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Possible Link between Gut Microbiota, Diet, and COVID-19 Infection

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ABSTRACT

***Background**:* Coronavirus disease 2019 (COVID-19) is a concern for world health since it may impact both the upper (nose, throat, sinuses) and lower (trachea, lungs) respiratory tracts. Death (at a rate of 10%), respiratory failure, multi-organ failure, and acute respiratory distress syndrome (ARDS) are among the problems that might arise. Recent years have seen a global spread of zoonotic coronaviruses, which have caused human epidemics such as MERS and SARS. Various clinical symptoms may be seen in this sickness because to the numerous changes in intestinal homeostasis caused by SARS-CoV-2. Because of the beneficial impact that probiotics have on the host immune system, gastrointestinal disorders may now be effectively treated. This article discusses the close relationship between what we eat, the bacteria in our gut, and the risk of contracting the COV-19 virus.

***Conclusion**:* The relationship between gut microbiota, dietary factors, and COVID-19 severity indicates that the microbiome may influence immune regulation. Imbalances in microbial communities and reduced diversity can intensify inflammation, potentially worsening COVID-19 outcomes. Strategies such as probiotics, prebiotics, and dietary changes might provide therapeutic benefits by improving gut health and strengthening immune defenses. However, further research is required to clarify these mechanisms and establish effective interventions.

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Introduction

COVID-19 is a global health threat since it affects the upper (sinuses, nose, throat) and lower (trachea and lungs) respiratory tracts and can result in issues including acute respiratory distress syndrome (ARDS), respiratory failure, multi-organ failure, or even death (10)% (1, 2).

The entry of the coronavirus is carried out by the viral spike glycoprotein (S). Then the binding is done through angiotensin-converting enzyme 2 (ACE2) (3). The Binding of the virus to ACE2 causes the virus to attack the cells of the oropharynx epithelium and cause severe inflammation and lung damage (4, 5). ACE2 is exhibited on alveolar, bronchial, and tracheal epithelial cells, as well as alveolar monocytes, bronchial serous glands, and macrophages (6, 7).

Since ACE2 expression declines after a viral infection, COVID-19 patients have reduced structure, function, and diversity of their gut microbiota. Additionally, ACE2 controls tryptophan (Trp) absorption in the gut via regulating the manifestation of the B0AT1 amino acid transporter. Trp controls the mRNA levels of antimicrobial peptides through the mammalian TOR (mTOR) pathway, which affects the microbiota. Thus, a decrease in ACE2 expression leads to a decrease in the absorption of Trp in the intestine and the production of antimicrobial pepides, as well as an increase in pathogen invasion and, ultimately, gut dysbiosis (3, 4, 6).

The gut microbiome plays an important role in health and disease. Gut microbiota has a great influence on the host's immune system through local interactions. The relationship between the respiratory system and the distal immune system (digestive system) is considered the gut-lung axis (8-10). According to studies, making changes in the function and composition of the intestinal microbiome causes changes in immune responses and changes in homeostasis in the respiratory system, and intestinal dysfunction can lead to a more severe clinical course of respiratory infections (11, 12). Several metabolites produced by gut microbes have been identified to play a role in the immune response during respiratory disease. Specific strains of microbiota (such as probiotics) have shown beneficial effects on host immunity, which have led to the successful treatment of intestinal disorders (13). This article discusses the close relationship between gut microbiota, diet and COVID-19 infection.

Role of gut microbiota on immunity and homeostasis

The microbiome of humans includes the set of microorganisms both in the Inside (mouth, lungs and intestines, vaginal mucosa) and outside of the human body (eyes and skin) (14).

The human body has a large number of bacteria (*Bacteroides*, *Facalibacterium*, *Bifidobacterium*, *Eubacterium*, *Ruminococcus*, *Peptostreptococcus*, *Clostridium*, and *Peptococcus*), Viruses (Enterovirus, Norovirus, Rotavirus), fungi (*Aspergillus*, *Candida*, *Malassezia*, *Penicillium*, *Debaryomyces*, *Saccharomyces*) and protozoa (*Entamoeba histolytica*, *Giardia intestinalis*, *Woesearchaeota*), which are essential for life (15, 16).

Mainly bacteria, that exist in the small and large intestines, and the colon has the largest amount and variety of bacteria. Intestinal microbes produce the lining of the intestinal mucosa through the intestinal fermentation of dietary fiber and are also capable of reproduction, and many functional actions. Some of these include the synthesis of anti-inflammatory substances such as butyric acid, strengthening the intestinal epithelial barrier, completing food digestion and drug metabolism and preventing infections, strengthening and regulating the immunity of the intestine and body, and regulating the lymphatic tissue associated with the intestine (17-20).

One of the most populous communities outside of the soil, subsoil, and oceans is the gut microbiota because the number of these microorganisms can reach 〖10〗^12-〖10〗^14 in the large intestine (21).

In a healthy adult human, the intestinal microbiota is dominated by two phyla: Firmicutes and Bacteroidetes. The Firmicutes branch has more than 200 different genera such as *Lactobacillus*, *Ruminococcus*, *Bacillus*, *Enterococcus*, and *Clostridium*. *Clostridium* makes up 95% of Firmicutes phyla. Bacteroidetes consist of dominant genera such as *Prevotella* and Bacteroides. The abundance of the *Actinobacteria* branch is relatively less and mainly includes the genus *Bifidobacterium*. *Auriarchyota*, *Proteobacteria,* and *Verucomicrobia* are present in lower concentrations in the intestine (22). Evidence shows that the intestine has a predominance of Bacteroidetes and Firmicutes, while the pulmonary compartment has significant populations of Bacteroidetes, Firmicutes, and Proteobacteria (23).

Acquisition of microbiota is a dynamic matter. A process that starts at birth and evolves in the first 2 to 3 years of life. After childhood, the microbiota stabilizes somewhat in adulthood, while its makeup can be influenced by long-term changes brought on by lifestyle choices, gastrointestinal infections, food, geographic origin, antibiotic usage, and surgery (24-26).

