c) Clementines (Clementines are small oranges that are seedless, easy to peel, and—when well grown and ripe—perfectly sweet to eat)
   d) Tangerines (The tangerine (*Citrus reticula L. var.*, sometimes referred as *Citrus tangerina*) is a group of orange-colored citrus fruit consisting of hybrids of mandarin orange (*Citrus reticulata*).
   e) Lemons
   f) Lime

2. REDBELL PEPPER: Red bell pepper contains almost 3 times as much vitamin C as oranges may have and are rich source of beta carotene. Besides boosting immune system, Vitamin C helps maintaining healthy skin. Beta carotene, which body converts into vitamin A, helps keep eyes and skin healthy.

3. BROCCOLI: Broccoli is one of the healthiest vegetables and is a rich source of vitamins (A, C & E), minerals fibre and many antioxidants.

4. GARLIC: Whole garlic contains a compound called alliin. When garlic is crushed or chewed, this compound turns into allicin, which is the main active ingredient in garlic. Allicin contains sulfur, which gives garlic its distinctive smell and taste. However, allicin is unstable, so it quickly converts to other sulphur-containing compounds thought to give garlic its medicinal properties. To maximize the health benefits of garlic, it should be used in following way:

- Crushing or slicing garlic, increases the allicin content.
- Let the crushed garlic stand for 10 minutes, before cooking.
- Consuming more than one garlic clove per meal, is beneficial for health.

The minimum effective dose for raw garlic is one segment (clove) consumed two to three times per day.

5. GINGER: It is packed with active constituents such as phenolic and terpene compounds. Ginger may help decrease inflammation, which can help reduce a Sore throat, inflammatory and nausea as well. While it is used in many sweet desserts, ginger packs some heat in the form of gingerol, a relative of capsaicin. Ginger may also decrease chronic pain and might even possess cholesterol lowering properties.

6. SPINACH: It is rich in vitamin C, beta carotine and has several antioxidants, they increase the infection-fighting ability of immune systems. However, light cooking makes it easier to absorb the vitamin A and allows other nutrients to be released from oxalic acid, an antinutrients.

7. PAPAYA: Papayas are rich source of vitamin C and also have a digestive enzyme called papain that has anti-inflammatory effects. Papayas have decent amounts of potassium, magnesium, and folate, all of which are beneficial to your overall health.

8. KIWI: Kiwi fruits are naturally full of essential nutrients, including folate, potassium, vitamin K, and vitamin C. They also have a lot of antioxidants and are also rich in fibre. Their small black seeds are edible, as is the fuzzy brown peel, though many prefer to peel it before use.

Other consumables: rich in Vitamin D, E, B6, Zn & Selenium

9. POULTRY:

Chicken and turkey are high in vitamin B-6. Vitamin B-6 is an important player in many of the chemical reactions occurring in the body. It is also vital for the formation of new and healthy red blood cells. About 3 ounces of l chicken meat contains nearly one-third of your daily recommended amount of B-6. Stock or broth made by boiling chicken bones contains gelatin, chondroitin, and other nutrients helpful for gut healing and immunity.

10. SHELLFISH:

It contains protein and omega-3 fatty acids. They also contain high amounts of certain micronutrients, including iron, zinc, magnesium, and vitamin B12. Varieties of shellfish that are high in zinc include: oysters, crabs, lobsters, mussels. Daily recommended amount of zinc in diet is: 11 mg for adult men & 8 mg for most adult women

11. GREEN TEA:

Green and black teas are packed with flavonoids, a type of antioxidant. Green tea has high level of epigallocatechin gallate (EGCG), a powerful antioxidant. EGCG has shown to enhance immune function. The fermentation process black tea goes through destroys a lot of the EGCG. Green tea, on the other hand, is steamed and not fermented, so the EGCG is preserved.

Apart from antioxidant, green tea is also a good source of the amino acid L-theanine. L-theanine may aid in the production of germ-fighting compounds in your T cells.

12. YOGHURT: Yogurt is also a great source of vitamin D. It helps regulate the immune system and is thought to boost our body's natural defenses against diseases.

13. SUNFLOWER SEEDS: Sunflower seeds are full of nutrients, including phosphorous, magnesium, selenium and vitamins B-6 and E. Vitamin E is important in regulating and maintaining immune system function. Other foods with high amounts of vitamin E include avocados and dark leafy greens.

