

Importance of gut microbiome regulation for the prevention and recovery process after SARS-CoV-2 respiratory viral infection (Review)

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Received September 20, 2021; Accepted December 9, 2021

DOI: 10.3892/br.2022.1508

Abstract. Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been reported to affect organs other than the lungs, including the liver, brain, kidneys and intestine, and gastrointestinal symptoms, such as nausea, vomiting, diarrhea and abdominal discomfort, have also been reported. Thus, SARS-CoV-2 could potentially directly or indirectly regulate the gut microbiome profile and its homeostasis. The abundance of *Coprobacillus*, *Clostridium ramosum* and *Clostridium* are associated with the severity of COVID-19, and *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria* are also related to COVID-19 infection. The four phyla are correlated with the severity of COVID-19 infection in patients. The modulation of factors that control the physiological growth of the gut microbiome will determine the proportionate ratio of microbiome types (profile). Taken together, gut microbiome profile alterations in COVID-19 patients may have a cross effect with the modulation of cytokine levels in COVID-19 infection. With these findings, several factors that regulate gut microbiome homeostasis may support the degree

of the clinical symptoms and hasten the recovery process after COVID-19 infection.

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1. Introduction

COVID-19 is a disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which was first documented in Wuhan, China. This disease has similarities with viral pneumonia and symptoms similar to those of SARS-CoV and MERS-CoV. A total of 3-6 days after infection, upper or lower respiratory tract symptoms, fever and diarrhea, or a combination of these, appear (1). Kang *et al* (2) reported that 45.8% of COVID-19 patients not only have respiratory symptoms, but also gastrointestinal (GI) symptoms, such as lack of appetite, diarrhea, vomiting and abdominal pain. Of 9,696 patients, 988 were reported to exhibit nausea and vomiting. Meanwhile, loss of appetite and abdominal pain were reported in 20 and 27 studies, respectively. Loss of appetite and other GI symptoms have also been found in other cases, for example in the UK (3). In cases of reinfection with the SARS-CoV-2 variant B.1.1.7, the symptoms and duration were similar; however, reinfection was rare (4).

Patients with GI tract symptoms have been reported to feel pain for a longer period of time than those without GI tract symptoms. These patients also have higher mean liver enzyme levels, lower monocyte counts, longer prothrombin times and require additional antimicrobial treatment (5). Intestinal dysfunction results in changes in intestinal microbes and increases the levels

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Abbreviations: ACE-2, angiotensin converting enzyme 2; COVID-19, coronavirus disease-19; HCQ, hydroxychloroquine; IL, interleukin; GI, gastrointestinal; MERS-CoV, Middle East respiratory syndrome coronavirus; RNA, ribonucleic acid; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SCFAs, short-chain fatty acids; TNF- α , tumor necrosis factor- α ; HDI, herb-drug interaction; AZ, azithromycin

Key words: microbiome, dysbiosis, SARS-CoV-2, supplement, herbal, exercise

of inflammatory cytokines (5). There are several means by which SARS-CoV-2 can damage the GI tract. First, the virus can damage the GI tract via an inflammatory response. Second, it directly damages the intestinal mucosa and causes disturbances in the GI system. Third, it can induce changes in the composition of the intestinal flora, causing digestive disorders. The modification in the composition of intestinal flora causes respiratory disorders through the 'gut-lung axis' (6).

In patients with comorbidities, the immune system is affected, and the severity of COVID-19 infection worsens. One common comorbidity in children and adults is obesity, which can compromise the function of several organs and biological systems due to excessive adipose tissue, a deficit in lean mass, insulin resistance, dyslipidemia, hypertension, high levels of pro-inflammatory cytokines and low levels of essential nutrients. Furthermore, obesity is not only associated with the immune, respiratory, cardiovascular and urinary systems, but can also modify the gut microbiota (dysbiosis) (7,8). Obese patients also have longer hospitalization periods, and have higher levels of C-reactive protein and lower lymphocyte counts, which are considered as early indicators of a more severe COVID-19 infection course (9). Another factor that can worsen COVID-19 infection is diabetes, which was shown by the high percentage of ICU admissions among diabetics and a longer hospitalization period, although diabetes was not associated with mortality (10). It was shown that the most common symptoms of COVID-19 patients with diabetes were fever, dry cough, and fatigue (11). Li *et al* (12) reported that COVID-19 infection caused ketosis or ketoacidosis and induced diabetic ketoacidosis in diabetic patients, which prolonged hospitalization and increased mortality (12).

Infection with COVID-19 might affect the microbiome profile, which is associated with the abundance of some microbiome phylum. Khan *et al* (13) reported that several phyla related to COVID-19 infection included *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Actinobacteria*, which are also associated with the severity of COVID-19 infection. The correlation between the gut microbiome and COVID-19 infection is interesting. In this review, the link between COVID-19 and the gut microbiome, as well as its potential clinical application in the future is discussed.

