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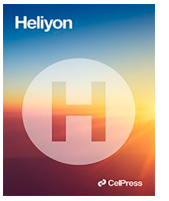

Review article

Influenza and the gut microbiota: A hidden therapeutic link

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ABSTRACT

Background: The extensive community of gut microbiota significantly influences various biological functions throughout the body, making its characterization a focal point in biomedicine research. Over the past few decades, studies have revealed a potential link between specific gut bacteria, their associated metabolic pathways, and influenza. Bacterial metabolites can communicate directly or indirectly with organs beyond the gut via the intestinal barrier, thereby impacting the physiological functions of the host. As the microbiota increasingly emerges as a 'gut signature' in influenza, gaining a deeper understanding of its role may offer new insights into its pathophysiological relevance and open avenues for novel therapeutic targets. In this Review, we explore the differences in gut microbiota between healthy individuals and those with influenza, the relationship between gut microbiota metabolites and influenza, and potential strategies for preventing and treating influenza through the regulation of gut microbiota and its metabolites, including fecal microbiota transplantation and microecological preparations.

Methods: We utilized PubMed and Web of Science as our search databases, employing keywords such as "influenza," "gut microbiota," "traditional Chinese medicine," "metabolites," "prebiotics," "probiotics," and "machine learning" to retrieve studies examining the potential therapeutic connections between the modulation of gut microbiota and its metabolites in the treatment of influenza. The search encompassed literature from the inception of the databases up to December 2023.

Results: Fecal microbiota transplantation (FMT), microbial preparations (probiotics and prebiotics), and traditional Chinese medicine have unique advantages in regulating intestinal microbiota and its metabolites to improve influenza outcomes. The primary mechanism involves increasing beneficial intestinal bacteria such as *Bacteroidetes* and *Bifidobacterium* while reducing harmful bacteria such as *Proteobacteria*. These interventions act directly or indirectly on metabolites such as short-chain fatty acids (SCFAs), amino acids (AAs), bile acids, and monoamines to alleviate lung inflammation, reduce viral load, and exert anti-influenza virus effects.

Conclusion: The gut microbiota and its metabolites have direct or indirect therapeutic effects on influenza, presenting broad research potential for providing new directions in influenza research

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and offering references for clinical prevention and treatment. Future research should focus on identifying key strains, specific metabolites, and immune regulation mechanisms within the gut microbiota to accurately target microbiota interventions and prevent respiratory viral infections such as influenza.

1. Introduction

Influenza viruses are single-stranded, negative-sense RNA viruses from the Orthomyxoviridae family [1]. They are typically round or filamentous and are classified into A [2], B [3], C [4], and D [5] according to their different nuclear proteins, but only A, B, and C are known to infect humans, with influenza A and B viruses are the most common [6]. Influenza is one of the common respiratory infectious diseases that causes seasonal epidemics and unpredictable pandemics around the world every year, mainly during winter and spring [7,8]. According to the World Health Organization, there are approximately 4 million influenza cases and about 500,000 deaths annually [9]. Current prevention and treatment methods include effective vaccines and specific antiviral drugs [1]. However, these are only effective in the early stages of infection, have side effects, and face some challenges like drug resistance and viral mutations, making the search for new prevention and treatment strategies crucial.

