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A Systemic Review and Survey on Therapeutic Effect of Nutraceuticals In Covid-19

Rinshu Dabas*, Satyam Bhardwaj, Kshitiz Kashyap, Praful Tiwari
Delhi Pharmaceutical Sciences and Research University

ABSTRACT

SARSCoV2 infection has caused and will continue to cause considerable human suffering. Research on the pathogenesis of viruses has yielded consistent results from various tests of virus entry and spread to the host. These studies also revealed a strong association between harmless inflammations, aging and metabolic disorders, and SARSCoV2 infection and its prognosis. Diet helps regulate inflammation, and nutritious foods can inhibit the entry of viruses. Therefore, we have compiled the literature on antiviral health products that are effective against other similar coronaviruses. The purpose of this study is to comprehensively review the available information about the antiviral activity of nutritious foods and discuss the impact of these findings on the design of diets that can enhance innate immunity and prevent COVID19. This review emphasizes the fundamental impact of nutritious food and diet on inhibiting virus entry, and provides a new perspective for the prevention and treatment of COVID19.

Keywords: SARSCoV2, diet, plant protease inhibitors, polyphenols, biologically active peptides

*Corresponding Author Email: rinshudabas013@gmail.com
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INTRODUCTION

Since the beginning of 2020, SARS CoV2 has disrupted global health and economic well-being. The World Health Organization (WHO) China Regional Office issued an alert for the virus infection in Wuhan for the first time on December 31, 2019, and classified the infection as an epidemic on March 11, 2020. Since then, laboratories around the world have been collaborating to develop vaccines and therapeutics against this new type of coronavirus. SARSCoV2 belongs to a group of viruses called coronaviruses. These are single-stranded, positive-stranded RNA viruses, wrapped in a spiral capsid, with spike-like transmembrane proteins. In addition, they can be divided into four subtypes: α, β, δ, and γ. [1] Coronavirus can infect humans and animals, and has the ability to cross species barriers, thereby accelerating the spread of diseases or diseases in epidemics. Pandemic. Severe acute respiratory syndrome coronavirus (SARSCoV and SARSCoV2) and Middle East respiratory syndrome coronavirus (MERSCoV) are three highly pathogenic coronaviruses. The remaining four human coronaviruses (HCoVNL63, HCoV229E, HCoVOC43 and HCOVHKU1) have low virulence. [2]

It is not only viral infection that makes SARSCoV2 a threat, but also the cytokine storm and other related complications that follow. Analysis of clinical data of 326 confirmed COVID19 patients in Shanghai showed that IL6 and IL8 showed the most significant changes, and the levels of these two interleukins were negatively correlated with lymphocyte counts. [3] The reduction in the ratio of CD4 + / CD8 + is also a manifestation of the disease. Host immune response and virus evasion methods will be explained in detail later in this article.

Initial genome phylogeny testing showed that the SARSCoV2 virus has approximately 79% and 50% genetic similarity to SARSCoV and MERSCoV, respectively.[2] Therefore, initial treatment includes SARSCoV2, which is known to be effective against SARSCoV and MERSCoV.

What makes the SARS-CoV-2 threatening is not just the viral contamination but the accompanying cytokine storm and other associated comorbidities. Investigation of clinical data from 326 confirmed COVID-19 patients in Shanghai revealed IL-6 and IL-8 to show the most significant changes and the levels of these 2 interleukins inversely co-related with the lymphocyte count.[3] A reduced $CD4^+/CD8^+$ ratio is also a manifestation of the disease. A detailed description of the host immune response and the viral evasion methods follows in the later part of this paper.

In this article, we describe the current understanding of the virus life cycle and host immune response, which will form the basis for the selection of nutritious foods and natural products, which can be explored as treatment and preventive interventions for SARS CoV2 infection.

Nutraceutical:

It is a food or a part of meals that give health benefits, as well as a prevention or a cure of a disease.

Nutraceuticals play a very essential function in boosting immunity without harming the body a usual protection mechanism examples of essential nutraceuticals include vitamin C, zinc, and selenium, they increase the immunity of the human frame system.

So, Nutraceuticals has proven their health benefits and disease prevention capability, which should be taken according to their acceptable recommended intake.