14. ALMONDS: Nuts, such as almonds, are packed with the vitamin and have healthy fats. Almonds are powerful antioxidant and key to a healthy immune system. It's a fat-soluble vitamin, which means it requires the presence of fat to be absorbed properly. Adults need about 15 mg of vitamin E daily. A half-cup serving of almonds, which is about 46 whole, shelled almonds, provides around 100 percent of the recommended daily amount.

FEW IMMUNITIES BOOSTING HERBS/SPICES

All kinds of berries, along with foods rich in omega-3 fatty acids such as beans, flax seeds, and even some nuts can be consumed to strengthen immunity.

Some of the immunity-boosting herbs (18) includes turmeric, garlic, black cumin, licorice (Glycyrrhiza glabra), moench, astragalus, angelica and chamomile Licorice is a plant used for flavoring food, beverages, and tobacco. The root issued as a natural, herbal supplement for medicinal purposes. Chemicals in licorice may reduce inflammation, thin mucus secretions, decrease cough, and increase the body's ability to heal ulcers. The major component of licorice is saponin known as glycyrrhizin, also known as glycyrrhizic acid, which is extremely sweet, foaming triterpene glycoside. It initiates the production of harmones such as hydrocortisone. Glycyrrhiza consists mainly of 20% starch, up to 6.5% glucose, 2-4% asparagines, 8% fat, resins, mannitol, gumprotein, a trace of tannin, .03% volatile oils, bitter principles and other constituents.

15. ECHINACEA PURPUREA (L.) Moench is one of the most important and well-known medicinal plants in the world, belonging to the Asteraceae (Compositae) family. It has been mainly used in chemo-preventive and chemotherapy for infectious diseases in both upper and lower respiratory systems. Alkamides, caffeic acid derivatives, and polysaccharides have been considered important constituents of the plant. A number of studies revealed that aklomides are involved in the immunomodulatory properties. The polysaccharides play an important role in the anti-inflammatory effect of *Echinacea* preparations.

16. ASTRAGALUS: It is an herb, and its root is used to make medicine. Used in treatment of hay fever, diabetes, kidney disease, and many other conditions, but there is no good scientific evidence to support these uses. Some species of astragalus contains a nerve toxin and have been linked to livestock poisonings. Most astragalus supplements contain Astragalus membranous. Although astragalus may have some antiviral activity, there is no strong evidence to support it. Astragalus seems to stimulate and increase the immune system.

17. ANGELICA: It is a plant whose root, seed, leaf, and fruit are used to make medicine. The dominant component of it is **α-pinene** (15.7–20.8%). Other constituents include δ-3-carene (15.4–16.9%), limonene (8.0–9.2%), sabinene (5.0–7.5%) and δ-phel-landrene (13.5–15.4%), δ-3-carene (13.2–14.2%) and α-phellandrene (8.0–9.1%). Apart from other uses it is widely used to modulate the immune system (**19**).

18. CHAMOMILE: It has been investigated to exhibit the antioxidative and antimicrobial activity. The obtained results proved the presence of 52 components, wherein the highest content of β-farnesene (29.8 %), α-farnesene (9.3 %), α-bisabolol and its oxide (15.7 %), chamazulene (6.4 %), germacrene D (6.2 %) and spiroether (5.6 %) is determined. Chamomile essential oil has shown the best antioxidant properties after 90 minutes of incubation with EC_{50} value of 2.07 mg/ml.

19. TURMERIC: High concentrations of curcumin, gives turmeric its distinctive color, can help decrease exercise-induced muscle damage. Based on findings curcumin is a promising immune booster and an antiviral. Antimicrobial activity of curcumin made it a good candidate to enhance the inhibitory effect of existing antimicrobial agents through synergism.

IMMUNITY BOOSTING DRINKS

20. **KADHA (DECOCTION): An Ayurvedic immune-boosting drink** (**20**)

Kadha is an ayurvedic drink including herbs and spices which are typically boiled in water for a length of time, allowing the extraction of its content for all of the medicinal benefits. Cardamom and black pepper are helpful in flu and different allergic problems. Cinnamon and ginger also aid digestion, which directly impacts our immunity, as our first line of defense is in the gut.