2. Literature search

A total of 160 articles from PubMed and Google Scholar were initially obtained; 40 articles were excluded as they did not match the research theme. The key words relevant for this review were: 'gut microbiota COVID-19,' 'gastrointestinal tract COVID-19,' 'gut-lung-axis COVID-19,' 'probiotics microbiome COVID-19,' 'drugs COVID-19,' and 'exercise microbiome.' Articles written in English published between 2011 and 2021 as well as relevant articles from the reference lists were retrieved and reviewed. A flow chart showing the literature review process is shown in Fig. 1.

3. Microbiome profile and COVID-19

The composition of the gut microbiome changes during a mild, moderate or severe infection, and when a person recovers from infection (14). The abundance of *Coprobacillus*,

Clostridium ramosum and *Clostridium* is associated with the severity of COVID-19. In addition, there was an inverse correlation between the abundance of *Faecalibacterium prausnitzii* (anti-inflammatory bacteria) and the severity of the disease (Table I). Kim *et al* (15) reported that the abundance of *Firmicutes* was positively correlated with the severity of COVID-19 symptoms. However, *Firmicutes*-negative patients have also been reported. Moreira-Rosário *et al* (16) reported that the ratio of *Firmicutes* and *Bacteroidetes* decreased in COVID-19 patients admitted to the ICU from ambulatory wards. The diversity of the gut microbiome affects the condition of patients with COVID-19. According to Ren *et al* (17), *Faecalibacterium* has anti-inflammatory properties and has been recognized as a potential biomarker of human health (17). According to Zuo *et al* (14), COVID-19 patients exhibit changes in the composition of the microbiome compared with healthy people, which results in an increased probability of being infected with opportunistic pathogens during hospitalization. In other respiratory infections, such as with the respiratory syncytial virus, microbiota diversity is associated with weight loss. Viral respiratory infections can lead to reduced intake of nutrients that can alter the gut microbiota (18). In similar cases, Middle East Respiratory Syndrome (MERS) is associated with the gut microbiome. *Proteobacteria* were more abundant in fatal cases than in non-fatal cases, including species from the *Acinetobacter* and *Klebsiella* genera. Patients infected with 2009 influenza A H1N1 pneumonia were found to have increased numbers of *Proteobacteria* compared with non-viral cases of pneumonia (19). However, information on the detailed mechanism of COVID-19 infection on bacteria in the intestine and the function of the intestine itself is sparse. Several factors can affect homeostasis in the gut, and genetic factors that can affect the gut microbiota cannot be excluded. The present study revealed the possible regulatory effects of COVID-19 on microbiota homeostasis that may impact a patient's health. In this review, the possibility of modulating the balance of gut microbiota through various factors, such as exercise, nutrition-probiotics, prebiotics, vitamins, drugs and herbal medicines are discussed, and these may be considered as future treatment modalities to hasten recovery of COVID-19 patients. The microbiome profile associated with COVID-19 effects are summarized in Table I.

Pathophysiology of viral infections on the effects of the gut microbiota. There are many variants of the SARS-CoV-2 virus, and all have specific genetic markers associated with changes that can result in increased transmissibility or virulence, reduced neutralization by antibodies acquired through infection or vaccination, and increased ability to evade detection or decreased effectiveness of therapy or vaccination (20). SARS-CoV-2 infects human lungs, but other studies have highlighted the vulnerability of other organs, including the liver, brain, kidneys and intestine, to SARS-CoV-2 infection (21). Common symptoms of SARS-CoV-2 infection include a cough, nausea, vomiting and diarrhea followed by abdominal discomfort (22-24) Patients with mild respiratory symptoms accompanied by GI symptoms can experience rapid progression of infection (25). The gastric, duodenal and rectal epithelium showed positive immunofluorescent staining of the viral host receptor and the SARS-CoV-2 viral

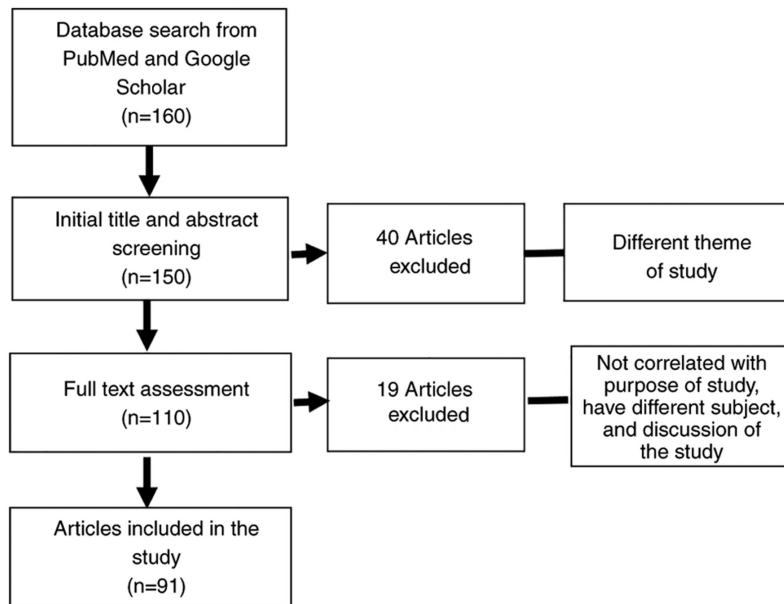


Figure 1. Flow chart of the literature review process.

protein nucleocapsid. In addition, evidence has shown that GI SARS-CoV-2 infection has the potential for fecal-oral transmission (26).

