Heliyon 9 (2023) e15668

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

# Dietary intervention with functional foods modulating gut microbiota for improving the efficacy of COVID-19 vaccines

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ARTICLE INFO

*Keywords:*
COVID-19 vaccine efficacy
Older adults
Gut microbiota
Probiotics
*Bifidobacterium*

ABSTRACT

Dysbiosis of the gut microbiota with aging contributes to a reduction in important cross-feeding bacterial reactions in the gut and immunosenescence, which could contribute to a decrease in vaccine efficacy. Fever, cough, and fatigue are the main signs of coronavirus disease 2019 (COVID-19); however, some patients with COVID-19 present with gastrointestinal symptoms. COVID-19 vaccination against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is one of the best measures to reduce SARS-CoV-2 infection rates and the severity of COVID-19. The immunogenicity of COVID-19 vaccines is influenced by the composition of the gut microbiota, and the immune response to COVID-19 vaccines decreases with age. In this review, we discuss gut microbiota dysbiosis and immunosenescence in the older adults, the role of gut microbiota in improving the efficacy of COVID-19 vaccines, and dietary interventions to improve the efficacy of COVID-19 vaccines in the older adults.

## 1. Introduction

The severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the causative agent of the coronavirus disease 2019 (COVID-19), a pandemic that started in Wuhan, China, in December 2019 [1]. One of the most effective ways to reduce SARS-CoV-2 infection rates and COVID-19 severity is COVID-19 immunization against SARS-CoV-2 [2–4]. However, as the efficacy of COVID-19 vaccines decreases with the emergence of SARS-CoV-2 variants and immunosenescence in the older adults, it is crucial to improve the efficacy of COVID-19 vaccines [5,6]. Adjuvant usage is a successful tactic to increase the immunogenicity of vaccinations in the older adults [7]. However, owing to the side effects of vaccine adjuvants, there is a huge demand for the development of safe vaccine adjuvants [8].

Although COVID-19 typically manifests with respiratory symptoms, gastrointestinal symptoms, such as diarrhea, vomiting, and abdominal discomfort, can occur at high incidence [9]. The angiotensin-converting enzyme 2 (ACE2) receptor interacts with SARS-CoV-2, allowing it to enter host cells [10]. SARS-CoV-2 mainly infects humans through the respiratory tract; however, it can also invade the gastrointestinal tract because ACE2 receptor is expressed in the cells of most human organs [11].

The maturation of immune cells and the normal development of immune function are both facilitated by the gut microbiota, which is crucial for innate and adaptive immunity [12,13]. Gut microbiota dysbiosis, defined as altered composition and decreased diversity of gut microbiota, is common with advancing age. This could contribute to higher rates of SARS-CoV-2 infection and mortality from COVID-19 in the older adults [14,15]. The gut microbiota can influence the adaptive immune response to vaccination [16–19]. Thus,

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https://doi.org/10.1016/j.heliyon.2023.e15668
Received 6 January 2023; Received in revised form 17 April 2023; Accepted 18 April 2023
Available online 21 April 2023

the efficacy of vaccines could be improved with natural adjuvants, such as probiotics targeting the gut microbiota [20–23].

In this review, we summarize the studies on gut microbiota and immunity, gut-lung axis, and interaction between gut microbiota and COVID-19. We provide evidence that alteration of the gut microbiota through dietary interventions could be a promising strategy to improve the efficacy of COVID-19 vaccines in the older adults.

## 2. Gut microbiota and immunity

### 2.1. Interaction between gut microbiota and immunity

Microbes exist throughout the human body, including the skin, oral cavity, vagina, respiratory system, and gastrointestinal tract; more than 70% of the human microbiota are present in the gastrointestinal tract. The number of organisms constituting the gut microbiota increases steadily from the stomach to the rectum, estimated at $10^{13}$–$10^{14}$ per gram [24,25]. The composition of the gut microbiota varies with dietary habits and lifestyles [26].

The gut, the body's main immunological organ, contains more than 70% of all immune cells [27]. By interacting with the host's immune system, the gut microbiota plays a critical role in the development of appropriate immunological function [28]. In the absence of microbial stimulus, the gut immune system has difficulty in developing immune functions [29–31]. In germ-free (GF) mice, mucosal immunoglobulin A (IgA) production is induced by gut microbiota colonization. Gut microbiota colonizing GF mice promotes B-cell development, contributing to the establishment of clonal diversity in the B-cell repertoire.

The dysbiosis of gut microbiota is related to immunological imbalances [32,33]. The dysbiosis of gut microbiota in pregnant women with inflammatory bowel disease (IBD) reduces the numbers of class-switched memory B cells and regulatory T cells. In addition, the dysbiosis of gut microbiota is associated with various diseases, such as hepatitis, IBD, cardiovascular diseases, and nervous system disorders [34–36].

### 2.2. Gut microbiota dysbiosis and immunosenescence in the older adults

The composition of the human gut microbiota changes with age [37]. This altered gut microbiota contributes to immunosenescence, in which the immune response declines with aging (Fig. 1) [38]. At the phylum level, the relative abundance of Actinobacteria decreases with age [37], and at the genus level, that of *Bifidobacterium* (belonging to the phylum Actinobacteria) decreases with age. This reduction is presumed to be associated with aging-related immune decline [39]. *Bifidobacterium* is an early colonizer of the neonatal gut and is predominant in infants during lactation. This could have beneficial effects on host health through immunomodulation [40].

Ingestion of *Bifidobacterium* as probiotics improves both innate and acquired immunity, as seen in Table 1. Depending on their interaction with microbes in the gastrointestinal barrier, they can trigger either a normal immune response or the development of an infection. Tight junctions between intestinal epithelial cells can maintain the integrity of the intestinal barrier, and the ingestion of *Bifidobacterium* can improve intestinal epithelial tight junction barrier and increase mucus layer thickness [41–43]. *Bifidobacterium bifidum* enhanced the intestinal epithelial tight junction barrier in a Toll-like receptor-2 pathway-dependent manner in Caco-2 cells. *Bifidobacterium breve* B-3 improved intestinal tight junction barrier integrity by the transcriptional regulation of claudin-4 in Caco-2 cells. *Bifidobacterium pseudolongum* Patronus altered gut microbiota and increased mucus layer thicknesses in rats. Viral infection in the human body involves several steps, including the attachment of virions to the cell surface. The most common routes of viral infection are the respiratory and digestive tracts. Beneficial bacteria, such as *Bifidobacterium*, are involved in preventing viral entry into the human body [44–48]. *Bifidobacterium thermophilum* RBL67 inhibits the binding of rotavirus to Caco-2 and HT-29 cells. *Bifidobacterium adolescentis* LMG10502 inhibits the binding of norovirus to Caco-2 and HT-29 cells. The inhibitory effect of microbiota against virus invasion into cells is observed across various mammalian cells. *Bifidobacterium infantis* MCC12 and *B. breve* MCC1274 reduce the binding of rotavirus to porcine intestinal epithelial cells. *B. breve* DSM20091 and *Bifidobacterium longum* Q46 directly bind to vesicular stomatitis virus, prevent its adsorption and internalization into porcine intestinal and lung cells, and produce metabolites with antiviral effects. Therefore, the dietary intake of *Bifidobacterium*, which reduces with aging, could inhibit the entry of viruses into the human body.