More than 90% of serotonin is produced in the intestine (27), microbiota plays a critical role in regulating the optimal function of the innate and acquired immune system, and secondary metabolites and antimicrobial peptides derived from intestinal commensals play a role in cellular homeostasis (28). For example, Bifidobacteria, Bacteroidetes, and *Lactobacillus* release a large number of short-chain fatty acids (SCFA) such as butyrate, propionate, and acetate, which bind to macrophages and dendritic cells (DCs), thereby modulating immune and inflammatory responses (29).

For example, it has been shown that F. prausnitzii plays a role in the priming of human colon regulatory T cells and causes the secretion of the anti-inflammatory cytokine IL-10 (30).

Bacteroidetes and clostridia enhance immunity against influenza infection by producing secondary metabolites such as SCFA, largely by inducing CD8+ T cell function and type I IFN signaling in macrophages(31), thus the gut microbiome plays an important role in regulating the response. Immunity plays a role in systemic and distant mucosal sites, including the lungs (32).

SCFAs can increase the number and function of regulatory T cells, T helper cells, and Th17 cells by inhibiting histone deacetylase (HDAC). Such butyrate activates G protein-coupled receptors (GPCRs), such as GPR43, and by inhibiting the NF-κB pathway exhibits diverse anti-inflammatory functions and can prevent excessive inflammatory responses (33-40). Butyrate can also increase the differentiation of regulatory T cells and IL-10/18 producing T cells through the activation of GPR41 and GPR109A (39, 40). These SCFAs have also been found in very small amounts in the lung compartment, thus suggesting a possible connection between the gut and the respiratory tract (41).

Studies have shown that SCFAs play a role in the formation of precursors of macrophages and dendritic cells (DCs) in the bone marrow, and by strengthening the function of T cells, they lead to improved immune function in respiratory tract infections (40, 42). From SCFAs, other intestinal flora metabolites such as tryptophan, retinoic acid, lactate, pyruvate and desaminotyrosine, niacin have a part in host immunity as well (39, 43-47).

Gut microbiota affects metabolic pathways in alveolar macrophages and leads to changes in cellular response. According to research conducted in mice depleted of microbiota, macrophages have a reduced capacity to phagocytose Staphylococcal pneumonia, and the cellular response to lipoteichoic acid and lipopolysaccharide is reduced in them (48). Metabolites produced by gut microbiota not only modulate gastrointestinal immunity but also affect end organs such as the lung and brain (49). Also, bacteriocins produced by bifidobacteria and lactobacilli are effective against pathogenic viruses and bacteria (50).

Evidence of the relationship between SARS-CoV-2 infection and pharyngeal microbiota composition has been reported. A dysbiosis microbiome may lead to an inflammatory environment that the coronavirus can take advantage of because when infected with the coronavirus, gut-related inflammatory proteins (cytokines) are amplified with more cytokines that may cause a "cytokine storm" This has the potential to do greater harm than the virus itself. (including multi-organ damage) (51).

An imbalance in the microbial population of the digestive and respiratory tracts, which damages the lung mucosa, results in respiratory tract infections (RTIs) (52).

Type 1 IFNs have a complex function in a variety of bacterial and viral illnesses, and pDCs use specific TLRs to identify bacteria and viruses. TLR9 identifies microbial nucleic acids by detecting unmethylated CpG patterns in DNA, and it also recognizes RNA, microbial TLR7, or generated guanosine analogs. Type 1 IFNs are produced as the initial line of defense against infection as a result of pDC activation, and they inhibit the virus. IFN- is produced in response to pathogenic bacteria, and type 1 IFNs are frequently produced in response to viral infections (53).

Modern and hygienic lifestyles may increase allergic prevalence by reducing bacterial diversity and other inflammatory disorders in industrialized societies (54). In summary, due to the fact that the gut microbiota is crucial for immunity , there is a need to properly study the relationship between SARS-Cov2 infection and gut and lung microorganisms (55).

Role of diet in shaping gut microbiota diversity

Although one-third of the gut microbiota of humans is equivalent, the remaining two-thirds are unique to each individual, as its composition is determined by the geographic location in which they live, diet, lifestyle, host genotype, blood parameters such as RBC count and hemoglobin concentration, and The use of drugs is determined. Among these, diet is the most important factor (24, 56, 57).

Studies on the impact of nutrition on gut microbial diversity in humans have generally focused on the abundance or lack of three key dietary elements: lipids, carbohydrates, and proteins (which serve as a source of energy for microbes). Branch level and genus differences account for the majority of gut microbiota variations.(58) A comparison of pre-agricultural societies in Africa with urban and rural groups in North America and Western Europe has clearly shown that diet, lifestyle, and environment are related to the composition of the gut microbiome (59).

In western countries, most parasites have been eradicated, but in African countries, due to colonization with parasites, the diversity of intestinal microbiota may increase (60).

The diet is different from the west to the east due to the diversity in drinks and foods, and various rituals and customs.

Western diet (WD) (American and European population)

In WD, plant nutrition predominates along with animal items that are heavy in sugar and fat but low in fiber and plant polysaccharides, all of which are associated with economic expansion (61).

Bacteroides enterotype increases in the intestines of the population of western countries (The western diet, which is more prevalent in industrialized countries,) where the consumption of fat and refined sugars, animal proteins and salt is higher, and the *Prevotella* enterotype increases in the population of non-western countries (consumption High fiber) is more common than other regions (62).

In WD, by consuming animal protein, bile-resistant microorganisms such as *Bilophila*, *Bacteroides*, and *Alistipes* increase, but Firmicutes such as *Roseburia*, *Ruminococcus bromii*, *Reubacterium rectale*, which metabolize plant polysaccharides, decrease. WD causes dysbiosis of the intestinal microbiota and causes adverse effects in the intestinal mucosa, which causes inflammation and is also associated with obesity and metabolic diseases. The growth of pathogenic bacteria increases in this type of diet, which is detrimental to beneficial bacteria and leads to changes in the intestinal barrier (63, 64).