In the present scenario of self-medication, nutraceuticals play a major role in therapeutic development. But their success depends on maintaining their quality, purity, safety, efficacy and they help to maintain the health of the individual and reduce the risk of various diseases.

Yi et al[11] conducted in vitro and animal experiments with multiple small molecules and found that luteolin can effectively block the S2 protein of the SARS CoV virus. The amino acid similarity between SARSCoV and SARSCoV2 protein S is approximately 76%. [7] Since these two viruses bind to the same host receptor, molecules that block or interact with the SARSCoV S protein are more likely to be effective against the SARS CoV2 S protein. The authors also tested quercetin using a pseudotyped virus assay. . The basic principle of quercetin's function is that quercetin and luteolin have structural similarities. Quercetin is a component of antioxidant and anti-allergy medications approved by the US Food and Drug Administration.

This strategy by Yi et al.[11] can be extended to current searches by identifying structures similar to those that have shown promise in computers and in vitro, but have a Generally Recognized Safety Status (GRAS) due to their records of food use or medicines. . This can greatly reduce the time required for regulatory approvals and provide more confidence in clinical trials. In fact, Lin et al[12] used a similar strategy when deciding to test the efficacy of resveratrol (a derivative of stilbene), which is based on preliminary studies showing antiviral activity against the SARS coronavirus.

Despite the sequence variation, the major protease (MPro or 3CLPro) from coronavirus has a conserved framework and active site conformation. [13] Therefore, nutritional supplements, such as epigallocatechin gallate (EGCG), gallocatechin gallate (GCG), hesperetin, and quercetin, which have been shown to be effective before, can be tested with 3CLPro Efficacy of SARSCoV2 infection. Nguyen et al.[14] found that the galloyl residue (belonging to the flavonoids) present at the position of the potential inhibitor 3′OH is essential to inhibit 3CLPro in SARSCoV. Enzyme kinetics showed that GCG competitively inhibits 3CLPro with an inhibition constant of 25 μM.

Quercetin appears to have multiple targets and may be a better candidate molecule for therapeutic development. The administration of quercetin (1000 mg) showed a reduction in the incidence and degree of upper respiratory tract infection (URTI). Abian et al. [17] identified quercetin as an effective inhibitor of the SARSCoV2 protease 3CLpro with an inhibition constant of –Ki ~ 7 µM. Quercetin also regulates the unfolded cellular protein (UPR) response. Since the coronavirus can use UPR to complete different stages of the virus life cycle during the infection process, this is an important discovery.[18] Early clinical data shows that quercetin has a wide range of antiviral properties and plays a role in various life cycle steps of the virus. As a pharmacological ingredient approved by the FDA with potent antiviral effects, quercetin is expected to become a potential drug candidate for the clinical treatment of SARS.

LITERATURE REVIEW

Virus Replication Cycle and Potential Therapeutic Targets

Accepting the cellular basis of SARS-CoV-2 infection could reveal treatments that prevent the improvement to a severe disease, and thus decrease mortality. This represents a simplified illustration of the infection cycle of SARS-CoV-2. (I) The spike protein (S) on SARS-CoV-2 facilitates attachment to the host cell through the ACE2, TMPRSS2. The S protein has two subunits, S1 and S2

- The S1 subunit attaches to ACE2
- Following which TMPRSS2 cleaves ACE2
- The S2 subunit facilitates fusion of the viral particle with the host cell membrane thereby leading to viral entry (c).

(II and III) Alternatively, the viral entry can also occur via endocytosis.

(IV) Release of the viral genome (+ strand) after entry.

(V) Translation of the strand leads to the formation of polyproteins (pp1a and pp1ab) which are cleaved by the main protease (MPro) and papain-like protease (PLPro) into the nonstructural proteins (nsps).

(VI) The genome is replicated by RdRp.

(VII) The transcription of the genome gives the sub genomic transcripts which encode the structural proteins.

(VIII) The nucleocapsid is translated in the cytoplasm.

(IX) The other structural proteins are translated in the endoplasmic reticulum (ER).

(X) The nucleocapsid and the genomic strand form the genomic RNA.

(XI) The structural proteins are glycosylated in the golgi bodies.

(XII) A budding vesicle forms with the virion particles assembling.