The factors contributing to the decreased immunity in the older adults include the decrease in the function of innate immunity [49]. Probiotics are living microorganisms that, when consumed in moderation, have beneficial health effects on the host. Ingesting *Bifidobacterium* as probiotics could enhance cellular immunity in the innate immune system in senile rats as well as in the older adults [50–54]. *Bifidobacterium lactis* HN019 and *B. lactis* Bi-07 restored innate immunity by enhancing the activities of natural killer (NK) cells, monocytes, and granulocytes. *B. longum* BB536 significantly increases the activities of NK cells and neutrophils in the older adults. *B. infantis* CCUG52486 and *B. longum* SP07/3 considerably improve the decreased NK cell activity in the older adults. The effect of probiotic *Bifidobacterium* on the innate immune response was confirmed not only in rats but also in humans. *B. adolescentis* ATCC15704, *B. breve* ATCC15700, and *B. longum* ATCC15707 significantly increase the decreased total leukocyte count in aging rats. The increase in the leukocyte count induced by *B. adolescentis* intake could be attributed to the increase in neutrophil and monocyte counts. The level of IL-8, a chemokine that recruits and activates neutrophils and monocytes, was significantly decreased in aging rats. The intake of *B. adolescentis* restored IL-8 levels to normal levels.

The genus *Bifidobacterium* exhibits immune effects in innate immunity as well as in cell-mediated response in adaptive immunity [50,53,55–59]. *B. longum* BB536 improved the Th1 immune response by increasing the number of IFN-γ-secreting cells in healthy infants. *B. breve* Yakult induced the development of IL-10-producing Tr1 cells in the colon by activating intestinal dendritic cells in

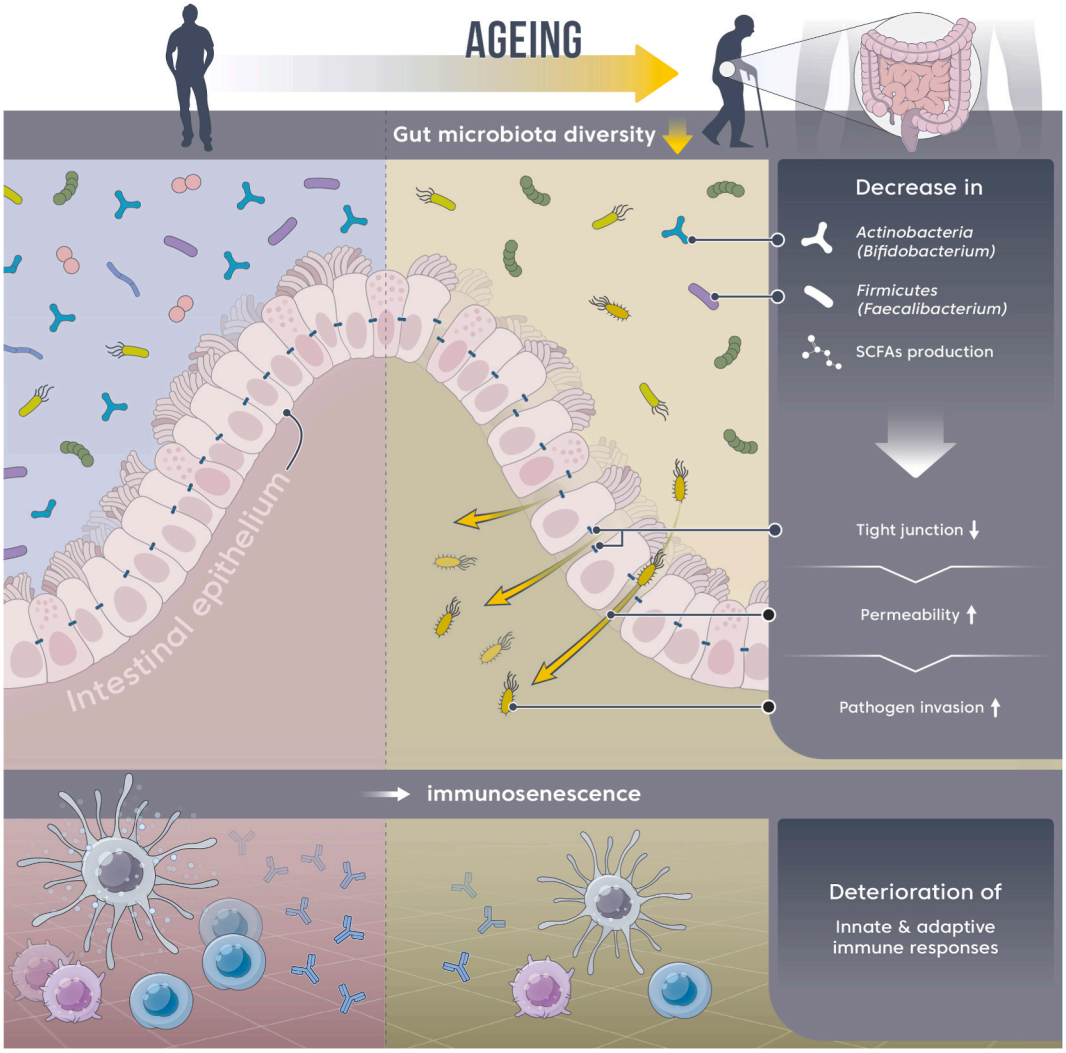


**Fig. 1.** Aging-induced gut microbiota dysbiosis and decreased immune responses.

mice. *B. lactis* HN019 increases the number of helper T cells in the older adults. In aging mice, *B. longum* AH1206 induces a protective effect against respiratory allergic inflammation by increasing the number of regulatory T cells. *B. bifidum* enhances the function of intestinal regulatory T cells by promoting the IL-10/IL-10Rα self-stimulatory loop.

The human B-cell cluster decreases both quantitatively and qualitatively in the older adults, with a decrease in the number of B cells as well as in their ability to produce antibodies [60]. Within the adaptive immune response, the ability to produce antibodies, a humoral response, is enhanced by the genus *Bifidobacterium* [53,59]. The level of IgA, a major intestinal antibody, is significantly increased in aged rats, with the ingestion of *B. adolescentis* ATCC15704, *B. breve* ATCC15700, and *B. longum* ATCC15707; in addition, *B. longum* BB536 increases serum IgA levels in the older adults.