The composition of the intestinal microbiome of different populations, including Europe, the United States of America, and Japan, mainly includes large amounts of *Protella* and Bacteroidetes bacteria (65, 66). The fecal microbial populations of American children and adults were examined in a different investigation and were compared with those of Malawians and Americans (Venezuelans). The diversity of the microbiota of the residents of Venezuela and Malawi was greater than that of the residents of the United States (26).

In a study, it was discovered that the intestinal microbiota of Colombians is mainly consisting of Firmicutes (mean ± standard deviation: 79 ± 13%) and Bacteroidetes (17 ± 12%), and other phyla are exist in small amounts (67).

The population of Western nations, such as Europe and America, includes intestinal microbiota with a high concentration of Firmicutes (*Blautia*, *Dorea*, *Roseburia*, *Faecalibacterium*, *Ruminococcus*, *Oscillospira*, *C. perfringens*, *C. difficile*, and *S. aureus*); *Verrucomicrobia* (*A. muciniphila*), and *Bacteroides* (*Bacteroides*), which are Actinobacteri (*B. adolescentis* and *B. catenulatum*) (68).

In Sweden, France, Germany, Italy, and other countries, adult Europeans and elderly individuals' feces were examined. The impact of regional variations was demonstrated. *Atopobium*, *C. coccoides*, *F. prausnitzii*, and the groupings of Eubacterium rectal *C. coccoides*, *Bacteroides Prevotella*, and were shown to differ significantly between groups, particularly between Germany and Italy.The Italian group's senior participants had a lower prevalence of these germs than those from the other three nations. Compared to adults from Sweden, France, and Italy, Germans had levels of *Bacteroides-Prevotella* that were 2 to 3.5 times lower. Among Swedish adults, *F. prausnitzii* had the highest prevalence. Compared to the old group, Italian adults had a significantly greater concentration of *F. rausnitzii* (69).

Eastern diet

In a country like India, there are ethnicity, diet, and many other variables may affect the composition of the gut microbiome (70). In a study from India, the South Indian group had more Bacteroidetes, *Facalibacterium*, and *Ruminococcus*, while the gut microbiome of the North Indian population was high in *Provetella* (71, 72).

The largest study on the gut microbiome of Indians to date (1004 individuals from across India) discovered that the richness of *Prevotella* and *Faecalibacterium* in the gut microbiome of Indians is high, with only 0.39% of the bacterial species observed being common with the intestinal microbiota of other parts of the world (73).

Also, another study in India reported the abundance of Firmicutes compared to Bacteroidetes. They also reported a higher prevalence of Prevotella in a population consuming a predominantly non-vegetarian diet. The researchers compared the gut microbiota profile of the Indian population with people living in different geographical regions of the world. In Mongolian, Malawian, Indian, and Venezuelan populations, the genus *Prevotella* was the highest, while *Faecalibacterium* was more abundant in Italian, American, and Tanzanian groups (74, 75).

In another study, the comparison of the intestinal microbiota composition of Korean, American and Japanese people showed that the amount of stool microbial community is different in different geographical areas, In contrast to other populations (55.6%), Americans had a greater firmicutes prevalence (61.0%). In addition, Japanese have a higher prevalence of actinobacteria (22.1%) than other people (2.5%). *Bifidobacterium* (20.6%) and *Clostridium* (10.3%) were more prevalent in the Japanese group, while *Bacteroides* (30.3%) were more prevalent in China than in the other nations. (76). A recent study of 7009 ethnically homogeneous residents of 14 randomly selected areas of Guangdong Province, China, revealed that geography has a significant impact on the composition of the gut microbiota and, consequently, the role that microbiota play in diseases (given the critical role that microbiota play in modifying pathological changes and their response to treatments) (77-82). Therefore, the microbiota is similar in people who live in the same area and are in contact with each other (26).

Also, in traditional societies, due to the greater communication of a person with his surroundings as well as with other members of the village and family, the possibility of transmission and dispersion of microbes is higher, which increases the convergence of intestinal microbiota (83, 84).

African diet

The African diet and the food of the Eastern nations are quite similar since they are both based on local ingredients and consist of a variety of beans, fish, rice, and occasionally meat. Africans consume more grains but less fruits (85).

A study (75) of Burkina Faso (BF) children who consumed a diet rich in millet and local vegetables and very low in lipids and animal proteins was conducted compared to European children fed WD.(86) which showed that the microbiota of BF children has a large amount of *Prevotella* and *Xylanibacter* compared to European children. On the other hand, proteobacteria are more in European children than in BF children. Another study (26) compared the intestinal microbiota of Italian (Europe) and BF (Africa) children, which showed that due to the difference in food patterns between the rural African diet in BF and the modern western diet in Italy, the composition of the People's intestines microbiome are different (87).

Large amounts of Actinobacteria and *Enterobacteriaceae* (*Shigella* and *Escherichia*) were reported in BF children.(88) while the Firmicutes were more present in Italian children. And *Treponema* (Spirochaetes), *Prevotella*, *Xylanibacter* (*Bacteroidetes*) bacteria were found only in BF children (89).

Another study was conducted to compare the difference in intestinal microbiota composition of 6-month-old Malawian and Finnish infants (Turku and neighboring areas in southwest Finland). The total number of bacteria detected in Malawian infants and the number of *C. histolyticum*, *Bacteroides*, *Prevotella*, *Bifidobacterium*, *B. longum* was much more compared to Finnish children. But, bacteria belonging to the species *C. perfringens*, *B. adolescentis*, and *S. aureus* were present only in Finnish infants. In addition, in Malawi, more and more diverse *Lactobacillus* species are transmitted from mother to infant (90).