Contents of Kadha

a) Cardamom: It contains steam volatile oil, fixed (fatty) oil, pigments, proteins, cellulose, pentosans, sugars, starch, silica, calcium oxalate and minerals.
b) Cinnamon: Cinnamon consists of a variety of resinous compounds, including cinnamaldehyde, cinnamate, cinnamic acid, and numerous essential oils.
c) Dried Ginger: Ginger (*Zingiber officinale*. Chemical analysis of ginger shows that it contains over 400 different compounds. The major constituents in ginger rhizomes are carbohydrates (50–70%), lipids (3–8%), terpenes, and phenolic compounds. Terpene components of ginger include zingiberene, *β*-bisabolene, *α*-farnesene, *β*-sesquiphellandrene, and *α*-curcumene, while phenolic compounds include gingerol, paradols, and shogaol. These gingerols (23–25%) and shogaol (18–25%) are found in higher quantity than others. Besides these, amino acids, raw fiber, ash, protein, phytosterols, vitamins (e.g., nicotinic acid and vitamin A), and minerals are also present.
d) Black pepper: Contains piperine as the main bioactive compound (naturally occurring alkaloid) it also contains volatile essential oils.
e) Water, honey – optional to taste

1. **HONEY IN DRINKS**

Honey contains several enzymes, including invertase, which converts sucrose to glucose and fructose; amylase, which breaks starch down into smaller units; glucose oxidase, which converts glucose to gluconolactone, which in turn yields gluconic acid and hydrogen peroxide; catalase, which breaks down the peroxide formed by glucose oxidase to water and oxygen; and acid phosphorylase, which removes inorganic phosphate from organic phosphates.

Honey also contains eighteen free amino acids, of which the most abundant is proline.

Vitamins, minerals, and antioxidants

Honey contains trace amounts of the B vitamins riboflavin, niacin, folic acid, pantothenic acid, and vitamin B6. It also contains ascorbic acid (vitamin C), and the minerals calcium, iron, zinc, potassium, phosphorous, magnesium, selenium, chromium, and manganese.

The main group of antioxidants in honey includes flavonoids, of which one, pinocembrin, is unique to honey and bee propolis. Ascorbic acid, catalase and selenium are also antioxidants. It is general observation that the darker the honey, the greater its antioxidizing properties.

Other compounds

Honey also contains organic acids such as acetic, butanoic, formic, citric, succinic, lactic, malic, pyroglutamic and gluconic acids, and a number of aromatic acids. The main acid present is gluconic acid, formed in the breakdown of glucose-by-glucose oxidase. Honey also contains hydroxymethyl furfural, a natural product of the breakdown of simple sugars below pH 5 (21).

1. **FRUIT/VEGETABLE JUICES:** As mentioned above, fruits like tomato, carrot, berries, kiwi, watermelon, orange, apple, spinach & herbal tea
2. **PROBIOTICS:** Human body is infested with different kinds of bacteria of which some bacteria are actually very good for us. These “good bugs” live in the stomach. They help to properly digest the food, as well as aid in other essential bodily functions. Probiotics contain good bacteria that stomach craves. Lactobacillus probiotics are things like yogurt and other fermented foods which, when eaten, aid in the digestive process. There is also some research that indicates that probiotics may help aid: skin conditions, urinary and vaginal health, oral disease, as well as allergy management. A study showed, 28 bacterial strains isolated from spontaneous fermentation of soymilk were assessed for probiotic characteristics such as low pH resistance, bile salts resistance, antibacterial activity, and hemolysis test. From the 28 organisms, 9 were selected as probiotics because they showed resistance to pH 2.5, bile salt (0.4%) and none of them had hemolytic activity. They also showed resistance to a spectrum of antibiotics and were able to inhibit the growth of pathogenic Gram positive and Gram-negative indicator organisms. Few of the bacteria; strains were able to degrade both raffinose and stachyose which are regarded as non-digestible oligosaccharides by humans. Probiotics are available in both pills as well as in food items (22).
3. **NUTRACEUTICALS:** Nutraceuticals are high-absorbing nutritional supplements. They are pharmaceutical grade vitamins that are derived from food and designed for the management of certain health conditions. People will commonly confuse nutraceuticals with their distant cousins: vitamins or nutritional supplements. These are super-powered vitamins used to manage oral diseases and aid in the mouths recovery. They are formulated to give

the body the essential nutrients to build jaw bone, protect tooth enamel, and maintain the health of your gums. They are such foodstuff (as a fortified food or dietary supplement) that has been shown to provide health benefits in addition to its basic nutritional value.