The decreased immune function in the older adults is associated with lower levels of short-chain fatty acids (SCFAs) [61], which could be attributed to the low abundance of SCFA-producing bacteria [62,63]. Gut microbiota dysbiosis due to a decrease in the abundance of SCFA-producing bacteria, such as *Faecalibacterium prausnitzii*, *Roseburia faecis*, *Anaerostipes butyraticus*, and Ruminococcaceae, with aging contributes to a decrease in immune function, such as decreased immune cell activity.

## 3. Gut-lung axis

### *3.1. Bidirectional interaction between the gut and the lung*

Although the gut and the lung are anatomically distinct, there is a bidirectional crosstalk between the respiratory tract and gastrointestinal tract. The connection between the two organs is called the gut-lung axis [64]. Chronic respiratory diseases and respiratory viral infections are correlated with gastrointestinal diseases [65–70]. Patients with chronic gastrointestinal disorders, such as

**Table 1**
Improvement of innate and adaptive immunity through dietary *Bifidobacterium* intake as a probiotic.

| Probiotics | Host | Immune response | References |
|---|---|---|---|
| **Innate immunity: Improving tight junction barrier and strengthening the mucus layer** | | | |
| · *B. bifidum* | · Human cell | · Enhancement of the intestinal epithelial tight junction barrier in a Toll-like receptor-2 (TLR-2) pathway-dependent manner | [41] |
| · *B. breve* B-3 | · Human cell | · Improving intestinal tight junction barrier integrity by transcriptional regulation of claudin-4 | [42] |
| · *B. pseudolongum* Patronus | · Rat | · Alterations in gut microbiota and increases in mucus layer thickness | [43] |
| **Innate immunity: Inhibition of viral invasion** | | | |
| · *B. thermophilum* RBL67 | · Human cell | · Reduced entry into epithelial cells by binding to rotavirus | [45] |
| · *B. adolescentis* LMG10502 | · Human cell | · Reduced entry into epithelial cells by binding to norovirus | [47] |
| · *B. infantis* MCC12, *B. breve* MCC1274 | · Pig cell | · Reduced entry into epithelial cells by binding to rotavirus | [46] |
| · *B. breve* DSM20091, *B. longum* Q46 | · Pig cell | · Reduced entry into epithelial cells by binding to vesicular stomatitis virus<br>· Production of metabolites with antiviral effects | [48] |
| **Innate immunity: Monocytes, granulocytes, NK cells, and cytokines** | | | |
| · *B. lactis* HN019, *B. lactis* Bi-07 | · Human | · Enhancement of natural killer (NK) cell, monocyte, and granulocyte activities | [50,51] |
| · *B. longum* BB536 | · Human | · Enhancement of NK cell and neutrophil activities | [52] |
| · *B. infantis* CCUG52486, *B. longum* SP07/3 | · Human | · Enhancement of NK cell activity | [54] |
| · *B. adolescentis* ATCC15704, *B. breve* ATCC15700, *B. longum* ATCC15707 | · Rat | · Significant increase in total white blood cell count<br>· Significant increase in the level of IL-8 that attracts and activates monocytes | [53] |
| **Adaptive immunity: Cell-mediated reaction: T lymphocytes and B lymphocytes** | | | |
| · *B. longum* BB536 | · Human | · Improvement of Th1 immune response by increasing the number of IFN-γ secreting cells | [55] |
| · *B. breve* Yakult | · Mice | · Induces the development of IL-10-producing Tr1 cells in the large intestine by activating intestinal dendritic cells | [56] |
| · *B. lactis* HN019 | · Human | · Increase in the number of helper T cells (Th) | [50] |
| · *B. longum* AH1206 | · Mice | · Increase in the number of regulatory T cells (Treg) | [57] |
| · *B. bifidum* PRI1 | · Mice | · Improvement of Treg functionality | [58] |
| **Adaptive immunity: Humoral reaction: Antibodies** | | | |
| · *B. adolescentis* ATCC15704, *B. breve* ATCC15700, *B. longum* ATCC15707 | · Rat | · Significant increase in the level of IgA, the major antibody in the intestine | [53] |
| · *B. longum* BB536 | · Human | · Significant increase in the level of IgA, the major antibody in the intestine | [59] |

irritable bowel syndrome (IBS) and IBD, are more likely to develop chronic lung diseases, such as asthma and chronic obstructive pulmonary disease (COPD). In addition, gastrointestinal symptoms, such as diarrhea and vomiting, are common symptoms of respiratory viral infections. IBS increases the risk of chronic lung diseases, such as asthma and COPD.

Absence or dysbiosis of gut microbiota contributes to several lung diseases by affecting both intestinal and pulmonary immunity [71–73]. Correlations between lung diseases and dysbiosis of gut microbiota have been reported widely [74–80]. Early exposure to the gut microbiota is essential for the development and maturation of the immune system, and the absence of gut microbiota may increase susceptibility to asthma. There is a decrease in gut microbiota diversity in patients with asthma, and a low diversity of the gut microbiota in infancy is correlated with asthma in childhood. In addition, there are specific alterations in the composition of the gut microbiota in patients with asthma. The abundance of the butyrate-producing bacterium *F. prausnitzii* was decreased, whereas that of *Clostridium* and *Eggerthella lenta* was increased in individuals with asthma. Similarly, a lower relative abundance of SCFA-producing bacteria, such as the genera *Bifidobacterium*, *Akkermansia*, and *Faecalibacterium*, and a higher relative abundance of particular fungi (*Candida* and *Rhodotorula*) increase the incidence of atopy and asthma in childhood. According to a clinical study, patients with COPD and healthy controls have distinct gut microbiota compositions. In addition, non-clinical studies have suggested that the gut microbiota significantly influences the development of cigarette smoking-induced COPD. A non-clinical study showed that the transplantation of gut microbiota from healthy controls and the symbiotic bacterium *Parabacteroides goldsteinii* restored gut health in patients with COPD. Cystic fibrosis (CF) is another chronic lung disease that affects the gastrointestinal tract, resulting in intestinal inflammation. Dysbiosis of the gut microbiota plays a role in the etiology of intestinal inflammation in CF.

### *3.2. Association between gut microbiota and lung diseases in the older adults*

The prevalence of lung diseases, such as COPD, asthma, and tuberculosis, is high among the older adults, who are particularly susceptible to lung infections [81]. The incidence of respiratory tract infections increase significantly in the older adults owing to immunosenescence with advancing age; this contributes to the mortality from these infections [82].