(XIII) Exocytosis of the assembled viral particle occurs.

(XIV) The newly released viral particles can now infect other host cells.

The spike glycoprotein (S) is a 180-200 kDa transmembrane homotrimer that recognizes and binds to the host's angiotensin converting enzyme 2 (ACE2) receptor. [4]The S protein can be subdivided into S1 (homotrimer head) and S2 protein (tail). ACE2 is a human receptor, found mainly in the respiratory tract and intestinal epithelial cells, but also in the kidneys, heart, brain, etc. ACE2 has a short C-terminal intracellular domain and a long N-terminal extracellular domain. Its S2 head is located.[5] The spike protein mediates two basic events: binding to ACE2 through the amino terminal region, and virus and virus fusion through the carboxy terminal region Cell membrane.

The spike protein that binds to ACE2 can be cleaved by two enzymes, transmembrane serine protease 2 (TMPRSS2) at the S2 site and furin at the S1 / S2 binding site. [6] TMPRSS2 acts at a single base cleavage site, that is, it cuts arginine or lysine residues at a single cleavage site. However, furin is cleaved at multiple sites. [6] Infection of lung cells requires host proteolysis to activate spikes at the cleavage site of multiple furins. Therefore, furin lysis can expand the cell tropism of SARSCoV2 and can promote the spread from bats to humans. Therefore, the tropism of SARS CoV2 depends on the expression of cellular proteases and ACE2.

However, TMPRSS2 is not expressed in all ACE2-expressing cells, indicating that there are alternative pathways for virus entry, such as through the use of cathepsin L and cathepsin B. [7] However, this is a controversial issue because research has also found that cathepsin is not required for SARSCoV2 infection. [6] After lysis, the virus can enter the host cell through membrane fusion or endocytosis. [5]

Two-thirds of the viral genome produce two polypeptides, pp1a and pp1ab, which are processed by the viral protease chymotrypsin (such as cysteine protease) (3CLPro) or the major protease (MPro) and one or two similar papain The protease is It is converted into 16 non-structural proteins (nsps), which play different roles in subsequent virus replication and infection. [8] The remaining third of the genome encodes the major viral proteins, namely spike protein, nucleocapsid protein, membrane protein, and envelope protein. Replication occurs in double membrane vesicles (DMV) that contain RNA-dependent RNA polymerase (RdRp) and nsps. The subgenomic particles made here enter the Golgi complex compartment of the endoplasmic reticulum, where they undergo maturation. The toxic particles present in the vesicles are further

released by exocytosis. [1] Therefore, the life cycle of a virus and its host includes five steps: attachment, penetration, biosynthesis, maturation, and release.

Therapeutics can target viral proteins or host proteases. Since host proteases perform multiple functions in the human body, host proteases can also interfere with other physiological activities in the host, so caution should be exercised in this method. Therefore, viral proteins seem to be more attractive and safer targets.

Regarding the SARSCoV2 virus, the following have been identified as possible therapeutic targets: peak glycoprotein (S), envelope glycoprotein (E), nucleocapsid protein (NP), membrane protein (M), protease equal to papain (PLPro) or chymotrypsin-like cysteine protease (CLPro), (also known as the MPro major protease) and RNA-dependent RNA polymerase (RdRp). Also, some nsps can also be targeted. The nsp13 helicase is an important part of virus replication and is the target of many virus inhibitors. [9] Nsp10 plays an important role in viral transcription, among which exonuclease nsp14 3′5′ and nsp16 2′O methyltransferase are stimulated, playing a major role in viral mRNA cap methylation.[10]

The protease inhibitors of plants as potential therapeutic molecules for the SARSCOV2

Virus use proteases (generally proteases of reception) to obtain the entry to the host. Synthetic protease inhibitors have been widely used as treatment tools for various viral diseases, such as those caused by HIV, HCV, picornavirus, SAR, rotavirus and the like. [19] diabetes, cancer and inflammation potential, has been investigated as a treatment option. Virus protease inhibitors HIV, HCV, Picornavirus and SARS have also been studied from bacterial and fungal origins.[21] TMPRS2 and Furin are serine host proteases that promote the entry into the Sarscov2 host cell. TMPRSS2 is trypsin, such as serine protease, but Furulin is a cysteine protease of cysteine [20], plopo and turbulin chemotrypsin, MPRO plays an important role in viral replication. The epithelial cells of the respiratory tract are removed from the protease / protease inhibitor that help maintain the homeostasis required for healthy pulmonary function. [22] Balance of protease / protease inhibitors determines the degree of virulence of the respiratory virus. The change to the most proteases can increase viral etiology, but the reverse subsequent can help protect it.