There are approximately 100 trillion symbiotic microorganisms in the human body, which are ten times larger than human cells and mainly located in the gastrointestinal tract, known as the gut microbiota [10]. They play an important role in maintaining human health, such as promoting mucosal development, helping the body to metabolize nutrients, providing resistance to intestinal infections, and maintaining intestinal barrier function [11,12]. In addition, beyond local effects, the gut microbiota also has systemic impacts outside the gastrointestinal tract, producing short-chain fatty acids (SCFAs) and other metabolites that play significant anti-inflammatory roles and influence neurotransmitter synthesis and transport [13–15]. Recent studies have highlighted the gut microbiota's impact on distant organs like brain, lungs, and liver, leading to concepts such as the gut-brain [16], gut-lung [17], and gut-liver axis [18], with the gut-lung axis receiving particular attention. The gut microbiota is involved in a variety of acute/chronic respiratory diseases, including chronic obstructive pulmonary disease, acute lung injury, and lung cancer [19–21]. While diet primarily influences the gastrointestinal microbiota, respiratory viral infections, broad-spectrum antibiotic use, and chronic inflammation can also cause changes. Research indicates that these changes result from gut inflammation due to the lung's inflammatory response rather than direct viral action [22]. Broad-spectrum antibiotics, used before influenza season, can alter the gut microbiome, increasing inflammation and dendritic cell activation, disrupting metabolism, and weakening the immune response to influenza vaccination. This underscores the critical role of gut microbes in regulating immunity [23]. Furthermore, germ-free mice lacking gut microbiota showed significantly reduced antimicrobial peptide expression, reduced effector B cells, and inadequate T cell function, making them susceptible to influenza virus infection [24,25]. Therefore, the gut microbiota has a potential link with influenza virus infection and may be a therapeutic target. In the case of viral respiratory infections caused by influenza viruses, treatment with antibiotics can also have an impact on the gut microbiota, thereby weakening the host's innate and adaptive defenses [26–29]. The composition and homeostasis of the gut microbiota are crucial for maintaining the health of the host. Based on the above evidence, regulating the gut microbiota to prevent and treat the influenza virus is a promising research direction.

2. Methods

We utilized PubMed and Web of Science as our search databases, employing keywords such as "influenza," "gut microbiota," "traditional Chinese medicine," "metabolites," "prebiotics," "probiotics," and "machine learning" to retrieve studies examining the potential therapeutic connections between the modulation of gut microbiota and its metabolites in the treatment of influenza. The search encompassed literature from the inception of the databases up to December 2023.

3. Potential association of gut microbiota and its metabolites with influenza

3.1. Differences in intestinal flora between healthy people and influenza people

The human gut hosts approximately 40 trillion microorganisms, including around 1000 different types of bacteria, with populations reaching magnitudes of 10^{13}~10^{14}. Among these, about 30–40 types are commonly found [30]. The total mass of gut microbiota is roughly 1 kg, comparable to the weight of the human brain, earning it the nicknames "second gene pool" or "second brain," due to its significant influence on host health [31,32]. In healthy individuals, gut microbiota colonizes the intestines in a balanced and stable manner, working alongside the intestinal mucosal barrier and bacteriostatic substances to maintain intestinal microecology. The gut environment predominantly supports six bacterial groups: *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, *Proteobacteria*, *Verrucomicrob*, and *Fusobacteria* [33], *Firmicutes*, *Bacteroidetes*, *Actinobacteria*, and *Proteobacteria* constitute 99% of the intestinal bacteria in the four phylum [32]; At the genus level, *Bifidobacterium*, *Bacteroides*, *Blautia* and *Faecalibacterium* are the most abundant [34,35]. Over time, the gut microbiota has evolved through the host's self-adaptation and natural selection, maintaining a dynamic balance among the flora of different species, the flora and the host, and the flora and the host and the environment. This balance forms an interdependent system crucial for systemic metabolic homeostasis and overall host health.

Existing studies have demonstrated that in sepsis patients, the gut microbiota often becomes the source of bacteria in the lungs post-