The dysbiosis of the gut microbiota in the older adults affects not only intestinal immunity but also pulmonary immunity, thus contributing to lung-related diseases [83]. Age-related alterations in gut microbiota contribute to the pathogenesis of allergic airway diseases. As there are few studies on respiratory infections, further research is needed to determine whether dysbiosis of the gut microbiota caused by aging increases the susceptibility to respiratory infections.

## 4. Gut microbiota as a natural adjuvant for respiratory vaccines

Vaccination is the most effective method to protect against infections. However, live vaccines have serious side effects. Therefore, vaccines currently on the market are mostly inactivated or contain only pathogenic components and thus with low immunostimulatory potential. Vaccine efficacy varies for each individual depending on age, genetics, sex, and environmental factors [84–87]. Age has a major influence on the vaccine response. With age, the ability to develop an immune response following vaccination and the resistance against infections decrease gradually, leading to a reduction in vaccine efficacy in the older adults [88–91]. Influenza vaccine efficacy is lower in the older adults than in young adults, which could be attributed to the reduction in antibody production and T cell immune response owing to the reduced migration of dendritic cells to draining lymph nodes. Therefore, it is crucial to alleviate the reduction in vaccine immune response in the older adults.

High-dose vaccination and the use of adjuvants could improve the decrease in vaccine immune responses due to aging. Appropriate use of adjuvants enhances the rate and magnitude of immune responses against antigens in the vaccine [92–95]. Aluminum salt-based vaccine adjuvants are used as adjuvants for diphtheria, tetanus, and pertussis (DTaP), *haemophilus influenzae* B (Hib), pneumococcal, and hepatitis A and B vaccines. In addition, the use of virosome as an adjuvant in influenza vaccines stimulates a strong antibody response and activates T lymphocytes. An oil-in-water emulsion adjuvant enhances the efficacy of influenza vaccines in children. However, aluminum salt-based vaccine adjuvants can cause side effects [96–98]. Aluminum salt-based vaccine adjuvants can have serious and widespread adverse effects on health, as they carry the risk of autoimmunity, long-term brain inflammation, neurological deficits similar to those in Alzheimer's disease in adults, and autism in children. Therefore, there is a high demand for the development of a safe adjuvant considering the side effects of artificial vaccine adjuvants.

The gut microbiota affects not only the innate immunity of the host, but also the immunity against infections. It influences the immune response of respiratory vaccines, exhibiting potential as a natural adjuvant for respiratory vaccines [21,99–102]. In addition, the decrease in vaccine efficacy due to aging can be restored by improving immunosenescence through the regulation of the gut microbiota [103–105]. As indicated in Table 2, the gut microbiota can be modulated by dietary probiotic intake, which enhances the efficacy of respiratory vaccines. Antigen-specific antibody titers increased after influenza vaccination in a group of people aged 70 years or older that consumed a mixture of *Lactobacillus paracasei*, *Streptococcus thermophilus*, and *L. bulgaricus*. Similarly, antigen-specific IgG and IgA antibody levels were significantly increased in a group of people aged 65−85 years taking *L. plantarum* CECT7315/7316; in addition, IgM antibody levels were increased although not significantly. Ingesting a mixture of *L. plantarum* PBS067, *B. animalis* subsp. *lactis* BL050, *B. longum* subsp. *infantis* BI221, and *B. longum* subsp. *longum* BLG240 improves the efficacy of vaccines by regulating the composition of the gut microbiota in older adults people aged 60−80 years, improving the immune response and lowering the incidence of influenza symptoms.

## 5. Interaction of gut microbiota and COVID-19

### 5.1. Gut microbiota dysbiosis and COVID-19

SARS-CoV-2 RNA was detected in the fecal samples of patients with COVID-19, suggesting SARS-CoV-2 infection in the gut [106] (Fig. 2, upper left). ACE2 is a cellular receptor used by SARS-CoV-2 to enter human cells. Transmembrane serine protease (TMPRSS2) plays a priming role in the entry of SARS-CoV-2 into host cells through the cleavage of the spike protein of SARS-CoV-2 [107,108]. A high co-expression of ACE2 receptor and TMPRSS2 was detected in the gut as well as in the lung, providing evidence that SARS-CoV-2 can infect the gastrointestinal tract [109] (Fig. 2, upper left). In particular, the expression of ACE2 and TMPRSS2 was the highest in the small intestine compared with that in other tissues [110–112].

In most clinical studies of COVID-19, the main symptoms are fever, cough, and fatigue [113–115]. However, gastrointestinal SARS-CoV-2 infection through ACE2 receptors on gastrointestinal epithelial cells causes COVID-19 in some patients who exhibit gastrointestinal symptoms [115–117]. In a study on the clinical symptoms of COVID-19, majority of the 204 patients with COVID-19 visited the hospital with fever or respiratory symptoms. However, 103 patients (50.5%) showed gastrointestinal symptoms. In a meta-analysis, the prevalence of gastrointestinal symptoms was 17.6% (95% confidence interval [CI], 12.3–24.5) in 4243 patients with COVID-19. Anorexia (26.8%) was the most prevalent gastrointestinal symptom, followed by diarrhea (12.5%), nausea/vomiting (10.2%), and abdominal pain/discomfort (9.2%). These gastrointestinal symptoms could be attributed to the SARS-CoV-2 infection from the lungs; the virus crosses the mucosal immune barrier and affects the gut along the "gut-lung axis."

The rate of detection of viral RNA and the viral load in feces were higher in patients with diarrhea than in patients without diarrhea [117]. In addition, the gastrointestinal symptoms caused by SARS-CoV-2 are highly correlated with the severity of COVID-19 [117, 118]. In a meta-analysis of 4243 patients with COVID-19, 17.1% (95% CI, 6.9–36.7) of patients with severe COVID-19 and 11.8% (95% CI, 4.1–29.1) of patients with non-severe COVID-19 had gastrointestinal symptoms. In a meta-analysis focused on the correlation between gastrointestinal symptoms and severity of COVID-19, more than 40% of patients with COVID-19 with gastrointestinal symptoms showed severity; in addition, abdominal pain increased the risk of COVID-19 severity by almost 2.8 times.