Deng et al. Animal studies [24] can provide a rapid resistance to coronavirus to 3 clicks inhibitors, but this resistance can obtain the cost of the virus, which cannot reduce compatibility costs with the infection virus. TMPRSS2 is a transmembrane serine protease of type 2 secretion 2, and it has been shown to be sensitive to reflective beds in the middle of the infection. [23]Therefore, protease inhibitors or anti-light salts for these protease enzymes can be examined as potential therapeutic molecules.

Comments with Hellinger and Gruber[25] and Srikanth and Chen[26] describe some plant protease inhibitors, some of which are collected. This is a good starting point to start evaluating these molecules for its effectiveness for SARSCOV2 viruses. 3 Clpro and Papang Protease.

Although the main function of anti-proteases is to inhibit or inactivate proteases, recent studies have found that they have more effects in controlling excessive inflammation and microbial infections. [22] Therefore, the identification of multifunctional plant protease inhibitors may allow multi-step protection against coronavirus infection.

IMMUNE BOOSTERS AND NUTRALCEUTICALS USED IN COVID 19

Probiotics and Prebiotics

Probiotics or gut microbiota plays an important role in slowing down inflammation and related metabolic diseases. Bifidobacterium and Lactobacillus strains are common natural probiotics and are available on the market. The brain-gut axis promotes the expression of anti-inflammatory cytokines by inhibiting TLRs.[44] The intestinal tract has a high expression of ACE2, so it is vulnerable to SARS CoV attacks, as evidenced by the gastrointestinal symptoms of some patients. [45] Therefore, supplementing patients with probiotics is a treatment method to control the spread of infection, and it can also be used as a preventive treatment. There are also reports of microorganisms in the lungs. Bacteroides, Firmicutes and Proteobacteria are the three main characteristic phyla.[45] Similar to the brain-gut axis, the gut-lung axis is the link between the gut microbiota. They work through blood vessels, so intestinal metabolites affect the function of the lungs. They work through signals from Nod2 and GMCSF. In turn, respiratory diseases may cause dysbiosis.[44]

Several studies reported alleviation of symptoms of the common cold and a reduction in its duration by supplementation with *Lactobacillus plantarum* HEAL9 (DSM 15312) and *Lactobacillus paracasei* 8700:2 (DSM 13434) at a concentration of 1×10^9cfu/day[46] and *Lactobacillus gasseri* PA 16/8, *Bifidobacterium longum* SP 07/3, *Bifidobacterium bifidum* MF 20/5 at a concentration of 5×10^7cfu/day. [47]When these probiotics were administered along with the influenza vaccine, an increase in the antibody titer was observed.[48] An on-going clinical trial is noteworthy in this regard.[49,50]

Prebiotics can also confer anti-inflammatory activity by inducing the production of IL10 and IL17.[51], thereby exerting beneficial effects. , Leading to down-regulation of NFκB and MAPK pathways.[52] The levels of certain LPS-induced pro-inflammatory cytokines and chemokines (such as TNFα, CXCL8, CCL20) showed down-regulation during systemic butyrate administration. [51] SCFA also shows immune regulatory function T cell function through

regulation.[51] Oat bran and Psyllium husk fiber produce SCFA through the fermentation of the intestinal microbiota, which acts as a natural prebiotic. These can also bind to PPAR and promote homeostasis[53.]