SARS-CoV-2 enters our body via the lung parenchyma. The angiotensin converting enzyme 2 (ACE-2) receptor, which is widely expressed in endocrine organs, including the testes, pancreas, thyroid, adrenal and pituitary glands, is used by coronaviruses as the route of entry into the host cell (27). ACE-2 expression is highest in erythrocytes and is also expressed in the small intestine, large intestine and duodenum (25). SARS-CoV-2 is associated with ACE-2, which can also be expressed by fat. Obesity can inhibit macrophage activation and migration, impair the generation of neutralizing antibodies and memory T cells, and decrease the activation of effector cells of the immune system, hence its correlation with chronic inflammation (28). In addition, type 2 diabetes mellitus can increase ACE-2 expression in the lungs and other tissues due to the hyperglycemic response. Hyperglycemia can lead to alveolar-capillary microangiopathy and non-enzymatic protein glycation in the lungs. This makes collagen less susceptible to proteolysis, which causes collagen accumulation in connective tissues in the lungs, resulting in restrictive lung disease (29). The role of ACE-2 is essential for numerous organs, including the lungs, kidneys and gut. ACE-2 participates in the degradation of digestive enzymes that yields free amino acids and influences bacterial metabolism, generating bioactive peptide fragments that include angiotensin ACE-2 (30,31). ACE-2 possesses RAS-independent functions that regulate intestinal amino acid homeostasis, antimicrobial peptide expression, and gut microbiome ecology. ACE-2 is also a key regulator of dietary amino acid homeostasis, innate immunity, gut microbial ecology and infectious susceptibility to colitis (31).

Yang *et al* (32) reported that the gut microbiota is important for the regulation of colonic ACE-2 expression. Additionally, it may contribute to the gut-lung axis pathology during COVID-19 (32). The human gut microbiota has

important roles in human physiology, including maintenance of the epithelial barrier, inhibition of adhesion of pathogens to the intestinal surface, modulation of the maturation of the immune system and degradation of indigestible carbons, such as plant polysaccharides and metabolite production (33). Humans naturally obtain gut microbiota from the mother during breastfeeding. Thereafter, microbiota are obtained from food intake and the environment (34). A healthy gut microbiota is rich in *Bifidobacterium* spp., *Faecalibacterium* spp., *Ruminococcus* spp. and *Prevotella* spp. (35,36). The dominant bacterial phyla found in the intestine are *Firmicutes* and *Bacteroidetes* (37). The intestinal barrier epithelium has important roles; apart from being protective, it also acts as a reservoir for host-produced antimicrobial molecules, such as secretory and defensive IgA. There are host-microbial interactions that are regulated through host recognition of microbe-associated molecular patterns and bacterial metabolites; thus, if there are changes in the host conditions and the microbiome composition, this will contribute to differences in mucus composition and increased susceptibility to infection (38).

Gut microbiome manipulation to alter the gut-lung axis may potentially protect humans against respiratory infections. The gut-lung axis can be described as a common mucosal immunological system. There is a correlation between the gut and lung, particularly with regard to respiratory immune and anti-infective responses. In COVID-19, the gut can downregulate the expression of ACE-2 in the intestine. Probiotics may have potential use for reducing upper respiratory tract infection symptoms (39). The gut and respiratory tract are associated with the modulation of the immune response and dysbiosis. There is microbial translocation with the decrease in intestinal barrier integrity followed by a secondary infection. Chronic lung diseases can develop along with GI tract diseases (40). Genetic or exogenous factors, including diets and antibiotic treatment, can alter the composition of the gut microbiota and can result in a reduced capacity to mount adequate local and

Table I. Microbiome profile associated with a specific COVID-19 effect.