SARS-CoV-2 infection causes dysbiosis of the gut microbiota in patients with COVID-19 [119–123]. Patients with COVID-19 have lower diversity and richness of gut microbiota than healthy people. The gut microbiota of patients with COVID-19 shows an increased relative abundance of opportunistic pathogens, such as *Streptococcus*, *Rothia*, *Veillonella*, *Erysipelatoclostridium*, and *Actinomyces*, harmful bacteria, such as *Clostridium hathewayi* and *Actinomyces viscosus*, and pathogens associated with Crohn's disease (*Ruminococcus gnocavus* and *Ruminococcus torques*), compared with that in healthy controls. The relative abundance of beneficial bacteria, such as *F.*

**Table 2**
Mechanism of respiratory vaccine efficacy improvement via gut microbiota regulation through dietary probiotic intake.

| Probiotics | Dose | Vaccine | Study design and mechanisms to improve respiratory vaccine efficacy | References |
|---|---|---|---|---|
| **Study individual age: Infant (Human)** | | | | |
| · *B. bifidum* DSMZ20082, *B. infantis* ATCC15697, *B. longum* ATCC157078, *L. acidophilus* ATCC4356 | · $3 \times 10^9$ CFU per strain | · Measles, mumps, rubella, and varicella (MMRV) attenuated live vaccine | · MMRV vaccination after taking probiotics for 2 months<br>· Continue taking probiotics for up to 3 months after vaccination<br>· In the group taking probiotics, IgG antibody levels increased, but not significantly | [100] |
| · *L. paracasei* F19 | · $10^8$–$10^{10}$ CFU | · Diphtheria, tetanus, pertussis (DTaP)- polio (IPV)- *Haemophilus influenzae* type B (Hib)-conjugate vaccine | · Daily probiotic intake from 4th month to 13th month<br>· 1st dose at 3rd month, 2nd dose at 5th month, 3rd dose at 12th month<br>· Significantly increased IgG antibody levels against diphtheria in the group taking probiotics | [101] |
| **Study individual age: Adult (Human)** | | | | |
| · *B. animalis* ssp. *lactis* BB-12, *L. paracasei ssp. paracasei 431* | · $1 \times 10^9$ CFU | · Inactivated trivalent influenza vaccine | · Increased antigen-specific IgG and IgA levels<br>· Increased seroconversion rates for IgG | [172] |
| · *L. GG* ATCC53101 | ·$1 \times 10^{10}$ CFU | · Trivalent influenza attenuated live vaccine | · Taking probiotics twice a day for 28 days after vaccination<br>· Increased levels of antibodies against H3N2 antigen in the *Lactobacillus* GG group | [21] |
| · *L. fermentum* CECT5716 | · $1 \times 10^{10}$ CFU | · Inactivated influenza vaccine | · Daily probiotic intake for 2 weeks each before and after vaccination<br>· Increased antigen-specific IgA and total IgM concentrations in the probiotic group | [102] |
| **Study individual age: Older adults (Human)** | | | | |
| · *L. paracasei* DN-114 001, *L. bulgaricus, Streptococcus thermophilus* | · $2 \times 10^{10}$ CFU | · Trivalent inactivated influenza vaccine | · Daily probiotic intake from 4 weeks before vaccination to 9 weeks after vaccination<br>· Increased B antigen-specific antibody IgG titer in the group taking probiotics | [103] |
| · *L. plantarum* CECT7315/7316 | · $5 \times 10^8$–$10^9$ CFU | · Trivalent influenza vaccine | · Daily probiotic intake for 3–4 months after vaccination<br>· In the group taking probiotics, antigen-specific IgG and IgA antibody levels increased significantly, and IgM antibody levels increased, although not significantly | [104] |
| · *L. plantarum* PBS067, *B. animalis* subsp. *lactis* BL050, *B. longum* subsp. *infantis* BI221, *B. longum* subsp. *longum* BLG240 | · $1 \times 10^9$ CFU per strain | · Influenza vaccine | · Taking probiotics for 28 days after vaccination<br>· Probiotic intake improves the immune system and reduces the incidence of influenza symptoms by regulating the gut microbiota composition | [105] |

*prausnitzii*, *Eubacterium rectale*, and bifidobacteria with immunomodulatory potential was less. *F. prausnitzii* induces priming of human colon regulatory T cells, which secrete the anti-inflammatory cytokine, IL-10, and is a major producer of SCFAs.

The dysbiosis of gut microbiota, such as an increase in the relative abundance of pathogenic bacteria and a decrease in the relative abundance of beneficial bacteria, contributes to an abnormal immune response and severity of COVID-19 (Fig. 2) [121,122]. There is a positive correlation between the severity of COVID-19 and the genera *Coprobacillus*, *Clostridium ramosum*, and *C. hathewayi*. Both *C. ramosum* and *C. hathewayi* are associated with human infections and bacteremia, and the genus *Coprobacillus* strongly upregulates the expression of ACE2 in the gut. In contrast, *Lachnospiraceae bacterium* 5_1_63FAA, *Alistipes onderdonkii*, and *F. prausnitzii* show a negative correlation with COVID-19 severity. The genus *Alistipes* is involved in the maintenance of intestinal immune homeostasis, and *F. prausnitzii* has anti-inflammatory properties [122]. *F. prausnitzii* and *B. bifidum* show a negative correlation with severity after adjusting for confounding factors, including age and use of antibiotics. *F. prausnitzii* is a butyrate-producing bacterium. Butyrate improves the regeneration and integrity of the epithelial barrier and promotes the secretion of mucin and the antimicrobial peptide, defensin, thereby reducing the rate of respiratory viral infections [124–126]. In addition, butyrate exerts anti-inflammatory effects through several mechanisms [127].

The correlation between the gut microbiota and the severity of COVID-19 was confirmed indirectly (Fig. 2) [123]. When comparing the gut microbiota composition between feces with high SARS-CoV-2 infectivity and that with low or no SARS-CoV-2 infectivity, the opportunistic pathogens *Collinsella aerofaciens* and *Morganella morganii* were more abundant in the fecal samples with high SARS-CoV-2 infectivity. *C. aerofaciens* is an inflammatory bacterium [128], and *M. morganii* is an opportunistic pathogen capable of causing serious infections in immunocompromised hosts, such as neonates [129]. SCFA-producing microorganisms were more abundant in fecal samples with low or no SARS-CoV-2 infectivity, such as *Parabacteroides merdae*, *Bacteroides stercoris*, *A. onderdonkii*, and *Lachnospiraceae bacterium* 1_1_57FAA. *B. stercoris* downregulates the expression of ACE2 in the gut, suggesting that this could interfere with the entry of SARS-CoV-2 into intestinal cells [123].