Vitamin C

Vitamin C (ascorbic acid) has antioxidant and Immunomodulatory properties. Helps reduce damage caused by oxidative stress during viral infection.[54] ARDS patients have reduced levels of vitamin C (Vit C), and topical vitamin C may reduce the degree of lung inflammation in ARDS.[55] Inflammation is the main cause of the severity of COVID19. It has been hypothesized that vitamin C supplementation may help counteract the effects of pro-inflammatory cytokines, especially IL6. Treatment with vitamin C (500 mg twice daily) [56] and its intravenous administration (doses of 6 to 12 g / day and 24 g / day for 7 days) (NCT04264533) can reduce IL6 and other inflammatory cytokines (ferritin and D-dimer) levels) .[57] Vitamin C as adjunctive therapy may help reduce pneumonia-like symptoms and significantly reduce mortality.[58]

Clinical trials is undergoing to combine vitamin C with other substances such as quercetin, vitamin D, and zinc in different forms (intravenous or oral dose) to treat COVID19. [57] In mice infected with stress-induced H1N1, quercetin Curtain co-administration with vitamin C and vitamin B3 has been shown to delay the time to death and reduce mortality, which is in contrast to the administration of a single vitamin. Similar co-administration of vitamin C[59] A with quercetin, vitamin D, and B3 can help improve symptoms in severe cases of COVID19. It is well known that vitamin C can enhance the efficacy of quercetin[58], and in a three-month study, it was found that a combination therapy of quercetin (500 mg) -vitamin C (500 mg) -bromelain (50 mg) was used as medical treatment Preventive treatment of staff is effective.[60]

Vitamin D

Research has shown the role of vitamin D (Vit D) in immune regulation. Comment [60] by Grant et al. mentioned different mechanisms by which vitamin D exerts its antiviral effects. Vitamin D has been shown to down-regulate ACE2 receptors by negatively regulating the renin-angiotensin system (RAS). [61] A recent study observed an association between the severity of COVID19 and the lack of vitamin D in high-latitude countries receiving less sunlight. However, when making this observation, it should be understood that every population will show a mixed population with or without vitamin D deficiency, so it is difficult to generalize.[62]

Ghavideldarestani et al.[63] suggested the role of vitamin D in the prevention of local lung inflammation in patients with COVID19. Angiotensin II can increase vasoconstriction, oxidative stress and inflammation by binding to AT1 receptors. This angiotensin II can be cleaved by

ACE2 into angiotensin, thus counteracting the harmful effects of angiotensin II. However, in COVID19 patients, ACE2 is hijacked by the virus due to entry, so less ACE2 is used for this routine physiological effect. Vitamin D deficiency increases renin production, which in turn increases ACE and angiotensin II production. This can lead to the inflammation of the lungs seen in severe cases of COVID19.

Glinsky[16] uses a gene-first approach to study potential therapeutic targets for COVID19. They first identified the human genes responsible for the expression and function of ACE2 and FURIN (viral binding molecules). They then studied the expression profiles of these genes when they were infected by the coronavirus. After searching the literature for molecules that could negatively regulate the expression of related genes, three potential therapeutic molecules were discovered: vitamin D, quercetin, and estradiol. Vitamin D was found to change the expression of 84 genes out of 332 (25%) genes that encode human proteins, which are targets of SARSCoV2. The author recommends the use of two-component (quercetin vitamin D) or three-component (quercetin vitamin Destradiol) preparations as adjunctive treatment for coronavirus patients. In fact, there are two clinical studies on vitamin D.