First author, year	SARS-CoV-2 effect	Microbiome profile	Effect on GI tract	(Refs.)
Zuo <i>et al.</i> , 2020	Indicative of a prolonged effect of SARS-CoV-2 infection on the gut microbiomes of patients with COVID-19.	<i>Coprobacillus</i> , <i>Clostridium ramosum</i> , and <i>Clostridium hathewayi</i> <i>Faecalibacterium prausnitzii</i>	Correlated with COVID-19 severity	(14)
Khan <i>et al.</i> , 2021	Gut microbiome dysbiosis is an important predisposing factor for COVID-19 disease severity.	<i>Bacteroides dorei</i> , <i>Bacteroides thetaiotaomicron</i> , <i>Bacteroides massiliensis</i> , and <i>Bacteroides ovatus</i> <i>Faecalibacterium prausnitzii</i> , <i>Roseburia faecis</i> , <i>Roseburia inulinivorans</i> , <i>Dorea formicigenerans</i> , <i>Lachnospira pectinoschiza</i> , <i>Pseudobutyrvibrio xylanivorans</i> , <i>Clostridium ruminantium</i> , <i>Butyricoccus pullicaecorum</i> <i>Shigella sonnei</i> , <i>Shigella dysenteriae</i>	Inverse correlation with disease severity (anti-inflammatory bacterium) Correlated inversely with SARS-CoV-2 <i>Firmicutes</i> phylum level, relative reduction abundance in asymptomatic, mild, and severe symptoms	(13)
Kim <i>et al.</i> , 2021	Gut microbiota changes in patients with asymptomatic or mild symptoms. The composition of the gut microbiota is recovered after negative conversion of SARS-CoV-2 RNA in the respiratory tract.	<i>Bacteroides caccae</i> , <i>Bacteroides ovatus</i> , <i>Parabacteroides distasonis</i> , <i>Bacteroides fragilis</i> <i>Ruminococcus gnavus</i> , <i>Clostridium bolteae</i> , <i>Clostridium citroniae</i> , <i>Clostridium hathewayi</i> <i>Atopobium rimae</i>	<i>Proteobacteria</i> phylum, positively associated with severely infected COVID-19 patients <i>Bacteroidetes</i> phylum, positively associated with severely infected COVID-19 patients <i>Firmicutes</i> phylum, positively associated with severely infected COVID-19 patients <i>Actinobacteria</i> phylum, positively associated with severely infected COVID-19 patients	(15)
Ren <i>et al.</i> , 2021	The microbiota may affect COVID-19 progression by secreting lipid molecules into the blood.	<i>Firmicutes</i> phylum <i>Bacteroidetes</i> phylum <i>Lachnospira</i> <i>Faecalibacterium</i>	The most dominant phylum in the patients with positive and negative SARS-CoV-2 The most abundant phylum in healthy controls	(17)
Moreira-Rosário <i>et al.</i> , 2021	Gut microbiota dysbiosis is present in moderate and severe COVID-19 patients in comparison with asymptomatic/mild patients.	<i>Bifidobacterium</i> genus, <i>Collinsella</i> genus, <i>Roseburia</i> , and <i>Lachnospira</i> genera <i>Ralstonia</i> genus (<i>Proteobacteria</i>) <i>Firmicutes</i> and <i>Bacteroidetes</i> Phylum	Can produce SCFAs by fermenting fiber and contribute to patient recovery Anti-inflammatory property and has been recognized as a potential biomarker for human health Decreased tendency from mild-to-moderate-to-severe symptoms Increases with the COVID-19 severity Ratio decreases in COVID-19 patients from ambulatory-ward-ICU	(16)

Table I. Continued.

First author, year	SARS-CoV-2 effect	Microbiome profile	Effect on GI tract	(Refs.)
Xu <i>et al</i> , 2021	The dynamic change of microbiome is complex during COVID-19. A synchronous restoration of both the upper respiratory and gut microbiomes from early dysbiosis towards late more diverse status has been observed in 6/8 mild COVID-19 adult patients.	<i>Bacteroides</i> genus (<i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Blautia</i> , and <i>Coprococcus</i>) <i>Neisseria</i> and <i>Actinomyce</i> <i>Pseudomonas</i>	Decrease gradually from community type I to III/IV	(76)

systemic immune responses. The gut microbe-derived components and metabolites include short-chain fatty acids (SCFAs) associated with the gut-lung axis. The direct effects of SCFAs is accomplished through the engagement of G protein-coupled receptors (41).

Microbiome interaction and cytokine regulation. There is an interaction between the microbiome and cytokines, and this host-microbiome interaction is associated with the production of tumor necrosis factor- α (TNF- α) and interferon (IFN)- γ . If there is a change in the composition of the microbiome in the digestive tract, the protective mechanism will be disrupted, leading to an increase in the risk of infection. The gut microbiome plays a role in homeostasis (42). Given the importance of the gut microbiota in the immune response, and knowing that SARS-CoV-2 progression appears to be associated with the 'cytokine storm', which leads to hyper-inflammation (elevated levels of pro-inflammatory cytokines, including TNF- α , IL-6 and IL-1 β), a particular focus should be given to the gut microbiota (20,27). The increase in cytokine levels is associated with severe COVID-19. In addition, the levels of leukocytes, lymphocytes and IL-6 are also increased (40). Excessive IL-6 signaling leads to a myriad of biological effects that contribute to organ damage, such as inducing vascular endothelial growth factor expression in epithelial cells and increasing vessel permeability (43).