A research group has demonstrated that immune and epithelial cells can discriminate between different microbial and bioactive plant species. This has extended the known mechanism(s) of action of nutraceuticals and probiotics beyond simple nutrition and/or antimicrobial effects. The progressive unravelling of their effects on systemic immune and intestinal epithelial cell function has led to new credence for the use of probiotics and nutraceuticals in clinical medicine. The use of nutraceuticals and probiotics as therapeutic agents for gastrointestinal disorders is rapidly moving into clinical usage. Thus, these products can support or mediate aspects of immunity via interaction with the digestive tract (23).

Supplements for Boosting Immunity

Many a time, it is not possible for us to cover all the essential vitamins and minerals in our natural diet. Our regular diet may sometimes fail to provide the body with all the vital immunity boosters. That's exactly where dietary supplements can help.

Vitamins B6, B complex, C, D and E, Zinc, selenium have been shown to help boost your immune system" Hansen says. Inverted comma to be introduced at the end i.e., after system. But your body can only absorb so much of any vitamin in each day. So, if you are taking too many of these vitamins, you're going to get rid of the extra in your urine. However, supplements can cause side effects as well.

Maintaining Immunity: Some healthy practices

Consuming immunity boosters in regular diet, and daily supplements are just a part of developing a healthy immune system. Some daily practices which are required to further maintain healthy living are as follows

- Regular exercise - This helps in blood circulation and keeps the heart healthy, and body relaxed
- Maintaining proper hygiene.
- Get vaccinations and immunizations to prevent diseases such as pneumonia, flu, hepatitis, and others
- Adequate sleep and hydration of body. This practice is one of the best ways to boost immunity naturally
- Quit smoking and consume limited alcohol. Smoking and excessive drinking weaken your immune system

By sticking to a healthy and nourishing diet, exercising regularly, and consuming daily supplements, one can have an excellent immune system and stay healthy, safe, and active.

CONCLUSION

The already established view suggests that immune system plays a fundamental role in not only fighting against infections, for acquiring immunity after vaccination, establishing the first line of defense after infection, but also for fighting to overcome the disease. As no exact pharmacological formulations is available till date to treat few cases of viral infections therefore presenting a life-threatening situation before us. Apart from maintaining correct hygienic practices in prevention of virus transmission, the intake of varied and balanced diet, rich in micronutrients and bioactive compounds, should be recommended to maintain good health thereby preparing our body to deal with foreign infectious agents. Therefore, our efforts should be directed towards improving the nutritional intake.

The role of certain essential nutrients (vitamins B6, B9, B12, A, D, C, and Cu, Fe, Zn, Se) to contribute significantly to the proper functioning of the immune system and have also shown favorable immune-modulatory effects in viral respiratory infections (24). Vitamins D, C, Zn, and Se have been thoroughly studied to show favorable immune response in viral respiratory infections and improves the immune system to fight against COVID-19 disease. Several nutraceutical and probiotics may also have some role in enhancing immune functions.

To validate scientific evidence, different clinical trials are ongoing currently, with promising preliminary results although inconclusive yet.

Thus, comprehensive scientific studies are still to prove that these bioactive components may not prevent the infection but can certainly help to fight against viral diseases like COVID-19.

In the present study, we have tried to evaluate the immunomodulatory activities of various naturally occurring fruits, vegetables, supplements, immune boosting drinks, probiotics & nutraceutical which play a vital role in maintaining good health. All these have different but definite immune modulatory capacities, and all this is because of the specific chemical content possessed by each of them. This review also aims to aware people to achieve a recommended amount of nutrition in terms of various vitamins (C, D, B6, and B12), minerals like Zn, Se etc. as well as micronutrients to enhance the immunity. Apart from bioactive components active lifestyle, physical exercise, healthy diet, relaxation, and sound sleep, are other certain other ways to boost immunity

The current global scenario challenges humans to meet the recommended amounts of calories and

micronutrient through balanced diet. Therefore, micronutrient supplementation is expected to be beneficial for elderly population.

CONFLICT OF INTEREST

The author has no conflicts of interest to declare. The author agrees with the contents of the manuscript and there is no financial interest to report. It is certified that the submission is original and is not under review at any other publication.

ETHICAL APPROVAL

I have adhered to the accepted ethical standards of a genuine review study.

All the procedures performed in studies were in accordance with the ethical standards of the institutional and/or national research committee.

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