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Review Article

The microbiota-mediated dietary and nutritional interventions for COVID-19

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ABSTRACT

Worldwide, scientists are looking for specific treatment for COVID-19. Apart from the antiviral approach, the interventions to support healthy immune responses to the virus are feasible through diet, nutrition, and lifestyle approaches. This narrative review explores the recent studies on dietary, nutritional, and lifestyle interventions that influence the microbiota-mediated immunomodulatory effects against viral infections. Cumulative studies reported that the airway microbiota and SARS-CoV-2 leverage each other and determine the pathogen-microbiota-host responses. Cigarette smoking can disrupt microbiota abundance. The composition and diversification of intestinal microbiota influence the airway microbiota and the innate and adaptive immunity, which require supports from the balance of macro- and micronutrients from the diet. Colorful vegetables supplied fermentable prebiotics and anti-inflammatory, antioxidant phytonutrients. Fermented foods and beverages support intestinal microbiota. In sensitive individuals, the avoidance of the high immunoreactive food antigens contributes to antiviral immunity. This review suggests associations between airway and intestinal microbiota, antiviral host immunity, and the influences of dietary, nutritional, and lifestyle interventions to prevent the clinical course toward severe COVID-19.

1. Introduction

Since its start in December 2019, the coronavirus disease 2019 (COVID-19) outbreak became a global pandemic in just three months due to the high infectivity and transmission of the causative virus—the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1–3]. According to the WHO-China Joint Mission on Coronavirus Disease 2019, 78% of the infected individuals were asymptomatic [4,5]. 81%, 14%, and 5% of COVID-19 cases had mild, moderate, and severe clinical symptoms, respectively [6]. Individual host metabolic status, including diet, nutrition, lifestyle, and environmental factors, critically determine these different clinical manifestations of SARS-CoV-2 infection [7–10].

The clinical events of COVID-19 include dry cough, fever, breathing

difficulties, pneumonia, and respiratory failure [1]. The human airway epithelium is an entering site of SARS-CoV-2 [11]. The microbiome that inhabits the respiratory mucosa, from the upper to the lower respiratory tract, plays a crucial role in health and disease [12–17]. Several studies suggested the mutual relationship between the microbiota to host immunity, respiratory health, viral infection, and the immune responses to viral vaccines [18–20]. The balance of microbiota in the gut, oral cavity, and lung influences the host's immune tolerance to viruses and the clinical severity and duration of the viral infections [20,21]. Alterations in the intestinal microbiome species and metabolites have been highlighted during respiratory viral infections, which may impact the lungs via microbiome-mediated cross-talk along the gut-lung axis [19]. Gut dysbiosis and related lung complications have also been observed during

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COVID-19 disease progression [22–25]. Among many potential molecular targeted drugs and the newly arrived vaccines, diet and nutrition determine the microbiota's composition and diversity and thus affect host immunity. However, the discussion of these simple options is still limited, as though it is the elephant in the room [26–31]. Herein, we review the dietary and nutritional interventions to maintain the healthy microbiome balances that potentially modulate the host immunity to COVID-19.

2. Microbiota and host immunity

As humans do not live in sterile bubbles, the hosts dynamically interact with their external environments, including foods, environmental toxins, and germs such as bacteria, parasites, fungi, and viruses [32–34]. Microbiota mediates these interactions' healthy balances throughout all surface linings, including skin, gut, lung, cornea, and vagina [19,35–37]. The gastrointestinal tract, particularly the colon, harbors the most populated microbiota in a human body: with the number of microbial cells and their genomes' count at ten and a hundred times more than those of the host, respectively [15].

The barrier linings' integrated functions, protective mucous, and antimicrobial peptides initially protect the internal host environment from microbial translocation [38]. However, the tissue-resident antigen-presenting cells - such as dendritic cells and macrophages - continuously sampling and processing the external microbial antigens and relaying the messages to the host immune cells [38]. These processed molecular patterns comprise the various signals of self, non-self, damaging, or dangerous signals: the pathogen- and the danger-associated molecular patterns [39]. The combined processing of these external signals determines the dynamic internal balance of pro-inflammatory and anti-inflammatory responses, the host tolerances to pathogens, and the composition and diversification of microbiota [38]. These interactions modulate the proliferation, differentiation, and maturation of the various immune cells [40–42].

Apart from those, several microbe metabolites, particularly the short-chain fatty acids (SCFAs), serve as the metabolic fuel for colon cells, the messengers, and the mediators of microbe-host immunity synchronization [13,40–42]. The fermentable dietary fibers and the resulting colonic microbiota compositions determine the SCFAs synthesis, which maintains the intestinal health, barrier functions, and lumen homeostasis: thus, protects the host from several disorders, such as inflammatory bowel disease [43–45]. Interestingly, influenza A infection disrupts these SCFAs production, creating the microbiota imbalances that contribute to the clinical symptoms [46].