The gut microbiota and cytokines are correlated with each other due to butanoate metabolism and butyrate production (44). Butyrate is involved in the regulation of various inflammatory factors, including IL-10, IL-6 and IL-18 (44). In a study by Blanco-Melo (45), it was reported that there was a host response to viral infection. This response was determined by common type I and III IFNs coupled with increased chemokines and high IL-6 expression. SARS-CoV-2 also induces the levels of chemokines. Lin *et al* (46) reported that certain cytokines were associated with the gut microbiome in patients with Parkinson's Disease (46). In that study, a positive correlation between the abundance of *Bacteroides* genus and the plasma concentration of TNF- α in Parkinson's disease was identified. Microbial metabolites regulate the host immune system. *Bacteroidetes* and *Clostridium* produce SCFAs and desaminotyrosine, which can enhance influenza-specific CD8+ T-cell functions and type I IFN signaling in macrophages, increasing protection against influenza infection (47).

4. Modulation of the microbiome profile to regulate the inflammatory response

Exercise. During the pandemic, working from home resulted in changes in food intake and physical activity. According to research by Brancaccio *et al* (48), participation in physical activity decreased during the pandemic. However, since physical activity has several beneficial effects, certain individuals performed exercises by utilizing internet-based platforms, such as social media (48). Physical activity can help alter the composition of the gut microbiota (48). Quiroga *et al* (49) reported that in obese children who were physically active, changes in the microbiome significantly reduced *Proteobacteria* levels, which tended to be similar to those found in healthy children.

In addition, there is an interaction between the microbiota and host cell immunity (49). Toll-like and Nod-like receptor are signaling pathways responsible for a state of low-grade inflammation, and their expression levels are increased during physical exercise and obesity (49).

Exercise can affect the gut integrity and the composition of gut microbiota in the host. In a study by Campbell *et al* (50), comparisons between groups of animals showed the presence of a diverse range of gut microbiota (50). However, *Clostridiales* dominated the fecal microbiota present in all animal groups. *Faecalibacterium prausnitzii* was detected only in animals who exercised, whereas animals with typical diets without exercise, had large clusters of *Lachnospiraceae* spp., which were not present in animals fed high-fat diets. *Allobaculum* spp. and *Clostridium* spp. were found in animals with regular diets who exercised, whereas animals fed high-fat diets had microbial groups associated with *Peptococcus* spp (50).

In addition, a study of rugby athletes by Clarke *et al* (51) showed significant differences between the athletes and control group. The athletes had higher taxa microbiota: 22 phyla, 68 families and 113 genera. Exercise and protein intake increased gut microbiota diversity in the athletes. *Firmicutes* and *Ruminococcaceae* were abundantly present, whereas *Bacteroidetes* were less abundant in the athletes (51). During exercise, TNF receptors gradually produce TNF- α inhibitors, the levels of which increase during and after exercise. Similarly, IL-1 receptor antagonists are produced during exercise and remain elevated post-exercise (52). Physical exercise acts as a modulator of the immune system as it can increase pro- and anti-inflammatory cytokines and secular lymphocytes, and IFN-I can promote macrophage and lymphocyte activity. Suppression of the IFN-I response has been noted in COVID-19. In addition, severe COVID-19 infections have been associated with a pro-inflammatory cytokine storm, lymphopenia, circulatory changes and viral spread to other organs (53).

Nutrition

Probiotics. Probiotics are non-pathogenic microbes that are beneficial to humans. The most common species are *Lactobacillus* and *Bifidobacterium*, which are present in several fermented foods (54,55). Probiotics provide protection as they have a low disease activity index and cause considerably little histopathological damage in the large intestine. In addition, probiotics are more effective in modulating the host immune response, as they decrease IL-1 β and IL-6 levels and increase the expression of TGF- β and IL-10 (56). Consumption of *Lactobacillus reuteri* V3401 can reduce IL-6 and sVCAM levels (57). Probiotics have been reported to increase the levels of IFN-I and the number and activity of antigen-presenting cells, natural killer cells and T-cells, as well as systemic and mucosa-specific antibodies in the lungs. Clinical evidence indicates that modulation of the gut microbiota can positively influence COVID-19 disease progression (58).

Fermented milk and yogurt are the most common consumed forms of probiotics. In a study by McNulty *et al* (59), probiotic bacterial strains were shown to affect the gut microbiota. There were no significant changes in the bacterial composition or representation of gene-encoding enzymes after consuming fermented milk (59). However, the results of fecal

sample sequencing and urine metabolite spectrometry showed significant changes in the expression of microbiome-encoded enzymes involved in various metabolic pathways, the most prominent of which were related to carbohydrate metabolism. Bacterial strains present in fermented milk or yogurt were not associated with the abundance of these phyla microbiota in the gut. There were differences in *Bifidobacterium* strains in individuals who consumed fermented milk mixed with probiotic strains and *Bifidobacterium* probiotics compared to *Lactobacillus*-fermented milk. Fermented probiotic milk and yogurt intake were associated with the levels of ingested bacteria (60). The composition of different bacteria in probiotic products can affect the environment of the gut microbiota, and the interaction between the gut microbiota and host will provide protection against viral infections. Probiotics provide protection, treatment and prevention of illness in the digestive system.