Lactoferrin

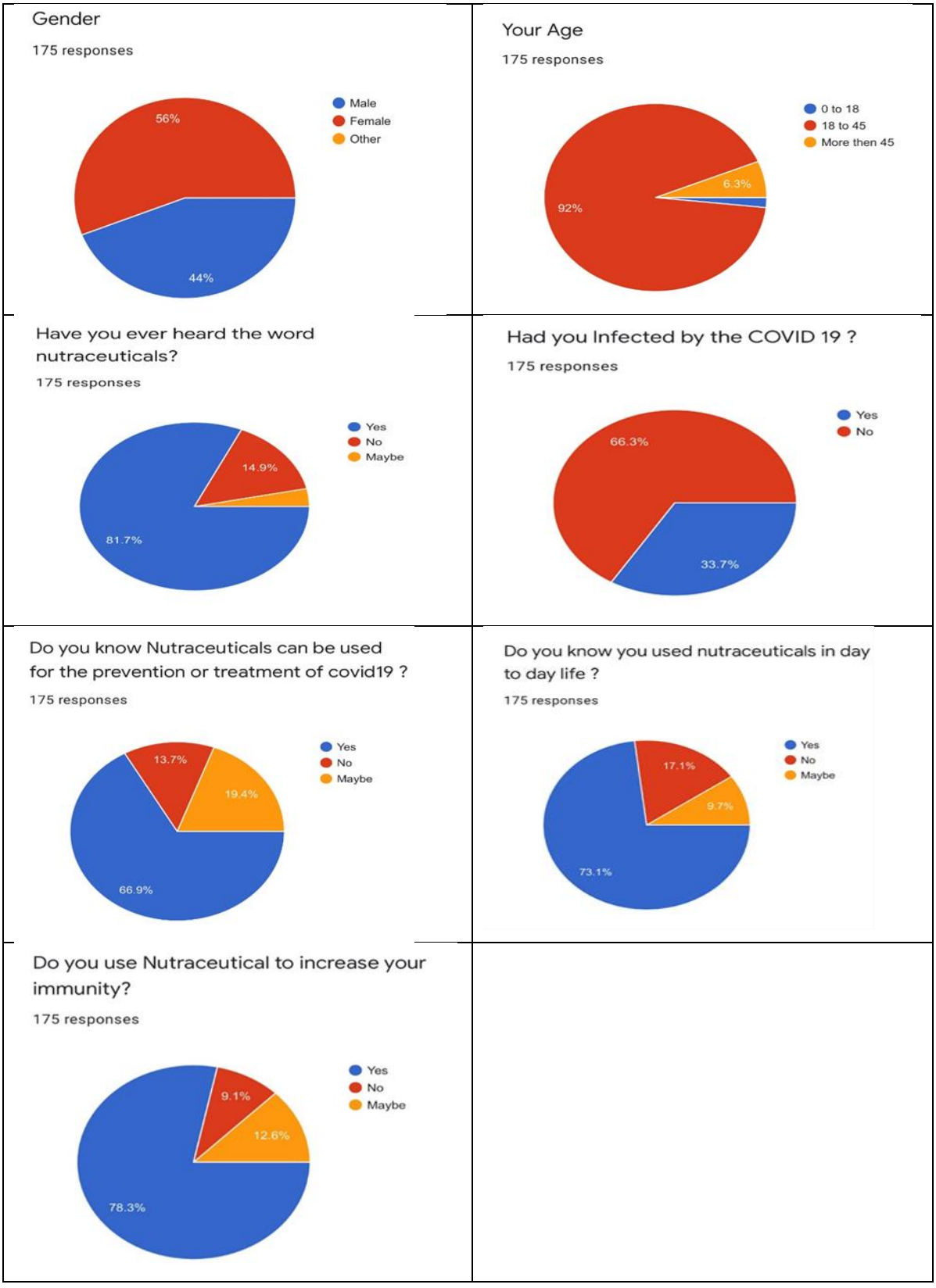
Experiments found that lactoferrin can inhibit virus entry into murine coronavirus, human coronavirus hCOVNL63, and SARSCoV pseudotype. In addition to preventing virus entry, lactoferrin can also inhibit virus replication after it enters. It shows that lactoferrin chelates ferritin, thereby down regulating IL6 and TNFα. A clinical trial is currently underway to study the effect of lactoferrin as an adjunctive treatment for COVID19.