3. The lungs and airways microbiota

Far from the historical concept of a sterile environment of lungs, the lung microbiota significantly contributes to the airway tolerance and immune responses to respiratory infection [15,47]. However, the lungs' microbial count is less compared to those in the colon [15]. The changes in microbial abundance and diversification in the upper and lower respiratory tracts correlate to the airway pathologies such as asthma and lung infections [48]. For example, the immunomodulatory *Prevotella* species promote lung homeostasis. The pro-inflammatory environment in the lung increases the outgrowth of several gram-negative bacteria, such as Gammaproteobacteria, through the nutrient enrichment processes: the mucous production and the enhanced vasculature, and the increased endothelial permeability [49].

The airway-associated lifestyle factors, such as cigarette smoking, significantly change the lung microbial composition toward the increased number of pro-inflammatory *Proteobacteria* and *Firmicutes* while decreasing the anti-inflammatory *Oceanospirillales*, *Desulfurimonadales*, *Nesterenkonia*, and *Lactobacillaceae* [50]. Interestingly, a recent systematic review suggested the associations between cigarette smoking and the negative clinical outcomes of COVID-19 [51].

However, recent studies agree that cigarette smoking increases significantly the risk of progressing and severe viral infection [8]. This finding suggests the close relationship between lifestyle, microbiota, and antiviral immunity.

4. The lung-intestinal microbiota connection

Animal studies reported the increased numbers and the gradual changes of lung microbiota composition during the first two-week of life [52]. These changes influenced the lung immune tolerance toward specific allergens by the increased number of regulatory T-cells [14]. Several studies revealed the association between the lung and intestinal microbiota [53,54]. The neomycin-induced microbiota imbalance, aka gut dysbiosis, increased the lung infection from influenza virus in the animal models through the inactivation of the inflammasome, dendritic cells, and T-cells responses [55]. During the *S. pneumoniae*-induced lung infection, the microbiota-depleted mice had higher inflammation, more organ damages, and fewer phagocytotic activities of the alveolar macrophages than their controls [56]. The healthy fecal microbiota transfer into the microbiota-depleted mice ameliorated their respiratory symptom severities and reduced the levels of pro-inflammatory cytokines [56]. Intestinal dysbiosis can predispose an individual to respiratory tract infection, including pneumonia and other respiratory conditions such as chronic obstructive pulmonary disease, cystic fibrosis, and lung cancer [57,58]. Despite their different locations, these two microbial communities are closely influencing and interacting with each other.

5. Microbiota and the protection against SARS-CoV-2 infections

Cumulative studies suggested that the microbiota is significantly involved in the host responses to many viral infections, either through the facilitation of viral attachment to host cells or the supports of antiviral immunity such as interferon and innate immune activation [59–61]. Specific evidence of microbiota and infection is starting to be available also for SARS-CoV-2 [62–66].

In the mice's lung, the commensal bacteria enhanced the antiviral activity of type I interferon, which was blunted by antibiotics [67]. While germ-free mice were prone to death from influenza infection, their intestinal microbiota's re-colonization promoted the anti-inflammatory polarization of macrophages [68]. Kanmani et al. reported that the colonization of a gram-positive bacteria, *Corynebacterium pseudodiphtheriticum*, in mice's nasal cavities reduced their symptoms of respiratory syncytial virus infections and prevented secondary pneumococcal pneumonia [69]. The mechanisms of these antiviral responses were the increased innate immune activation of toll-like receptor 3 signalings in the alveolar macrophages, the interferon signaling, and the T-cells activation [69]. Wu et al. also reported the intestinal microbiota-mediated activation of toll-like receptor 7 signalings in response to the respiratory influenza viral infection [70].

Apart from these mechanisms, the microbiota can exert antiviral effects through their metabolites, particularly the butyrate-an important SCFA. Trompetee et al. demonstrated that SCFAs enhanced the energy metabolism and the activities of effector T-cells and ameliorated influenza infection symptoms [71]. The seven-day pretreatment of SCFAs, including butyrate, restored the CD8+ T-cell functions, increased antibody responses, and prevented the influenza infection in mice [36,72]. Butyrate and propionate treatment in the mice model of asthma increased their production of the master transcription factor for anti-inflammatory regulatory T-cells, FOXP3, while suppressing the pro-inflammatory cytokines, interleukin 9, mast cell activation, and the lung infiltration with eosinophils and Th9 T-helper cells [73]. A study of 360 patients with immunosuppressive treatment during the allogeneic hematopoietic stem cell transplantation reported the five-fold associations between the abundance of butyrate-producing intestinal bacteria and the decreased chances of lower respiratory infection [74].