Prebiotics. Consumption of prebiotics is a dietary strategy that can modify the GI microbiota for health benefits (61). Prebiotics are substrates selectively utilized by host microorganisms that confer a health benefit. Prebiotics enhance the growth of *Bifidobacteria* and *Lactobacilli*, which have beneficial effects on system-wide metabolism and physiology. Prebiotics are predominantly carbohydrate-based, but other substances, such as polyphenols and polyunsaturated fatty acids, may exert prebiotic effects. *Bacteroides*, one of the microbiome genera, can break down high molecular weight polysaccharides (62).

Prebiotics are fibers that cannot be digested by the host but are metabolized by the colonic microbiome, resulting in the growth of certain bacteria. Intervention with prebiotics, probiotics, or synbiotics is important, as it can alter the composition of gut microbiota in the GI tract. This is essential for the development of appropriate immune regulatory networks, which influences disease risk later in life (63). Dietary consumption of certain food products can result in significant changes in the gut microbiota composition. The change in *Bifidobacteria* may be attributed to prebiotics (64). The concept of prebiotics is based on increasing the presence of beneficial microorganisms in the gut microbiota, such as *Bifidobacteria* and *Lactobacilli*. Since the diversity of the gut microbiota has expanded, there may be other potential beneficial genera, such as *Roseburia*, *Eubacterium*, *Faecalibacterium*, *Akkermansia*, *Christensenella* and *Propionibacteria* (58). Prebiotics, probiotics, fermented foods and synbiotics can modulate the gut and extend its benefits to distant sites, such as the respiratory tract (65).

Vitamins. COVID-19 is associated with vitamin D deficiency. The rate of SARS-CoV-2 infection was significantly lower in vitamin D-deficient patients supplemented with cholecalciferol than those without supplementation (66). According to Robles-Vera *et al* (67), the abundance of *Prevotella* and *Actinomyces* increased, whereas that of *Odoribacteraceae* and genus *Butyrivimonas* decreased in mice on a vitamin D-free diet. Vitamin D deficiency did not induce intestinal dysbiosis, but it resulted in several specific changes to the bacterial taxa, which might play a pathophysiological role in the immunological dysregulation associated with hypovitaminosis (67). Vitamin D is now recognized as a hormone with several extra-skeletal actions, including in the immune system.

The microbiome is correlated with the levels of vitamin D, and *Firmicutes* phylum, *Clostridia* class and *Clostridia* order have been recognized as butyrate producers. Some of the genera identified were *Ruminococcus*, *Coprococcus* and *Blautia obeum* species. Specific microbiota, known as butyrate producers, provide potential targets for intervention, either through dietary modification or vitamin D supplementation (68). Vitamin D deficiency is associated with the cytokine storm and an increased likelihood of requiring a ventilator in hospitalized COVID-19 patients. Meanwhile, dexamethasone appears to mitigate the adverse effects of vitamin D deficiency (69).

Vitamin A (VA) exhibits pharmacological activity in the management of pneumonia. The mechanisms of action of VA against SARS-CoV-2 include enrichment of immunoreactions, inhibition of inflammatory reactions and biological processes related to reactive oxygen species (70). VA can assist in promoting intestinal immunity and epithelial integrity (71). According to a study by Liang *et al* (28), VA may contribute to the clinical management of CHOL/COVID-19 by inducing cell repair, suppressing oxidative stress and inflammatory reactions, and ameliorating immunity (28). One of the roles of VA is regulating the proliferation of B- and T-cell differentiation and interaction, including induced T-cell migration (72). VA can affect gut immunity and epithelial integrity, factors that may, in turn, modulate microbiome development. In neonates, VA is associated with a relatively higher abundance of *Bifidobacterium*, and a good VA status is associated with a higher abundance of other genera, such as *Akkermansia* (71).

Drug-related. Over the course of a human's life, an individual will be exposed to numerous drugs, including vaccinations, painkillers, antibiotics and contraceptives. COVID-19 treatment requires limiting viral multiplication and neutralizing tissue damage induced by an inappropriate immune reaction (73). The microbiome can act as a drug as it can secrete enzymes with a biocatalyst effect (74). Drugs can affect the composition of the microbiome in terms of abundance, diversity and function. If there is a deviation, then this will result in dysbiosis. Changes in the microbiome due to administration of drugs can be temporary or long-term (74). There is a positive correlation between the quantity of drugs taken and overall microbiome composition (74). *Bifidobacterium* decreases during multidrug treatment, which in elderly COVID-19 patients, not only causes dysbiosis in the intestine but also increases bacterial resistance, and in adults the dynamic changes to the microbiome was complex during COVID-19 infection (75,76). Antibiotic use (and misuse) and polypharmacy may promote the selection of resistant commensal strains, which constitute a reservoir of transmittable resistance factors in elderly populations with comorbidities (75).