sepsis. This suggests that microorganisms colonizing the respiratory and digestive tracts form the basis for the lung-gut axis's bidirectional interaction, directly influencing tissue function and disease progression or recovery [36]. In an experiment on the relationship between influenza virus and gut microbiota, results indicated that compared with the normal control group, the mice infected with influenza virus showed an increased abundance of *Proteobacteria* and *Elusimicrobia* increased at the phylum level and a decreased abundance of *Bacteroidetes* decreased. At the genera level, though the intestinal microbiota of different genera showed different responses to influenza virus infection, they conjectured that *Lachnospiraceae*_NK4A136_group, *Parasutterella*, *Lactobacillus*, and *Bifidobacterium* may have the most prominent has the most. Furthermore, this test has also proved the anti-influenza effect of *Bifidobacterium* animalis. Hosts could enhance their resistance to influenza by increasing Bifidobacterium animalis in their intestines, suggesting its potential use in influenza prevention and as a prognostic indicator [37]. Additional studies confirmed that influenza viruses further increase the abundance of *Proteobacteria* and *Salmonella* by inducing the expression of type I interferon in the lungs [38]. In the mice model of respiratory syncytial virus and influenza virus infection, it was found that the abundance of *Bacteroidetes* increased and *Firmicutes* decreased in the intestinal tract compared with the normal group [39]. A significant increase in *Escherichia coil* was also found in avian influenza infected chicken models, while *Lactobacillus*, *Enterococcus*, and other probiotic organisms were significantly reduced [40]. Under normal circumstances, we found that *Bacteroidetes* in the intestine induced the production of IFN-β by the dendritic cells of the colon through the TLR4-TRIF signaling pathway to regulate the IFN-I response and enhance the anti-influenza virus effect [41]. Lipocalin 2 $(LCN2)^{-/-}$ mice exhibited inhibited dendritic cell function, leading to overactive CD8+T cells during influenza infection, higher mortality, and a more pronounced immune response. This demonstrates that LCN2 modulates dendritic cell activity and antiviral immune responses in a microbiome-dependent manner [42]. The effects of influenza A (H1N1) virus on the respiratory tract and gastrointestinal tract microbial structure and function of German Landrace Pigs were analyzed by a multi-omics method, and the richness and diversity of the respiratory tract and gastrointestinal tract microorganisms in German Landrace Pigs were significantly changed. Compared with the normal group, the abundance of *Prevotellaceae* increased, and the abundance of *Clostridiaceae* and *Lachnospiraceae* decreased [43].

These findings indicate that influenza virus has a significant impact on the gut microbiota. The changes in gut microbiota structure and quantity caused by different virus types or even different strains of the same virus are not the same. However, the overall manifestation is that compared with uninfected individuals, the number and abundance of probiotics in the gut microbiota of influenza infected individuals decrease, while the number and abundance of bacteria increase.

3.2. *The association of metabolites of gut microbiota with influenza*

The gut microbiota can metabolize nutrients into beneficial products, such as SCFAs, amino acids (AAs), tryptophan (TRP), bile acids, monoamines, and cannabinoids. These metabolites act as communication mediums between the microbiota and the host, playing a crucial role in maintaining host physiology. They can directly or indirectly interact with organs outside the gut, including the lungs, influencing the host's physiological functions. Notably, there are significant links between gut microbiota metabolites and influenza (Fig. 1).

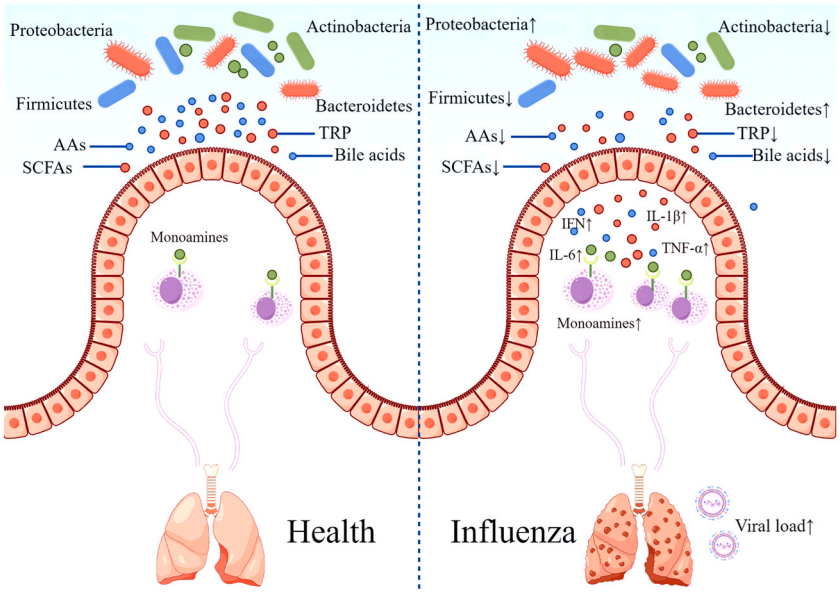

Fig. 1. Effects of gut microbiota and its metabolites on influenza in normal and influenza patients.