Among SARS-CoV-2 cases, the older adults have high rates of infection, hospitalization, and mortality [130,131]. Patients with severe COVID-19 are significantly older and have a higher frequency of abdominal pain than patients with non-severe COVID-19

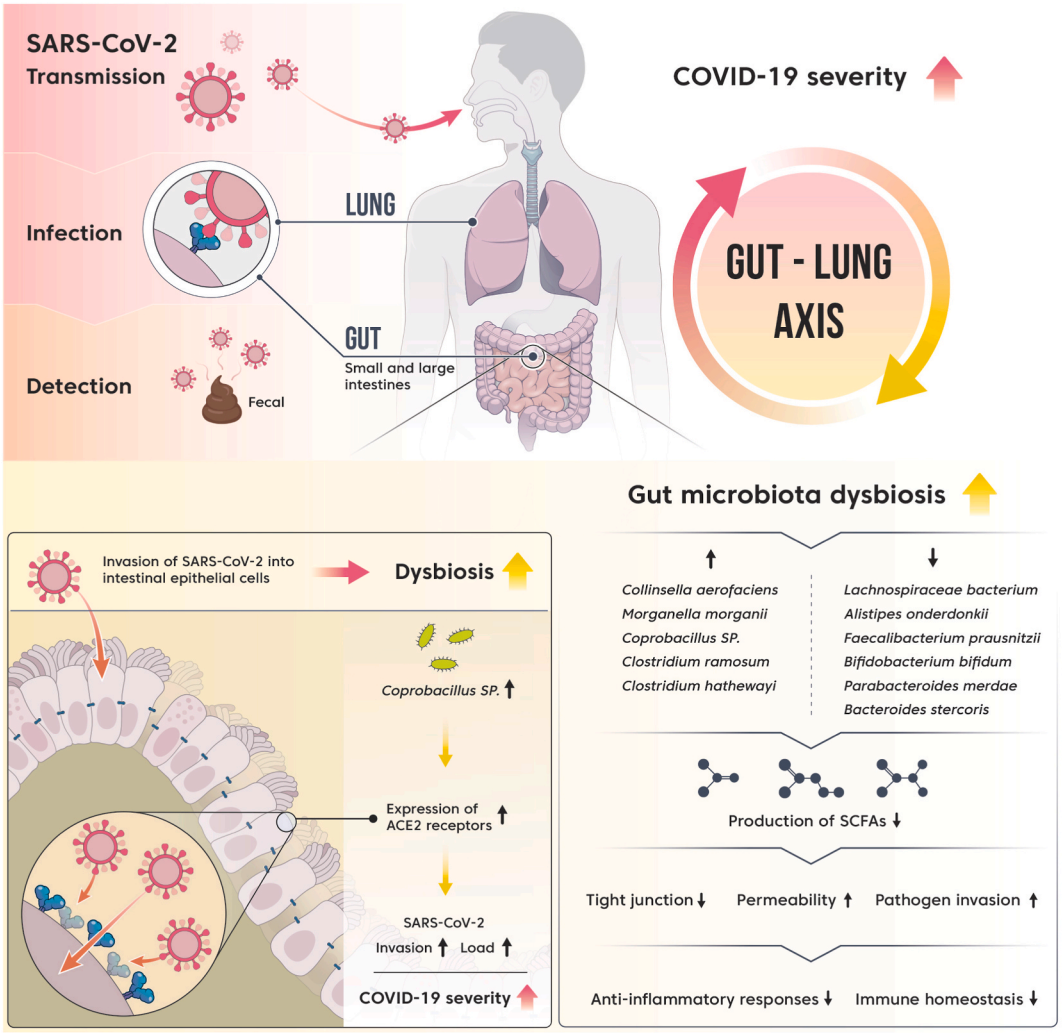


**Fig. 2.** Interaction between gut microbiota dysbiosis and COVID-19 severity.

[132–134]. The dysbiosis of the gut microbiota in the older adults [135] could have contributed to the severity of COVID-19 in them; however, additional studies are warranted.

### 5.2. *Potential of gut microbiota in improving the efficacy of COVID-19 vaccines*

Patients with IBD exhibit a lower immune response following COVID-19 vaccination than healthy controls [136,137]. The composition of the gut microbiota correlates with the immunogenicity of COVID-19 vaccines [138]. The higher the relative abundance of *B. adolescentis*, the higher the antibody response to COVID-19 vaccines, whereas the higher the relative abundance of *Bacteroides vulgatus*, *Bacteroides thetaiotaomicron*, and *Ruminococcus gnavus*, the lower the antibody response.

The level of anti-SARS-CoV-2 S1 RBD IgG antibody elicited in response to COVID-19 vaccination varies significantly with age; the antibody response is lower in the older adults [139,140]. The immune responses to mRNA vaccines in groups younger than 60 and older than 80 years were compared; significantly lower antibody titers were observed in the older group. Even in the real world, the effectiveness of COVID-19 vaccines is lower in older people [141]. Among 2,828,294 participants, the effectiveness of COVID-19 vaccines in preventing death after hospitalization due to COVID-19 was 91.0% (89.0–92.6) in those aged 60–69 years, 85.0% (83.1–86.7) in those aged 70–79, and 68.4% (65.7–70.9) in those over 80 years of age.

In the older adults, the decrease in the adaptive immune system function due to aging reduces the immune response elicited by COVID-19 vaccines. Therefore, the efficacy of COVID-19 vaccines has age-dependent limitations [140,142–147]. COVID-19 severity is associated with lymphopenia and low diversity of the T cell receptor (TCR) for the SARS-CoV-2 epitope. Immunosenescence occurs in the older adults, accompanied by a decrease in the naive TCR repertoire and a decrease in the number of naive T cells. This could contribute to the severity of SARS-CoV-2 infection in the older adults despite vaccination. In addition, the neutralizing antibody titer

after the second dose of COVID-19 vaccines is lower in the older adults than in the adult group. Immunosenescence through reduced B-cell response is another potential cause for the high SARS-CoV-2 infection rates and severe COVID-19. Gut microbiota dysbiosis could be involved in the decrease in COVID-19 vaccine efficacy in the older adults; however, further studies are required. Gut microbiota regulators are used as adjuvants in vaccines for other respiratory infections; this could also be considered for COVID-19 vaccines.

## 6. Dietary interventions to improve COVID-19 vaccine efficacy in the older adults

The efficacy of various respiratory vaccines is improved through the modulation of gut microbiota. Therefore, the modulation of gut microbiota through dietary intervention could alleviate the severity and reduce mortality in older adults patients with COVID-19 after vaccination (Fig. 3). Table 3 presents dietary interventions that can improve COVID-19 vaccine efficacy in the older adults by altering the gut microbiota.

### 6.1. Traditional probiotics

Ingestion of the genus *Bifidobacterium* as probiotics will increase the number of *Bifidobacterium* cells in the gut, thereby improving adaptive immunity [59,148] in the older adults. Ingestion of a mixture of *B. longum* Bar33 and *Lactobacillus helveticus* Bar13 does not significantly alter the number of total Th cells ($CD4^+$) or Tc cells ($CD8^+$) in the older adults; however, it significantly increases the number of B cells and naive T cells. In addition, it increases the number of $CD8^+$ activated memory T cells, contributing to the improvement of adaptive immunity. Ingestion of *B. longum* BB536 increased the abundance of bifidobacteria in the gut microbiota and serum IgA levels in the older adults, demonstrating its potential for regulating the adaptive immune function by improving the gut microbiota.