Antibiotic-induced alterations of the gut microbiome, as an ecologically complex system, may also result in metabolic changes in the host, increasing the risk of weight gain and obesity, altering the immune response and increasing susceptibility to other infections from a loss of colonization resistance (74,77). The top microbiome-associated drugs include proton pump inhibitors lipid-lowering statins, laxatives, metformin, β -blockers, ACE inhibitors and selective serotonin reuptake inhibitors (77).

The uncontrolled inflammatory process is of particular concern in cases of COVID-19. Research by Dormont *et al* (78) reported that cases of COVID-19 that resulted in death might be caused by virus-induced hyper-inflammation; multidrug nanoparticles (NPs) were the topic of this study. These multidrug NPs enable efficient encapsulation of drugs, reduce side effects and promise anti-inflammatory and protective effects in lethal endotoxemia and systemic shock models (78). The combination of traditional Chinese and Western medicine may carry risks of herb-drug interaction (HDI) (79). A study by Liu *et al* (79) reported that HDIs primarily occurred in the GI tract, and typically led to diarrhea, but this did not develop or was milder when taking a single drug. According to Dai *et al* (80), the consistency between the gut microflora and glycosidase system indicates the inhibition of darunavir on the activity of β -glucosidase and β -glucuronidase. Regarding darunavir (with a high HDI risk), when patients with COVID-19 use traditional herbal and anti-coronavirus medicines in combination, it is necessary to adjust the intake interval to avoid alteration of the efficacy and toxicity to prevent/mitigate adverse effects (80).

Hydroxychloroquine (HCQ) is an anti-malarial drug that can be used as treatment of COVID-19, and the combination of chloroquine and HCQ is already used in the treatment of COVID-19. Chloroquine does not affect the expression of ACE-2 on cell surfaces, but it inhibits terminal glycosylation of the ACE-2 receptor for cell entry, which is targeted by SARS-CoV and SARS-CoV-2. HCQ can be used as treatment for rheumatoid arthritis (73). Pan *et al* (81) reported that HCQ did not increase intestinal permeability. The effect of HCQ was detected on gene expression of tight junction-associated proteins in colonic tissue, and there was no statistically significant change in the mRNA expression levels of several claudins (1, 2, 4, 5, 8 and 14), occludin, cadherin 1, mucin 2 and zonula occludens 1 (ZO-1) after HCQ challenge for 14 days. However, HCQ could alter the gut microbiota composition, and the dominant phyla in these groups were *Bacteroidetes* and *Firmicutes* (81). Million *et al* (82) reported that simultaneous intake of HCQ and azithromycin (AZ) could be used as a treatment for COVID-19. Clinical results of a combination of HCQ and AZ reported mild adverse events (GI or skin symptoms, headache, insomnia and transient blurred vision). However, AZ can induce a modest decline in the microbiota and a shift in taxonomic composition driven by a reduction in *Proteobacteria* and *Verrucomicrobia* (specifically, *Akkermansia muciniphila*) (83). Moreover, the combination of AZ and florfenicol can alter the gut microbiota composition and decrease the abundance and diversity. At the phylum level, the ratio of *Firmicutes/Bacteroidetes* increased significantly in the antibiotic groups (84). Drug treatment in COVID-19 patients can affect the GI microbiome. However, the gut microbiome can provide efficacy and safety by changing the structure of the drug enzymatically and altering the bioavailability, bioactivity or toxicity of the drug.

Herbal. Herbal medicines have several benefits for the GI tract and can serve as alternative treatments. The Nutrition Care (NC) Gut Relief Formula contains a combination of herbs and nutrients, including curcumin, aloe vera, slippery elm, guar gum, pectin, peppermint oil and glutamine. The NC Gut Relief Formula significantly improved GI tract problems and