3.2.1. SCFAs and influenza

SCFAs, one of the important metabolites of intestinal microorganisms, are mainly composed of acetate, propionate, and butyrate. It plays a key role in regulating host metabolism, immune system, and preventing excessive inflammation [44,45]. Influenza virus infection reduces SCFAs production and impairs intestinal barrier function, increasing susceptibility to secondary intestinal bacterial infections. Supplementing SCFAs during influenza can mitigate the translocation of enteric pathogens like Salmonella Typhimurium and improve survival rates from co-infections [46]. Additionally, the concentrations of SCFAs in the cecum and colon contents of influenza virus-infected mice were reduced in a time-dependent manner, suggesting that intestinal SCFAs could be used as an important marker for predicting influenza [47]. It is well known that dietary fiber is digested in the intestines, but it is worth noting that dietary fiber is not digested by host digestive enzymes at the front end of the intestine. These fermentation products influence the host's immune response, extending beyond the gut to enhance lung immune capacity and reduce inflammation in both the gut and lungs [44]. It has been found that *Bifidobacterium pseudopodium* NjM1, isolated from the intestinal flora of NLRP3$^{-/-}$ mice, can protect normal mice from IAV infection. The mechanism is that NjM1 can metabolize acetate and then act on GPR43 receptor, and NLRP3 Bridges GPR43 and MAVS. Through NLRP3 signaling pathway, MAVS oligomerization and signal transduction are promoted, and IFN-I synthesis is enhanced, thus achieving an anti-IAV infection effect [48]. The experiment demonstrated that the acetate-GPR43-NLRP3-MAVS-IFN-I signaling axis could be used as a potential target against respiratory influenza infection. Influenza mice fed a high-fiber diet (HFD) considerably increased in the proportion of *Bacteroidaceae* together with a reduction in the numbers of operational taxonomic units (OTUs) belonging to the *Firmicutes* phylum, and also stimulated the growth of the *Bifidobacterium* and *Bacteroides*. Simultaneously, this diet shaped Ly6c-patrolling monocytes leading to an increase in numbers of alternatively activated macrophages, a decrease in CXCL1 levels and airway neutrophils levels, and activation and alteration of CD8+T cells, enhancing adaptive immunity, thus achieving an antiviral effect [49]. Through gut microbiota and proteomic analysis, Flammulina velutipes polysaccharide can lead to an increase in SCFAs, as well as an increase in the relative abundance of SCFAs-producing *Bacteroides* and *Alloprevotella*, while the abundance of *Lachnospiraceae*_NK4A136_group and f_*Lachnospiraceae*_Unclassified decreased. This indicates that Flammulina velutipes polysaccharide regulates intestinal microbiota structure and improves flora balance, thereby regulating the immune-related proteins Transferrin receptor protein 1 (TFRC) and Radical S-adenylyl methionine domain-containing protein 2 (RSAD2), achieving the purpose of anti-influenza virus [50]. This proves that dietary fiber and SCFAs can prevent influenza by reducing tissue injury and enhancing adaptive immunity.

SCFAs can resist influenza virus by adjusting the intestinal flora structure of the host infected by influenza virus, such as increasing the number of beneficial bacteria such as *Bifidobacterium* and *Bacteroides*, and enhancing immune adaptability.