In addition to *Bifidobacterium*, it has been reported that the ingestion of *Lactobacillus*, which is widely used as probiotics, increases the number of *Bifidobacterium* cells [149] and improves adaptive immunity [150,151]. Influenza antigen-specific antibody levels were significantly increased when heat-treated *L. paracasei* MCC1849 was consumed by the older adults aged 85 years or older. In addition, the ingestion of *Lactobacillus delbrueckii* subsp. *bulgaricus* 8481 conjugated with *Streptococcus thermophillus* NBIMCC No.8357 in the older adults aged 65 years or older increases the number of immature T cells, potential responders to novel antigens, and slows the aging of T-cell subpopulations.

### 6.2. Next-generation probiotics

Traditional probiotics, such as *Bifidobacterium* and *Lactobacillus*, do not target specific diseases. However, next-generation probiotics target specific diseases based on next generation sequencing and bioinformatics. *F. prausnitzii*, *Akkermansia muciniphila*, *Bacteroides fragilis*, and some *Clostridium* are included in next-generation probiotics [152]. The abundance of *F. prausnitzii*, a butyrate-producing bacterium, is greatly reduced in the gut of the older adults [153]. Therefore, dietary intake of *F. prausnitzii* as a next-generation probiotic could improve adaptive immunity in the older adults. However, as there are few clinical studies on the use of next-generation probiotics as probiotic formulation, further studies focusing on safety aspects are necessary.

### 6.3. Prebiotics

The intake of prebiotics that selectively promote the growth of beneficial bacteria among the gut microbiota is another dietary strategy for improving the health of the host; most dietary fibers are classified as prebiotics [154]. Galactooligosaccharides (GOS) and fructooligosaccharides (FOS) are included in prebiotics. The ingestion of prebiotics significantly increases the abundance of beneficial bacteria, particularly bifidobacteria, in the older adults, and improves the immune response of virus vaccines by modulating the gut microbiota [155–157]. Ingestion of GOS significantly increases the abundance of bifidobacteria in the gut microbiota and maintains the antibody titer against the viral A/H1N1 antigen for a long time through enhancing the gut microbiota.

### 6.4. Synbiotics

The ingestion of synbiotics, a mixture of probiotics and prebiotics, increases the abundance of beneficial bacteria in the gut microbiota and levels of metabolites in the older adults [158–160]. The ingestion of synbiotics (*B. bifidum* BB-02 + *B. lactis* BL-01 + FOS) significantly increases the abundance of bifidobacteria and lactobacilli in the gut microbiota. In addition, the ingestion of synbiotics (*B. longum* + inulin + oligofructose) significantly increases the abundance of bifidobacteria in the gut microbiota and butyrate production in the gut. However, to our knowledge, there are no reports on synbiotics increasing the adaptive immune response in the older adults for improving vaccine efficacy.

### 6.5. SCFAs

Table 4 lists dietary interventions that can improve COVID-19 vaccine efficacy by altering the gut microbiota in preclinical individuals. Adaptive immunity can be increased through SCFAs, which are the major metabolites of gut microbiota [161–163]. SCFAs are free fatty acids containing six carbons or less; the main SCFAs found in the intestine include acetate, propionate, and butyrate

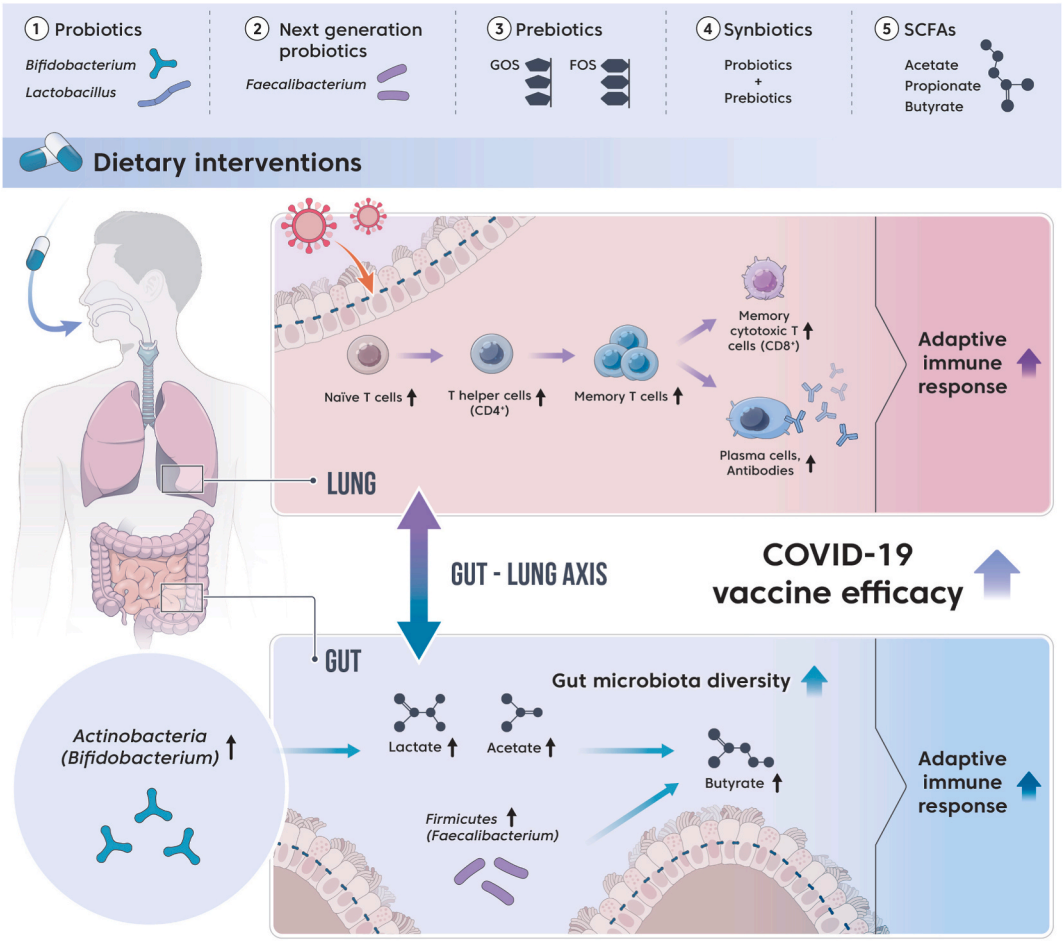


**Fig. 3.** Dietary interventions to improve COVID-19 vaccine efficacy by modulating the gut microbiota in the older adults.