Turmeric

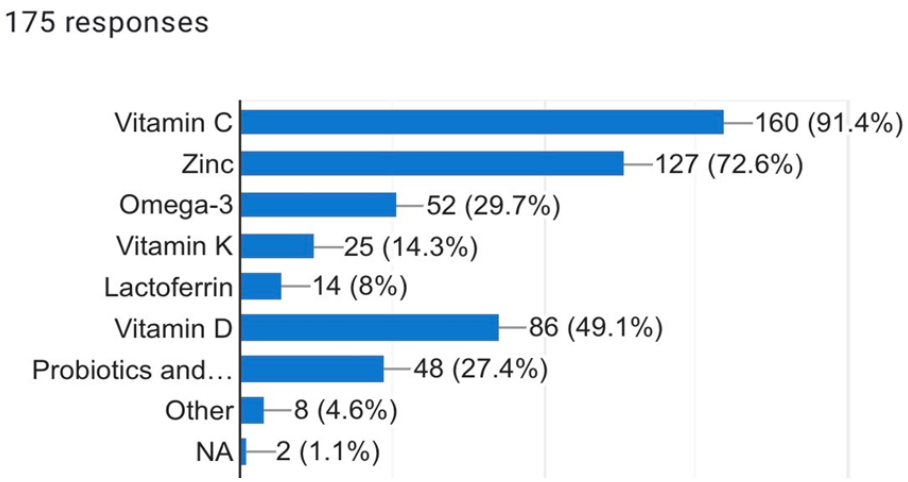
It is an integral part of Asian culture. For centuries, turmeric has been used in traditional medicine systems such as Ayurveda, Unani, and Siddha due to its wide range of medicinal properties. Curcumin is the main curcuminoid in turmeric, which can affect a variety of signal pathways and has been found to have anti-inflammatory, antioxidant, antibacterial, hypoglycemic, healing, chemoprevention, chemical sensitization, and radio sensitization properties. In order to increase the bioavailability of curcumin, new technologies such as adjuvants, nanoparticles, liposomes, micelles, and phospholipid complexes are evaluated during the drug development process. According to the records, it is most effective in high doses of 6-7 grams per day and is well tolerated orally. In Asia, it has been widely used as a common home remedy to treat coughs, sore throats, and respiratory illnesses.[64]

SURVEY CONDUCTED

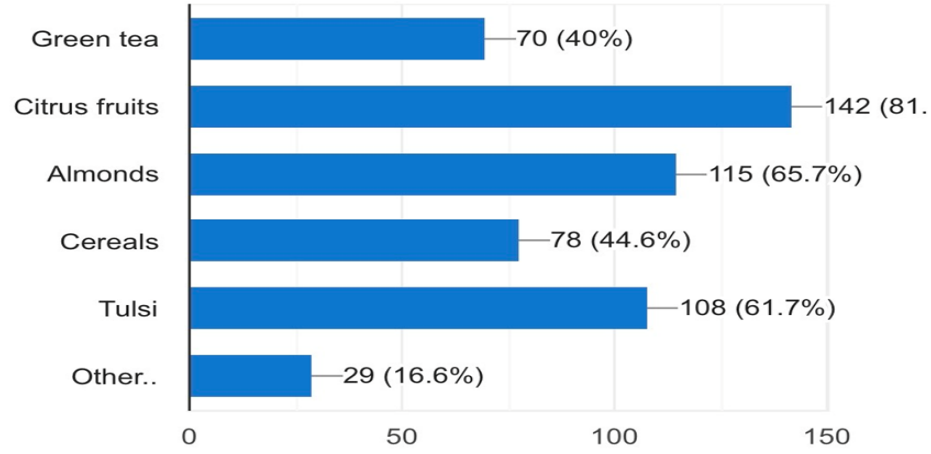
The survey has been conducted and get 175 responses. The responses we get in this survey as listed below:



Which nutraceuticals do you usually see or use people having covid19?



Which nutraceuticals you take to boost up your immunity?



CONCLUSION

Covid is currently a pandemic situation affecting worldwide, with new strains, highly mortality rate, no effective treatment. Studies have found out many information about the SARS-COV-2 virus infection. Although we've got won insights into the SARS-CoV-2 viral pathogenesis, a definitive remedy path remains distant. As we are familiar with words “precaution is better than cure” in such times, the wise manner is to hold the first-class viable fitness through taking appropriate adjuvants to keep away from falling ill. It is obvious that there are numerous components that may be covered in each day program to in all likelihood benefit immunity or safety towards coronavirus. Other bioactive polyphenols, which include GCG are not unusual place materials of inexperienced tea, quercetin is observed abundantly in apples even as hesperetin is found in citric meals. Spices which include turmeric, thyme, rosemary, garlic have anti-inflammatory houses and may be utilized in each day cuisine. So there are various things in which comes under the nutraceuticals which are already discussed in the above literature or in this project. Citrus food is most commonly used by the people in this pandemic where in the

vitamins the vitamin c is commonly used by the peoples. In conclusion, the cutting-edge assessment highlights the ability advantages of various nutraceuticals with inside the control of COVID-19. Further paintings aimed toward clarifying the mechanisms of moves and ability healing software calls for in addition investigation.

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