3.2.2. Amino acids and influenza

Branched-chain amino acids (BCAAs) are essential nutrients that link the gut and lungs. They are essential AAs that cannot be synthesized by themselves and can only be obtained from food, including leucine, isoleucine, and valine [51]. After the body eats a diet rich in protein (such as milk, meat, dairy products, etc.), the circulating BCAAs level can be increased by 2–3 times and can be reduced to the baseline level within 3 h [52]. BCAAs degradation is mainly carried out in the liver, heart, and skeletal muscle, and the stability of BCAAs level in vivo is finely regulated by many factors. Leucine, isoleucine, and valine are each reversibly generated into their corresponding branched chains via BCAAs aminotransferase (BCAT) catalysis α Ketoacid (BCKA) [53]. BCAAs are considered to be "potential biomarkers" of body health and play an important role in protein synthesis, secretion, and release of hormones such as insulin and growth hormone [54]. Studies have shown that intestinal microbiota disorder induced high levels of BCAAs in influenza mice after gentamicin treatment, thereby inhibiting the development of CD11b + Ly6G + cells and increasing the level of CD8+T cells, resulting in an increased degree of influenza virus infection [55]. Conversely, CD11b + Ly6G + cell transplantation has a protective effect on influenza virus infection, suggesting that high levels of BCAAs disrupt the body's immune balance, thereby increasing the body's susceptibility to influenza viruses. In addition, the AAs aspartate 605 and valine 606 are involved in the transcription and replication of influenza viruses by interacting with nucleoproteins (NP), and this interaction is disrupted when they are replaced [56]. In a mouse study of the H7N9 influenza virus, survival was increased and weight loss was enhanced by oral administration of valine or intraperitoneal injection of coenzyme A. Oral administration of isoleucine had little or no significant effect. However, in in vitro experiments, valine had no anti-influenza virus effect, which demonstrated that its anti-influenza effect may be indirect. Further experiments demonstrated that oral administration of valine or intraperitoneal injection of coenzyme A reduced the titer of H7N9 influenza virus and decreased the expression of inflammatory factors like IL-1β, IL-6, and IL-10, suggesting that the anti-influenza effect of valine may be attributed to its immunomodulatory properties after influenza infection, and that, on the other hand, the anti-influenza effect of coenzyme A may be due to its stimulation of the innate immune response in advance [37]. Another study found that intestinal microbiome-associated metabolite desaminotyrosine (DAT) protects against influenza by enhancing type I IFN signaling and reducing lung immunopathology, and confirmed in further experiments that intestinal *Clostridium orbiscindens* produced DAT to protect mice infected with influenza [51].

TRP is an amino acid necessary for the protein synthesis process in humans and animals and must be obtained from the diet. Its deficiency can impair gut immunity and alter the gut microbiome [57]. TRP can be directly absorbed by bacteria in the gut, mainly including three metabolic pathways: (1) Kynuridine pathway, about 95 % of human tryptophan is metabolized by indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase to produce kynuridine [58]; (2) In the 5-HT pathway, 1 %–2 % of tryptophan in the body produces 5-HTP under the action of TPH1 and TPH2, and 5-HTP finally decarboxylates to produce 5-HT [59]; (3) Microbial pathway: Under the coordinated action of intestinal symbiotic microorganisms, tryptophan can be directly transformed by bacterial enzymes into indole derivatives, such as indole-acetic acid, indole-3-aldehyde and skatine [60]. By examining the metabolites present in human plasma, TRP metabolism was identified as an important metabolic pathway in response to influenza. In a mouse model of

influenza infection, kynurenine was found to decrease in the elderly lung in an IDO1-dependent manner, due to age-related mitochondrial dysfunction leading to IDO1 expression and kynurenine pathway-mediated changes in TRP metabolism. The use of mitoquinol, a mitochondria-targeting antioxidant, improved mitochondrial dysfunction, and IDO1-mediated TRP to kynuridine metabolism in the lungs of elderly mice, thereby improving the host innate immune response and reducing morbidity and mortality during influenza [61]. In addition, influenza virus infection can increase IDO activity, resulting in a decrease in TRP, an increase in kynurenine, and an increase in the expression of inflammatory mediators, and inhibiting IDO activity or supplementing TRP may be a good therapeutic strategy to prevent influenza virus [62].

Overall, AAs like leucine, valine, and tryptophan play significant roles in combating influenza by enhancing the host's innate immune response. While current studies do not show a similar role for isoleucine, these findings highlight the importance of gut microbiota metabolites in influenza prevention and treatment. They primarily reduce the titer of the influenza virus by improving the innate immune response of the host.