Also, in a study to compare the intestinal microbiota of the population of Tanzania with Italy, the genera *Prevotella*, *Eubacterium*, *Butyricicoccus*, *Sporobacter*, *Oscillibacter*, *Succinivibrio* and *Treponema*, the opportunistic bacterial species in the members of the genus *Proteobacteria* were more in Tanzanian people, and in Italians, the genera *Faecalierium Bacteroides*, *Roseburia*, *Blautia*, *Dorea* had more numbers (91). In a study, the gut microbiota composition of Americans in the United States was compared with two ethnic groups in the Central African Republic (BaAk and Bantu). Higher bacterial diversity was observed in both BaAk and Bantu groups (no difference between the two African groups) compared to US Americans (92).

A study of BF and Bantu populations in the Central African Republic revealed that organisms capable of metabolizing carbohydrates and fibrous materials, such as *Treponema* and *Prevotella*, dominate the gut (75, 92).

Based on geographical origin, the intestinal microbial diversity of people who live Non-Western nations, particularly Africans, have greater rates than other areas. [89], which mostly includes *Actinobacteria* (*Bifidobacterium*); They are *Bacteroides* (*Bacteroides-Prevotella*). They are also rich in Firmicutes (*C. histolyticum*), *Butyricicoccus*, *Eubacterium*, *Oscillibacter* and *Proteobacteria* (*Succinivibrio*), *Shigella* and (*Escherichia* and Spirochaetes (*Treponema*).Only *Actinobacteria* (*Bifidobacterium*) and Firmicutes (*Akkermansia muciniphila*, *Clostridium difficile*) had small amounts (61).

Mediterranean diet

Around the Mediterranean Sea, a traditional way of eating, now known as the Mediterranean diet, was followed in the early 1960s by the inhabitants of the Mediterranean basin, in southern Italy and many parts of Greece, which included frequent and high consumption of fiber sources. Such as vegetables, olive oil, whole grains, fruits, and nuts, but low consumption of seafood and fish, chicken and eggs, and dairy products (93).

Mediterranean diet with regular consumption of MUFAs, PUFA polyphenols, omega 3 and other antioxidants, as well as low glycemic carbohydrates and higher consumption of vegetable proteins, has many beneficial effects on the microbiota of the body and human health such as reducing the risk of mortality and preventing Several disorders, including CVD, diabetes, metabolic disorders, mental retardation, and depression (94-97).

In this type of diet, a higher ratio of Firmicutes-Bacteroidetes is observed. Also, the number of bifidobacteria and SCFAs was higher in the population with this diet. Consuming complex polysaccharides and vegetable protein can increase beneficial intestinal bacteria and cause SCFA production.

Gut microbiota dysbiosis COVID-19

SARS-CoV-2, like other infectious diseases involving the digestive system, can cause various changes in intestinal homeostasis, which causes numerous clinical symptoms in this disease. In addition to being involved in the pathogenesis of gastrointestinal disease associated with COVID-19, intestinal microbiota are also considered an important therapeutic tool (98, 99).

Studies show that compared to healthy people, the composition of the gut microbiome in patients with COVID-19 changes significantly. The abundance distribution of members of the genera *Bacteroidetes*, *Coprococcus*, *Faecalibacterium prausnitzii*, and *Collinsella aerofaciens*, *Parabacteroides*, *Roseburia* was reduced in SARS-CoV-2, and according to another similar study, several members of the families *Ruminococcaceae* and *Lachnospiraceae* (including bacteria known to produce Fermentable short-chain fatty acids (SCFAs), were decreased compared to the uninfected control group (100). Also, *B. adolescentis*, which prevents pro-inflammatory cytokine activation by inhibiting NF-κB activity, was reduced (101).

While the abundance distribution of *Lactobacillus*, *Streptococcus*, *Bifidobacterium*, *Clostridium* (*Clostridium ramosum*, *Clostridium hattoi*), *Enterobacteriaceae*, and *Desulfovibrionaceae* has increased (102-104) These changes in gut microbiome composition correlate with the concentration of several inflammatory cytokines and disease severity (67). Disturbance in the gut microbiome may underlie the potential susceptibility of healthy individuals to the susceptibility and severity of SARS-CoV-2. Opportunistic pathogens such as *Bacteroides nordii*, *C. hathewayi*, and *Actinomyces viscosus* are very abundant in the intestines of COVID-19 patients (102).

In another comparison between SARS-CoV-2 patients and seasonal flu patients, in COVID-19 patients, the number of members of the genera *Soterella* and *Parabacteroids* has decreased,while the frequency of members of the genera *Escherichia*, *Streptococcus*, *Vilonella*, *Clostridium*, *Fusobacterium*, and *Bifido* has increased. The increase of *Streptococcus* in COVID-19 patients indicates the risk of infection by opportunistic pathogenic bacteria in these people (102, 105).

In a study of patients with COVID-19, Zhou et al (102) changes in stool microbiota were associated with the amount of SARS-CoV-2 in stool and the severity of COVID-19.

Some studies have even found a drop in fiber-consuming bacteria such as *Bacteroides plebeius*, *Prevotella*, and *Faecalibacterium prausnitzii* (*F. prausnitzii*), as well as a low Firmicute/ Bacteroidetes ratio (56).

In a pilot study of 15 hospitalized patients with COVID-19, a decrease in *F. prausnitzii* (known for its anti-inflammatory properties) and an increase in *Coprobacillus*, *Clostridium rhamnosus*, and *Clostridium hathewayi* were associated with the severity of COVID-19. In addition, the clinical condition of patients with COVID-19 can lead to a change in the intestinal microbiota, and hospitalization in intensive care units leads to an increase in pathogenic bacteria (such as *Staphylococcus*, *Peptostreptococcus*, *Enterobacteriaceae*) compared to the control group (106, 107).

The recent findings also show that *Erysipelastoclostridium*, *Streptococcus*, *Actinomyces rotia*, *Vilonella*, and others were abundant in COVID-19 patients, but bacterial genera such as *Faecalibacterium*, *Fusicatenibacter*, *Collinsella*, *Blautia*, *Bifidobacterium* and *Ebifidobacterium*, *Romboutsia* were higher in healthy people. Also, the abundance of *Anaerostipes*, *Fusicatenibacter*, *Agathobacter*, and *E. hallii* from the *Lachnospiraceae* family was reduced a lot in COVID-19 patients (101).