[164]. The ingestion of mixed SCFAs (acetate + butyrate + propionate) increases the antibody response to the influenza antigen in mice. The concentration of the three most abundant SCFAs (acetate + butyrate + propionate) was reduced in GF mice; this decreases the number of regulatory T cells. When GF mice ingest mixed SCFAs for 3 weeks, the number and function of intestinal regulatory T cells and the number of $CD4^+$ T cells increase, contributing to the improvement of adaptive immunity. SCFAs increase the number of IgA antibody-producing B cells and CXCR5+ follicular T helper cells in the gut while simultaneously modulating antibody production by regulating the expression of key genes related to plasma cell differentiation. SCFA production in the gut of the older adults decreases owing to alterations in the composition of the gut microbiota [165], and the level of SCFAs is inversely related to age; the abundance of the genus *Bifidobacterium* decreases with age [166,167]. Therefore, the decrease in the adaptive immune response due to the reduction in SCFA production in the older adults could influence the decrease in vaccine efficacy; however, additional clinical studies are needed.

Modulating the gut microbiota dysbiosis through dietary interventions should be considered for improving the efficacy of COVID-19 vaccines in the older adults. In addition, future studies should focus on identifying the most appropriate dietary interventions.

## 7. Conclusions and perspectives

COVID-19 started in Wuhan, China, in December 2019 and has spread worldwide, causing destruction in terms of the economy and the health and well-being of the population [168,169]. COVID-19 vaccination is one of the best methods to slow the spread of SARS-CoV-2 [170]. However, it is important to improve the efficacy of COVID-19 vaccines, as the efficacy is less in the older adults [171].

Dysbiosis of the gut microbiota occurs in the older adults [135], and this is positively correlated with the severity of COVID-19 in them [121–123]. A decrease in the efficacy of respiratory vaccines in the older adults is restored by modulating the gut microbiota [103–105]. This is achieved through simple dietary interventions, such as the ingestion of probiotics, next-generation probiotics, prebiotics, and synbiotics [59,148–153,155–157,159,160].

Therefore, we propose the development of an efficient strategy for improving the reduced efficacy of COVID-19 vaccines in the older adults by modulating the gut microbiota through simple dietary interventions. However, more experimental studies are needed

**Table 3**
Dietary interventions to improve COVID-19 vaccine efficacy in the older adults by modulating the gut microbiota.

| Dietary interventions | Study individual | Intervention period | Mechanism of improving the efficacy of COVID-19 vaccines | References |
|---|---|---|---|---|
| **Probiotics and next generation probiotics** | | | | |
| · 1:1 mixture of *B. longum* Bar33 + *L. helveticus* Bar13 1 × $10^9$ CFU | · Older adults over 75 years old (84.6 ± 7.8 years old) | · 30 days | · Significant increase in the numbers of B cells and naive T cells<br>· Significant increase in the number of $CD8^+$-activated memory T cells | [148] |
| · *B. longum* BB536 5 × $10^{10}$ CFU twice/day | · Older adults over 75 years old (81.7 ± 8.7 years old) | · 12 weeks | · Increased abundance of bifidobacteria in gut microbiota composition<br>· Increased titer of specific antibodies against influenza A/H1N1 antigen | [59] |
| · *L. plantarum* P-8 6 × $10^{10}$ CFU | · Adults and older adults | · 4 weeks | · Increased abundance of bifidobacteria in gut microbiota composition | [149,150] |
| · *L. paracasei* MCC1849 1 × $10^{10}$ CFU/day | · Older adults over 65 years old | · 12 weeks | · Increased titers of specific antibodies against influenza A/H1N1 and B antigens | |
| · *L. delbrueckii* subsp. *bulgaricus* 8481 + *Streptococcus thermophilus* NBIMCC No.8357 3 × $10^7$ CFU three times/day | · Older adults over 65 years old | · 6 months | · Increased number of immature T cells that are potential responders to new antigens<br>· Slowed down aging of T cell subpopulation | [151] |
| · *Faecalibacterium prausnitzii* | | | · Increased production of the metabolite butyrate | [152,153] |
| **Prebiotics and synbiotics** | | | | |
| · Prebiotics [Galactooligosaccharides (GOS) 5.5 g/day] | · Older adults (69.3 ± 4.0 years old) | · 4 weeks | · Significant increase in the abundance of beneficial bacteria, especially bifidobacteria, in the gut microbiota | [155–157] |
| · Prebiotics [GOS (0.4 g/100 kcal) + bifidogenic growth stimulator (1.65 μg/100 kcal) + fermented milk] | · Older adults (79.9 ± 9.5 years old) | · 14 weeks | · Long-term maintenance of antibody titer against viral A/H1N1 antigen through improvement of gut microbiota dysbiosis | |
| · Synbiotics (3.5 × $10^{10}$ CFU *B. bifidum* BB-02 + 3.5 × $10^{10}$ CFU *B. lactis* BL-01 + fructooligosaccharide) | · Older adults: control group 71 years old (63–85 years old), treatment group 73 years old (68–90 years old) | · 8 weeks | · Significant increase in the abundance of bifidobacteria and lactobacilli in the gut microbiota composition | [159] |
| · Synbiotics [2 × $10^{11}$ CFU *B. longum* + 6 g of prebiotic (inulin + oligofructose)] | · Older adults (71.9 ± 5.4 years old) | · 4 weeks | · Significant increase in the abundance of bifidobacteria in the gut microbiota<br>· Abundance of Actinobacteria and Firmicutes increased but that of Proteobacteria decreased<br>· Increase in butyrate production | [160] |

**Table 4**
Dietary interventions to improve COVID-19 vaccine efficacy by modulating gut microbiota in preclinical subjects.

| Dietary interventions | Study subject | Intervention period | Mechanism of improving the efficacy of COVID-19 vaccines | References |
|---|---|---|---|---|
| Metabolites (SCFAs) | | | | |
| · Mixed SCFAs: acetate (70 mM) + propionate (30 mM) + butyrate (20 mM) | · Mice | · 14 days | · Increased antibody production against influenza antigens | [161] |
| · Mixed SCFAs: acetate + propionate + butyrate (150 mM) | · Mice | · 3 weeks | · Improving adaptive immunity by increasing the number of $CD4^+$ T cells in the gut | [162] |
| · Mixed SCFAs: acetate (70 mM) + propionate (30 mM) + butyrate (20 mM) | · Mice | · 4 weeks | · Increased numbers of IgA antibody-producing B cells and $CXCR5^+$ follicular T helper cells in the gut<br>· Regulating antibody production by regulating the expression of key genes involved in plasma cell differentiation | [163] |

to prove the causal relationship between improved vaccine efficacy in the older adults and the modulation of gut microbiota through simple dietary interventions.

## Author contribution statement

All authors listed have significantly contributed to the development and the writing of this article.

## Data availability statement

No data was used for the research described in the article.

## Additional information

No additional information is available for this paper.

## Declaration of interest's statement

The authors declare no conflict of interest.

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