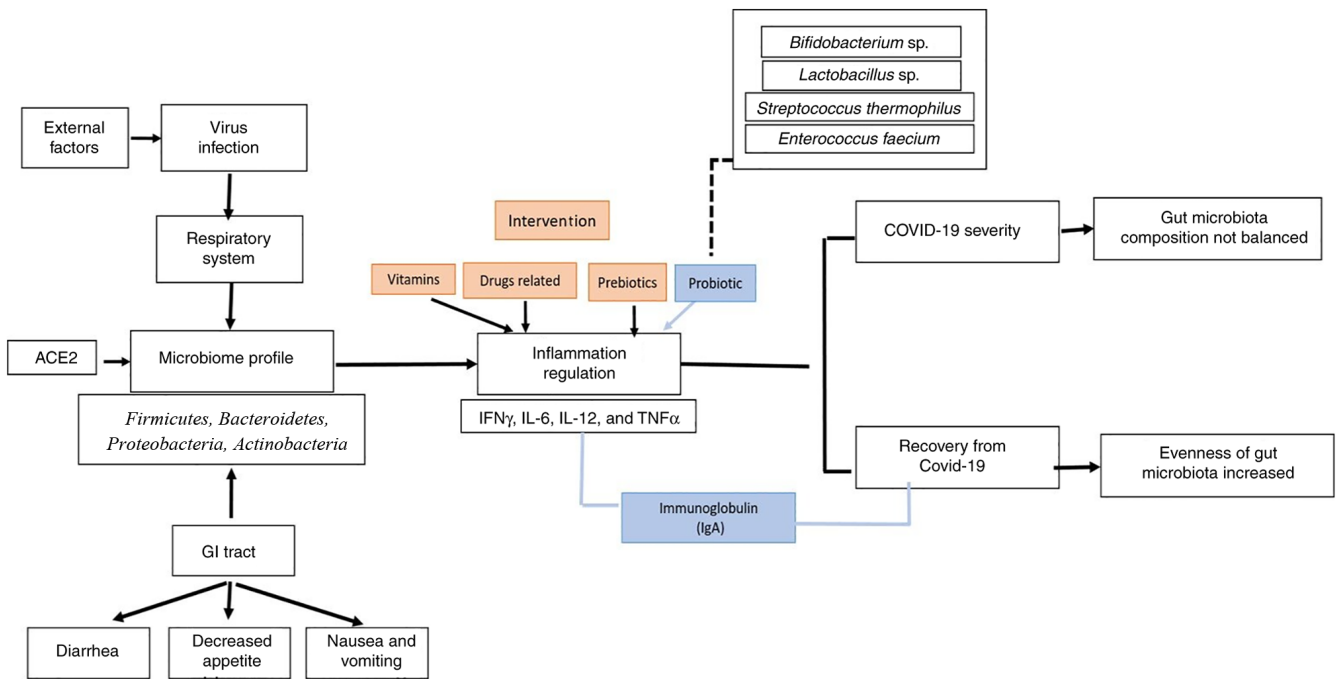


Figure 2. Schematic of microbiome regulation in association with COVID-19 viral infection. ACE-2, angiotensin converting enzyme 2; COVID-19, coronavirus disease-19; IL, interleukin; GI, gastrointestinal; TNF- α , tumor necrosis factor- α .

the microbiome profile, and reduced or increased inflammation (85). Traditional Chinese herbal medicines have played a vital role in the treatment of SARS, and combined with Western medicines, significantly improve the symptoms of SARS (86). Herbal medicines have fewer side effects than classic pharmaceuticals (87).

Herbal medicine and functional foods contain fiber, polyphenols and polysaccharides, exerting prebiotic-like activities to prevent and treat cardiometabolic diseases (88). The abundance of *Bacteroidetes* and *Akkermansia*, *Bifidobacteria*, *Lactobacillus*, *Bacteroides* and *Prevotella* is increased by herbal medicine and functional foods. A recent study showed that curcumin improved intestinal barrier function by modulating intracellular signaling and organizing tight junctions, providing a mechanism where curcumin modulates chronic inflammatory diseases (88). Peterson *et al* (89) reported that herbal medicines drove the formation of unique microbial communities. Herbal medicines also induced blooms of butyrate and propionate production.

Herbal medicines can modulate the gut microbiota in a manner predicted to improve colonic epithelium function, reduce inflammation and provide protection from opportunistic bacteria. Herbal medicine, or natural active ingredients, can reduce blood glucose and lipid levels and lower body and visceral adipose weights (90). Herbs can restore the structure of the intestinal flora, and herbs can aid COVID-19 treatment by modulating the immune system. The intestinal flora is closely related to the expression profile of tight junction proteins in the intestinal epithelial cells, including claudin-1, occludin and ZO-1. Five main categories of herbal ingredients can affect the intestinal flora: Glycosides, flavonoids, alkaloids, phenylpropanoids and organic acids. China's guidelines mentioned that herbs and prebiotics can be used in the treatment of COVID-19, especially for maintaining intestinal floral

homeostasis and preventing secondary bacterial infections. One of the beneficial effects of herbal based medicines is they inhibit the activity of SARS-CoV-2 3C-like protease (91).

5. Conclusions

The modulation of the factors that control the physiological growth of the gut microbiome will determine the proportionate ratio of microbiome types, which is important for modulating cytokine levels that impact inflammatory processes, such as in the case of COVID-19 infection (Fig. 2). This review highlights the potential future directions and clinical applications for subsequent studies. It hypothesized that modulation of the microbiome may hasten the recovery process or reduce the severity of an illness via regulation of the inflammatory process.

Acknowledgements

The authors would like to thank Mr. Deby Fajar Mardhian (Department of Dental Materials and Technol, Universitas Padjadjaran) who assisted in reviewing and proofreading the manuscript.

Funding

This study was supported by a WCR grant from the Ministry Education and Culture (grant no. 1207/UN6.3.1/PT.00/2021), and an Academic Leadership grant (grant no. 1959/UN6.3.1/PT.00/2021).

Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

NN, IM, LA, HG and RL performed the literature search and assisted in drafting and revising the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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