The intestinal and lung microbiota influence the host antiviral

immunity by several immunomodulating mechanisms. The interventions that balance the microbiota composition and diversification, thus, potentially play roles in COVID-19.

6. Potential microbiota-related dietary and nutritional interventions

6.1. General aspects

Healthy immunity requires integrating supports from various macro- and micronutrients derived from the individual dietary pattern. Specific nutrient deficiencies, such as vitamin D, zinc, and selenium, compromise host antiviral responses when the specific nutrient supplementation may be beneficial [7,10,75–82]. In general, a balanced diet, adequate nutritional status, together with regular consumption of anti-inflammatory and antioxidant phytonutrients, from the colorful vegetables, can support the host responses to SARS-CoV-2 and reduce the severity, duration, and mortality associated with COVID-19 [83,84].

6.2. Prebiotics

Dietary prebiotics is the fermentable and non-digestible fiber compounds that feed the intestinal microbes and contribute to SCFAs production [85]. These prebiotics, including galactooligosaccharides, transgalactooligosaccharides, and fructooligosaccharides, maintain the number of beneficial microbiota strains and sustain the production of beneficial SCFAs, therefore, potentially modulate the healthy host antiviral immunity. The fiber-rich diet protects mice from the severe pathological symptoms and the respiratory tract inflammation of the influenza virus infection [86]. Mice with a high-fiber diet and butyrate supplementation showed the reduction of chemokine expression, increasing circulating monocytes number, lowering neutrophil infiltration, and promoting T-cells bioenergetics, the reduction of lung inflammation, and enhancing the clearance of influenza virus [86].

Luoto et al. reported the incidence reduction in infants from the rhinovirus-induced respiratory tract infection with the combined usage of prebiotics and a probiotic, *Lactobacillus rhamnosus* GG [87]. The elders with the supplementation of an experimental formula containing the fermentable oligosaccharides, vitamins, and other antioxidants, showed shorter duration of symptoms to the influenza vaccine, higher antibody titers, and higher lymphocyte proliferation than their controls [88].

A recent study reported that COVID-19 patients showed intestinal dysbiosis and reduced *Lactobacillus* and *Bifidobacterium* [89]. Despite a few pieces of supporting evidence, prebiotics is a potential immunomodulatory strategy for COVID-19. However, the regular consumption of colorful vegetables also provides the non-digestible fibers for the prebiotics function and the phytonutrients that provide the anti-inflammatory and antioxidant effects. This dietary pattern can support microbiota-mediated antiviral immunity [89].

6.3. Probiotics

Probiotics are the pre-determined specific strains of beneficial microbiota that may mediate the intestinal microbiome balance and diversification, thus, augment the host immunity against pathogens, including the viral infection [90]. The combined usage of multivitamin and mineral, together with the probiotic strains of *Lactobacillus* and *Bifidobacterium*, reduces the duration and the severity of influenza-induced common cold while increasing the number of T-helper cells [85,91]. The administration of the probiotics, *Lactobacillus Plantarum* DK119 or the *Lactobacillus casei* DN-114001, protects the host against influenza infection and reduces the duration of common infectious diseases. These relevant mechanisms are the increased production of interleukin 12 and interferon γ , the modulation of macrophages and dendritic cells' activities, and the lowering of host inflammatory responses [92–94].

Therefore, probiotics are the sensible immunomodulatory option for COVID-19. However, the cumulating evidence is premature to conclude the role of specific probiotic strain in therapeutic management [89,95,96].

6.4. Fermented foods and drinks

Despite the limited number of available published studies, an omics-based study reported an association between fermented food consumption and differences in beneficial microbiota [97]. Fermentation processes break down the sugars in foods by bacteria and yeasts. Fermented foods and drinks contain live bacteria and prebiotic fibers. The fermentation of dairy products yields kefir, yogurt, and cottage cheese. Other fermented foods and beverages include fermented vegetables, tempeh, miso, pickles, sauerkraut, kimchi, kombucha, and other drinks such as beet kvass and apple cider. Consumption of these fermented foods is potentially beneficial for the microbiota and host metabolic health [97–99].

Kefir is an inexpensive, homemade, fermented milk drink that modulates the host immunity, reduces the chances of viral and bacterial infections, and benefits many host metabolic conditions [100,101]. The fermentation process of kefir involves the symbiotic activities of lactic acid bacteria and yeast [100,102]. The cell line studies reported the effects of kefir on reducing T-cell proliferation and cytopathic effects of Zika virus exposure [103]. Novel kefir that contains *Lactobacillus* acted as a natural adjuvant of dendritic cells to enhance the secretion of several cytokines, augmenting the activities of cytotoxic T-cells and acting against the viral infection [84,104].