Bacterial species belonging to the Bacteroidetes branch, such as *Bacteroides thetaiotaomicron*, *Bacteroides dorei*, *Bacteroides ovatus*, and *Bacteroides massiliensis* have an inverse relationship with the viral level of SARS-CoV-2 in patient stool samples (102).

Excessive release of nitrogen mediators and ROS by epithelial cells due to inflammatory conditions and transfer of neutrophils in the intestinal lumen, leading to an increase in Enterobacteriaceae such as *E. coli*, *Klebsiella* spp. and *Proteus* spp, which exist in a small amount in the human intestine (108).

In a study from China, *Lactobacillus* and *Bifidobacterium* levels decreased in some patients with COVID-19 due to intestinal microbiota dysbiosis (103). Dysbiosis of gut bacteria is observed even after recovery from COVID-19 (109).

Medicines used to treat COVID-19 such as remdesivir, chloroquine phosphate, ritonavir, and lopinavir also play a role in intestinal dysbiosis. Long-term use of hydroxychloroquine and doxycycline is significantly involved in changing gut bacteria. In stool samples of 30 COVID-19 patients, COVID-19 patients treated with antibiotics showed a decrease in favorable species compared to patients who did not take antibiotics. They experienced Decrease in desirable species such as *Eubacterium rectale*, *Lachnospiraceae*, *Ruminococcus obeum*, *Dorea formicigenerans*, and *Faecalibacterium prausnitzii* (102, 110, 111).

Total DNA collected from feces samples was used in a study to investigate the composition of the microbiome of COVID-19 patients.The number of intestinal commensals was reduced, which had a direct relationship with several factors representing the severity of the disease, such as C-reactive protein (CRP) and high concentration of inflammatory cytokines. Therefore, the composition of the microbiota is related to the severity of the disease (101).

The decrease of several bacterial species in the group of patients with COVID-19 is associated with the rise in concentration of CXCL10, CCL2, and IL-10, TNF-α, which indicates that a decrease in these bacterial species, may play a role in preventing excessive inflammation of the invading agent (112).

Changes in Fungal microbiomes were also studied during COVID-19. Two species of *Aspergillus niger* and *Aspergillus flavus* were discovered in the stool specimens of patients whose nasopharyngeal virus was cleared (113).

Considering that gut microbiota is related to the severity of COVID-19, research on how the severity of the disease may change the diversity of gut microbiota and immunity in COVID-19 patients needs more research (114).

Strategies for manipulating microbiota to fighting COVID-19 infection

Probiotics

Probiotics have a variety of physiological benefits, but one of the most significant is the strengthening of the epithelial cells of the small intestine. Probiotics also aid in the intestinal absorption of meals (115). Probiotics contain immunomodulatory qualities that can help the body's defensive mechanism in some way, usually by boosting the activity of macrophages or natural killer cells, or by regulating the release of immunoglobulins, cytokines, or other substances (116).

By maintaining the gut mucosal barrier and the microbial ecology, as well as by degrading enteral antigens and altering their immunogenicity, probiotic bacteria may be able to modulate the intestinal inflammatory reactions (117). Probiotics and synbiotics can lessen the intensity of symptoms in RTI patients, decrease the duration of the condition, and enhance quality of life (118).

Probiotics reduce pathogenicity via altering the SARS-CoV-2 virus-linked mediator monocyte chemoattractant protein-1 (MCP-1), which in turn reduces inflammation (119).

According to recent studies, probiotics may have immunological advantages in COVID-19 infection through the stimulation of IgA production, the improvement of phagocytosis and macrophage biological processes, and the modulation of regulatory cells (120).

Probiotics have the ability to boost overall health and well-being, decrease the frequency and duration of respiratory infections, and considerably raise plasma levels of cytokines, and plasma cytokine levels. Probiotics should be used in conjunction with other treatments to prevent COVID-19 because of their antiviral and immune-modulating properties as well as their capacity to increase interferon production One of the most prevalent bacterial or viral infections is RTI (121).

In animal and human studies, *Lactobacillus Plantarum* L-137 improved innate and acquired immune responses and decreased RTIs. In a natural setting, *Bifidobacterium animalis* subsp lactis Bl-04 was shown to reduce the risk of upper respiratory illnesses (122-124). Probiotic treatment may help lessen the severity of ARDS, a significant COVID-19 consequence, according to the findings of several research on the topic (124, 125).

Probiotics appear to be able to lessen the spread of coronavirus through the stomach, according to data showing that SARS-CoV-2 produces gastrointestinal issues; however, these probiotic strains have not yet been given to the respiratory system (126). Some authors have suggested that probiotics may have a role in the prevention and/or moderation of COVID-19 severity. *L. coryniformis* K8 boosted the elderly's vaccine-specific responses and the particular immune response following COVID-19 infection. *L. coryniformis* K8, helps maintain the immune humoral response induced by the COVID-19 vaccine over time. It was a randomized, placebo-controlled, double-blind trial (127).

In a systematic review study the most widely utilized probiotic strains (15%) were *L. paracasei* and *L. rhamnosus*. probiotics can reduce viral load. The respiratory viral titer and the percentage of participants who shed the virus in nasal secretions were both reduced by probiotics (56% in the probiotic groups and 91% in the control groups) (128).

The combined impact of *L. plantarum*, *L. paracasei*, and *Pediococcus acidilactici* on the severity and course of COVID-19 is being investigated in a research in Mexico.Researchers in Italy are examining the possibility that particular strains of *Streptococcus thermophilus* DSM322245, *Bifidobacterium lactis* DSM 32246, and *Lactobacillus helveticus* DSM 32242 might influence the proportion of patients who need orotracheal intubation.Iranian researchers are looking into how the Lactocare1 symbiosis affects symptoms including fever, COVID-19 infection, white blood cell count, amount of lymphocytes, cough, sore throat, nausea, vomiting, and diarrhea (124).

A balanced gut microbiome is essential for the effectiveness of vaccines. Studies have shown that in germ-free mice or mice who have received antibiotics, vaccinations are unable to trigger strong immune responses. A probiotic made of yeast named ABBC1 is now being tested in a clinical study to improve a COVID-19 vaccination. In addition to *Saccharomyces* *cerevisiae* that has been inactivated, ABBC1 also contains the trace elements selenium and zinc. It is anticipated that supplementation may alter the gut flora and improve vaccination effectiveness (129).

According to research conducted during the COVID-19 epidemic in China, 2-47% of critically sick patients need mechanical breathing. Contrarily, a clinical investigation found that probiotics treatments comprising live Bacillus subtilis, *Enterococcus faecalis*, and *Lactobacillus rhamnosus* GG dramatically reduced the incidence of ventilator-associated pneumonia. Colonic flora may lessen susceptibility to subsequent infections, and probiotics help treat antibiotic-induced diarrhea (125)

Lactobacillus globulin (LGG) has been shown to delay onset of COVID-19 infection and lower incidence of symptoms when given as post-exposure prophylaxis. These early results may have an influence on the development of preventive strategies, particularly in less developed countries. In those receiving LGG, the onset of symptoms was significantly postponed. Also, results showed that participants who received LGG had a significantly greater abundance of *L. rhamnosus* in their stool compared to those who received placebo. There was no difference in the overall structure of the stool microbiota (i.e., β-diversity). The presence of symptoms and a COVID-19 diagnosis also affected the level of bacteria present in the stool (130).

By directly interacting with viruses, lactic acid-producing bacteria like lactobacilli can exert their antiviral effect. It has been noted that *L. rhamnosus* GG protects against ventilator-associated pneumonia (131-133).

Prebiotics

Prebiotics are non-viable dietary components that the good bacteria in your intestine preferentially break down. By increasing the numbers and/or activity of bifidobacterial and lactobacilli through dietary modification of the gut microbiota, prebiotics aim to improve health. Prebiotics are crucial for maintaining human health. Asparagus, sugar beet, garlic, chicory, onion, Jerusalem artichoke, wheat, honey, banana, barley, tomato, rye, soybean, human and cow's milk, peas, beans, etc., as well as, more recently, seaweeds and microalgae, naturally occur in various dietary food products. They are produced on an industrial basis due to their low concentration in foods (134). The most extensively studied prebiotics are galacto-and fructo-oligosaccharides (135). One of all higher species' primary defenses against infection is glycan diversity, and as people age, especially in the vulnerable age ranges, their repertoire of glycans changes (136, 137).

By directly interfering with the virus (which has a negative charge on its surface), preventing viral invasion and adsorption, and also preventing direct interference with viral transcription and reproduction, oligosaccharides can combat pathogenic viruses (138). In a recent study, the antiviral properties of resveratrol oligosaccharides for SARS-CoV-2 were examined. Various amounts of resveratrol oligosaccharides were cultured with human MRC5 lung cells that had been exposed to the SARS-CoV-2 virus. According to this finding, resveratrol oligosaccharides at 5 and 10% successfully reduced SARS-CoV-2 infection of the MRC5 cells (139).

Prebiotics may have an impact on COVID-19 by promoting the development and survival of probiotics, as well as by boosting gut diversity and immunity, especially in an elderly population. The advantages of these prebiotics most likely result from encouraging the population growth of bacteria that produce SCFAs. The ability of SCFAs to control the immunological response is well established. When SARS-CoV-2 is infected, a 'cytokine storm' results from the increased production of inflammatory cytokines, possibly as a result of the immune system overreacting to the virus. These cytokine storms encourage the demise of sick cells while also disrupting several organ systems. It is generally known that SCFAs, such as butyrate, can lessen inflammatory reactions.

Theoretically, prebiotic treatment to promote the establishment of bacterial populations that produce SCFA can be a likely way to lessen COVID-19 problems (140-142).

Many plants, including the Jerusalem artichoke, onion, garlic, wheat, and asparagus, naturally contain inulin, a fructose polymer connected by a (2,1) glycosidic bond. Fructo-oligosaccharide is the term used when the amount of fructose residues in inulin is fewer than 10, even though inulin can have up to 200 fructose residues. The gut's synthesis of butyrate, isobutyrate, and isovalerate was boosted by the administration of inulin (20 g per day for 6 weeks). Additionally, by activating CD8+ T cells, it was said to have anti-influenza properties. Mice fed on inulin had more Ly6c-patrolling systemic monocytes, which led to more activated macrophages and less CXCL1 production in the respiratory tract. Additionally, dietary fibre raised the synthesis of butyrate, which stimulated effector CD8+ T cells to enhance pathogen clearance. In a feline experiment, giving 1-kestose—the simplest fructo oligosaccharide with two fructose residues—to the animal resulted in an increase in the number of butyrate-producing bacteria and Bifidobacterium (129).

Vitamin D

Vitamin D (VD) is a lipophilic vitamin and one of the most important components for the vital functions of the body (143). Many researches have been done about whether there is a relation between the infection or prevention of covid-19 and the level of VD. It seems that there is a negative correlation between the concentration of VD and the rate of infection and mortality by the Covid-19 virus (144, 145). The importance of VD in acute respiratory diseases is so considerable that according to the report of the National Health and Nutrition Examination Survey (NHANES) in 2001-2006, there is a negative relationship between the level of VD and these diseases (146).

Discrepancy in the results of the treatment with VD supplements is due to the difference in the dose and duration of drug consumption, which is an example of the A.L. Fernandes et.al's studies who used high doses of VD for the treatment of Covid-19 patients and did not find any significant results (147).

However, to compare the influence of VD on preventing the spread of Covid-19, a study conducted by Miguel A, showed that the infection rate of SARS-CoV-2 in vitamin D consumers (VDG) group was lower than placebo consumers group (PG) among hospital staffs (6.4 vs. 24.5%, $p < 0.001$) and concluded that the risk of SARS-CoV-2 infection in VDG group was lesser in comparison with PG group (RR: 0.23; 95% CI: 0.09-0.55) (148). The VD supplement used in this study was cholecalciferol 4000 IU daily and the placebo capsule was 450 mg of starch (148).