6.5. Restricted diet

Several studies reported that intestinal microbiota is among other host predisposing factors that influence the food sensitivities through the mechanisms of food antigen degradation, gut barrier integrity, and anti-inflammatory regulatory T cell promotion [105]. The virus-host interactions disrupt these homeostases and induce the pathogenic responses to food antigens [105,106]. This concern is particularly crucial in an individual with a known history of food sensitivities or allergy during the SARS-CoV-2 pandemics.

Apart from those interventions for the healthy microbiota balance, the dietary avoidance of foods that contain high immunoreactive antigens contributes to host antiviral potentials. Gluten sensitivity underlies the development of autoimmune celiac disease [107]. The virus-induced interferon γ responses aggravate celiac disease progression during several virus infections, including adenovirus, enterovirus, rotavirus, and hepatitis C virus [108–111]. Interestingly, a non-virulent species – reovirus – interacts with gluten and initiates the immune responses that lead to celiac disease progression [106].

With these pieces of evidence, an individual with known food sensitivities, allergy, or risk for autoimmune conditions, may consider the restricted diet to promote host tolerance during the outbreak of COVID-19.

7. Conclusion

Scientists are looking for specific treatment for COVID-19 to date. Apart from the antiviral approach, the interventions to support the healthy immune responses to the virus are feasible through diet, nutrition, and lifestyle approaches. As illustrated in Fig. 1, airway microbiota and SARS-CoV-2 influence each other and determine the host immune responses. Viral infection can disrupt microbiota abundance; however, the intestinal microbiota composition and diversification influence airway microbiota and its immunity. Smoking compromises airway microbiota. Healthy immunity requires the balance of macro- and micronutrients from the diet. Colorful vegetables supplied fermentable prebiotics and anti-inflammatory, antioxidant phytonutrients.

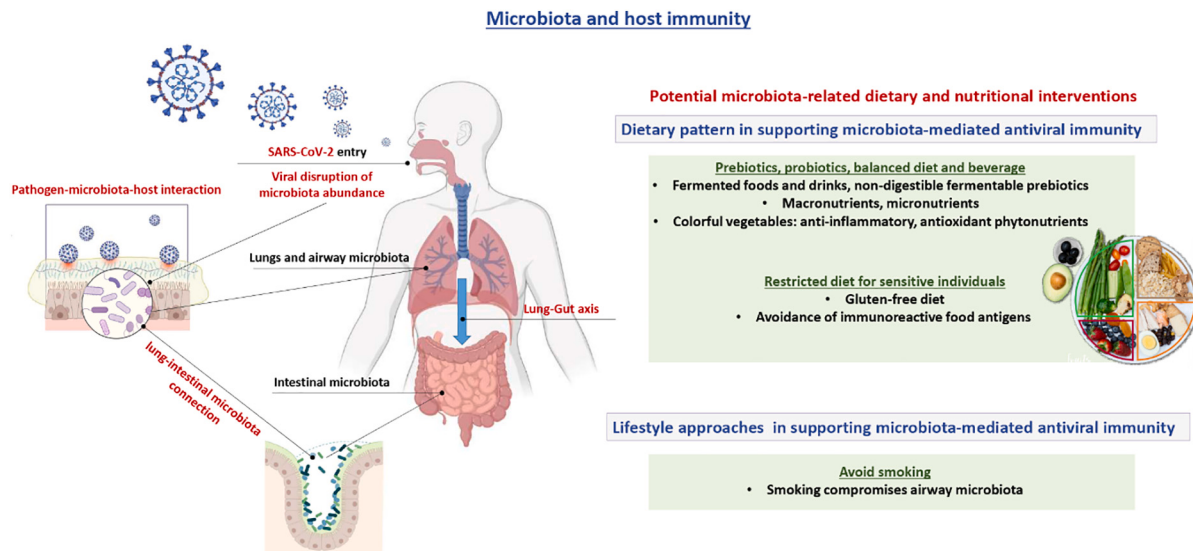


Fig. 1. The interrelationship between SARS-CoV-2 and airway microbiota determines the host immune responses. Intestinal microbiota composition and diversification influence airway microbiota, innate, and adaptive immunity. Viral infection disrupts microbiota abundance and the relevant host responses. Smoking compromises airway microbiota and its antiviral responses. Healthy immunity requires the balance of macro- and micronutrients from the diet. Colorful vegetables supplied fermentable prebiotics and anti-inflammatory, antioxidant phytonutrients. Fermented foods and beverages support intestinal microbiota. In the sensitive individual, avoiding the high immunoreactive food antigens contribute to antiviral immunity and prevents the clinical course toward severe COVID-19.

Fermented foods and beverages support intestinal microbiota. In the sensitive individual, avoiding the high immunoreactive food antigens contribute to antiviral immunity. These dietary and nutritional interventions can prevent the clinical course toward severe COVID-19.

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Declaration of Competing Interest

The authors declare they have no actual or potential competing financial interests.

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