Moreover, A.Rastogi et.al in India conducted a study on 40 people (16 intervention group and 24 control group) without symptoms or with mild symptoms of SARS-CoV-2 positive and VD deficiency, they found that by using Cholecalciferol drug with a dose of 6000 IU daily use for 7 days, a significant decrease in fibrinogen and virus RNA was observed in the intervention group than the controls with strong dose VD consumption (149). It has been shown that the covid-19 patients treated by VD reduced the hospitalization period in these patients. S.De Niet et al. in Belgium found that by prescribing daily 25,000 IU for 4 successive days, followed by weekly 25,000 IU for up to 6 weeks on 50 people (intervention and placebo groups) the length of hospitalization of individuals receiving VD was decreased by 2 times in comparison with placebo people (4 days against 8 days and P=0.003) (150). Based on a study, the amount of VD has an effect on the death rate of elderly people suffering from this disease, so that in the studies by the collaboration of researchers from Italy and Belgium on elderly people (average age 76 ± 13) admitted to Ghent hospital, Belgium, found that serum VD levels of those who died during hospitalization were significantly lower than those who survived (3.0 vs. 8.4 ng/ml). Furthermore, there was a significant positive correlation between VD level and Po2, So2 and a significant negative correlation with D-Dimer level (151). The role of VD is so crucial in covid-19 patients that even in some investigations, the lack of this vitamin has been suggested as a possible factor for contracting covid-19. F Saponaro et al. examined 93 patients with pneumonia caused by this disease in two hospitals of Pisa and found interestingly that 65% of patients had hypovitaminosis D and high levels of inflammatory cytokines including TNF-α and IL-6 compared to other milder patients and it was suggested that VD status should be evaluated in infected individuals for disease management (152). Also, an observational study in the multinational United Arab Emirates on 464 patients verifies that levels under 12 ng/ml are related to severity and mortality of COVID-19 (153).

Vitamin C

Vitamin C, also named ascorbic acid, is a hydrophilic component that cannot be produced in human body (154). In many studies relying on the antioxidant property of vitamin C and its effectiveness against the cytokine storm of the immune system, they reached to remarkable results.

For example, F. Liu et al. observed that daily injection of 24 grams in 100 ml of sterile distilled water for 7 days in two groups (vitamin C and placebo) of 308 adult patients from two Wuhan hospitals, the development of cytokine storm was significantly prevented and the lung function of these patients was improved and the risk of ARDS was reduced (155). S Tehrani et.al confirmed the effectiveness of the injection of this vitamin supplement by examining 44 patients (26 control patients and 18 patients receiving vitamin C) so that with intravenous injection of vitamin C at a dose of 2 grams every 6 hours for 5 day, the level of So2 increased significantly from 86±5% in the first day to 90±3% in the sixth day of hospitalization (P=0.02) and in the CT scan report, the level of lung involvement in the vitamin C group after treatment was considerably lesser than the control group (156).

In another study in United States, 17 hospitalized patients in the ICU were treated with vitamin C at a dose of 1 gram each 8 hours in 3 days, and it was observed that inflammatory indicators such as D-Dimer and ferritin decreased significantly (157). However, in another study in Saudi Arabia, 296 patients (158 drug recipients and 581 controls) consumed low-dose vitamin C (1000 mg per day for 11 days orally) and there was no significant correlation between drug administration and mortality reduction, although the incidence of thrombosis was reduced (6.1% vs 13%) in vitamin C group compared to the controls (158). It has been reported that vitamin C concentration in covid-19 patients is less than in healthy people, which confirms the significance of this vitamin in the cure of covid-19 patients. A study conducted by Y. Xing et al on 31 covid-19 patients and 51 healthy people showed that the mean plasma VC concentrations in patients was 2 mg/L (0.5-4.90), that was approximately 5 times lower than that of healthy controls (9.23 mg/L) (3.09-35.30) (159). In addition to covid-19 patients, a plethora of studies have explained antiviral effects of vitamin C and it has been shown that high doses of vitamin C are effective in treating patients with influenza and common cold (160).

However, some studies refuse the vitamin C effectiveness in cure of patients with SARS-COV-2, for instance in an investigation by S. Thomas et.al a high dose of vitamin C (8000 mg, which should be divided 2-3 times a day) was administered to 48 patients admitted to a hospital in Florida, and the duration of symptoms did not decrease compared to the control group (161).

Zinc

Zinc is an essential metal and known as the second signaling ion of intra- and intercellular information (162). This vital substance has various roles in the body, one of which is the effect on the immune system, including the proliferation, differentiation, and proliferation of lymphocytes (163), and its deficiency weaken the immune system (164).

According to diverse studies, zinc ion reduces the pathogenicity of respiratory viruses, including common cold (165), influenza virus, RSV and SARS-COV-2 (166). Due to the importance of zinc in viral and respiratory diseases, some researchers have examined covid-19 patients, the serum level of zinc and the prognosis of the disease. RA. Heller et.al in Germany, 35 patients with covid-19 (29 survived and 6 deceased) were assessed and in general the serum level of zinc in all patients was low compared to the normal state (mean ± SD; 246.2 ± 717.4 vs 294.0 ± 975.7 μg/L, $P < 0.0001$). However, this level was significantly reduced in deceased patients compared with survived patients (167). Several studies have been done focused on the preventive effect of zinc. A five-month prospective study by N. Stambouli et.al showed the preventive effect of zinc (15 mg per day) with doxycycline (100 mg/ day) among military hospitals staff in two intervention and control groups so that in preventive treatment, the number of Covid-19 infected people is significantly less than the control group (168).

In order to investigate the zinc as a supplement for covid-19 subjects, S Ben Abdallah et al. provided zinc supplement (25 mg, Opalia Recordati) orally two times each day to 231 patients (239 in the placebo group) for 15 days and concluded that the consumption of zinc for the treatment of these patients is effective. So that mortality within one month was 6.5% and 9.2% in the zinc and placebo group, respectively. Also, the rate of hospitalization in the ICU was 5.2% and 11.3%, respectively, and the length of hospitalization in the zinc group was shorter compared to the placebo group (169).

However, in another study, a significant result was not obtained regarding the application of zinc supplements in covid-19 patients. S. Thomas et.al administered zinc gluconate (50 mg for 10 days) to 58 patients and no considerable reduction in the symptoms of the patients was detected compared to the control group (161).

Selenium

Selenium, a crucial element in the body, is involved in many metabolic activities, DNA synthesis, resistance to infection and oxidative damage (170). Selenium plays a role in reducing viral infections (171, 172) and its deficiency leads to the vulnerability of the body against viral agents (173, 174). Accordingly, many studies have been conducted about the relationship between micronutrients such as selenium and the severity of symptoms in Covid-19. G. D. Vavougios et.al have suggested in a medical hypothesis study that the disorder in the synthesis of selenocysteine, through disorders in the physiological functions of endothelial homeostasis and non-thrombotic activation of platelets, potentially leads to the development of coagulopathy in covid-19 patients (175). In a similar study, M. Kieliszek et al suggested that sodium selenite ability to oxidize the thiol groups in the disulfide isomerase protein of the virus and make it incapable to infiltrate to the membrane of healthy cells. So selenite prevents viruses from entering healthy cells and eliminates their infection (176).

A. Skesters et.al in Latvia, by investigating the selenium content of 80 people with Covid-19 and 40 patients with an acute condition, showed that the amount of selenium and selenoprotein P for acute patients was significantly diminished compared to patients after the disease of Covid-19 which indicates the disease severity in people with selenium deficiency (177). A similar result was also reported regarding the elevated occurrence of micronutrient lacks in elder patients hospitalized due to COVID-19, especially for selenium in the study of M. Voelkle (178).

H. Y. Zhang in China has examined the lack of selenium even in the superficial soil of different cities and has stated its relationship with the agricultural products of those cities and the death possibility in Covid-19 patients. 14,045 patients were assessed in 147 cities and the mortality rate according to agricultural products were 1.17%, 1.28% and 3.16% for non-selenium, moderate selenium deficiency and severe selenium deficiency regions, respectively (P=0.002). Also in accordance with the selenium in superficial soil, the mortality rate increased from 0.76% to 1.70% and 1.85% in areas without selenium, with moderate selenium deficiency and severe selenium deficiency respectively (P < 0.001) (179). However, another study conducted by R. M. Nimer et.al on the use of nutritional supplements including selenium showed that there is no significant effect in reducing the hospitalization rate or the severity of disease (180).

Magnesium

Magnesium is an abundant mineral which participates as a cofactor in many enzymatic reactions in the body (181, 182). Magnesium is required for energy production, oxidative phosphorylation, glycolysis, stability, protein and nucleic acid synthesis (182). Antioxidant property and anti-inflammatory effects of magnesium are widely accepted (183, 184). One of the main challenges in worsening of the Covid-19 disease is the storm of cytokines and blood coagulation in these cases. Based on this, magnesium has been considered as a study option for covid-19 patients due to its protective properties against oxidative stress. Magnesium deficiency results in endothelial cells sensitivity to oxidative damage, endothelial defectiveness, decrease in fibrinolysis, and rise of coagulation (185). Accordingly, various researches have been done about the impact of dysmagnesemia in patients with covid-19, for example, in the Nancy hospital in France, serum magnesium was measured among 300 hospitalized patients, and it was observed that 13% of the patients were severely hypomagnesemic (<6.5) and 35% had hypomagnesemia between 0.74-0.65 and 25.7% had magnesium deficiency between 0.75-0.84, while 3% of hypermagnesemia people had >1.05 and only 25.7% of these patients had magnesium in the normal range (0.85-0.94), which confirms the high prevalence of hypomagnesemia in hospitalized patients (186).

Also, H. K. Al-Hakeim et.al, by measuring of several biomarkers in body including magnesium, concluded that there is magnesium deficiency in patients with Covid-19 who have So2 and suggested that this issue can be used as a drug target and leads to lessen the disease side effects (187). In majority of the interventional studies on the healing of Covid-19 patients, in addition to magnesium, other supplements such as vitamins or other minerals are applied, for instance, in a study by C.W. Tan et al., using 150 mg of oral magnesium (along with vitamin D and B12) for more than 14 days. 17 treated patients and 26 control patients were patients over 50 years old, then they observed that a smaller number of treated patients needed oxygen therapy during hospitalization compared to the control group (17.6% vs. 61.5%, P = 0.006) and the severity of the disease was far less among the intervention group in comparison with the control group (188).

Although, another study by J. Malinowska et al. in Warsaw, Poland, on 146 patients was shown that hypermagnesemia was common among their study population, which increases the risk of death by 1.5 times in these patients, and they suggested that this parameter should be controlled in covid 19 patients especially those with kidney function problems (189). Moreover, by examining a questionnaire among 2148 recovered people from covid-19 disease in Jordan as well as the effect of the consumption of minerals and vitamins on the severity of disease and the percentage of hospitalization, eventually, no significant differences for the consumption of minerals, including magnesium, in reduction of the hospitalization rate and disease severity were observed (180).

Conclusion

COVID-19 has the ability to affect the microbiota in the gut, which may cause dysbiosis and aggravate respiratory infections. There is hope that probiotics and prebiotics like inulin may help reduce the impact of COVID-19 by increasing gut diversity and immunity. Researchers have also looked at the anti-inflammatory and immune-boosting benefits of magnesium, zinc, selenium,

selenium, and vitamins D and C in COVID-19 patients. Still, we don't have all the answers about how diet, gut health, and the severity of COVID-19 interact with one another. In order to effectively manage and avoid the difficulties related with COVID-19, it is essential that we keep investigating these links.

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