3.2.3. Bile acids and influenza

Bile acids are metabolites produced in the liver through complex enzymatic reactions of cholesterol substances and secreted into the intestine, mainly including cholic acid (CA) and chenodeoxycholic acid, whose function is to emulsify, digest, and absorb lipids and fat-soluble vitamins [63]. When secreted bile acids pass through the intestine, they are reabsorbed in the ileum and returned to the liver via the portal vein. This entero-hepatic cycle is essential for maintaining the stability of bile acids and cholesterol. About 95 % of the primary bile acids are reabsorbed into the liver through the entero-hepatic cycle, and only 5 % of the primary bile acids are structurally modified by the microbiota in the intestine, a small fraction of uncoupled secondary bile acids are enriched in the enterohepatic circulation and may act as signaling molecules in the host to alter the structure of the gut microbiota [64]. Studies have shown that high-temperature exposed mice raise their basal body temperature to more than 38 °C, prompting the gut microbiota to produce more bile acids. Intestinal microbiota-derived deoxycholic acid (DCA) and its plasma membrane-binding receptor Takeda G protein-coupled Receptor 5 (TGR5) signaling increase host resistance to influenza virus infection by inhibiting viral replication and neutrophil-dependent tissue damage [65]. Taurocholic acid is a kind of bile acid. Sodium taurocholate hydrate (STH) inhibits influenza virus replication, reduces influenza virus RNA, complementary RNA, and mRNA levels, and exhibits broad-spectrum antiviral activity against a variety of influenza viral strains (H5N6, H5N1, H1N1, H3N2). Moreover, STH reduced the expression of inflammatory factors (TNF-α, IL-1β, IL-6) in influenza virus-infected mice, attenuated their clinical symptoms, inhibited weight loss, and reduced their mortality, which was attributed to STH's role in influenza resistance through the inhibition of the activation of the NF-B pathway [66].

Chenodeoxycholic acid has been shown to inhibit rotavirus [67], hepatitis B virus, and hepatitis D virus [68]. Whether it also has inhibitory effects on influenza viruses has also been discussed, and it is now clear that chenodeoxycholic acid has an inhibitory effect on influenza A viruses (H5N1, H9N2, and H1N1), and that it is able to inhibit the replication of influenza A viruses by blocking the nuclear export of the virus RNA complex as a result of a reliable cellular assay [69]. Therefore, chenodeoxycholic acid can be used as a new strategy to treat influenza. In addition, data from an elderly influenza vaccination suggests that the immune response of vaccination may be regulated by differences in bile acid metabolism, and its mechanism lies in their downstream capacity to induce genes associated with B-cell function and the ER stress pathway. This suggests that bile acid measurement may be a potential proxy for the efficacy of trivalent inactivated influenza vaccine (TIV) in the elderly [70].

The antiviral activity of bile acids should not be ignored, and they may have broad-spectrum antiviral activity. Existing studies have shown that they inhibit the replication of influenza virus mainly by blocking the output of viral RNA, and bile acids may also affect the immune response to vaccination, and its specific mechanism is worthy of further study.

3.2.4. Monoamine neurotransmitters and influenza

Neurotransmitters are chemical messengers responsible for transmitting information in the nervous system, including cholines, monoamines, AAs, and neuropeptides. 5-hydroxytryptamine (5-HT), dopamine, and norepinephrine (NE) are the three most common monoamine neurotransmitters, which play essential roles in maintaining homeostasis and improving mood disorders. 5-HT is an inhibitory neurotransmitter widely present in the cerebral cortex and synapses, which is converted by tryptophan catalyzed by tryptophan hydroxylase II (TPH2). The gut flora can regulate 5-HT levels in the brain through various mechanisms [71,72]. For instance, infection of mother mice with influenza virus(H1N1) can lead to an increase in the expression level of 5-HT2A receptors in offspring adult mice, and some highly pathogenic influenza viruses may replicate in the lungs and extrapulmonary tissues of offspring mice [73]. It has been proved that compared with oseltamivir alone, the combination of selective serotonin Reuptake inhibitor (SSRI) sertraline and oseltamivir reduces H1N1 virus-induced lung inflammation and mortality [74]. Dopamine is the most abundant catecholamine neurotransmitter in the brain, which is involved in the regulation of many neurophysiological functions. It has been shown that the disturbance of gut flora can significantly increase the amount of dopamine in the brain [75–77]. Oseltamivir affects dopamine D levels by regulating gut microbiota, thereby causing hypothermia in influenza mice [78]. In addition, the combination of neuraminidase inhibitors zanamivir with celecoxib and mesalazine improved the survival of mice infected with highly pathogenic influenza A H5N1 virus strains [79]. After deprivation of NE acting on lymphocytes through β-adrenoceptor influences antibody response, find that Propranolol decreased the total quadrivalent inactivated influenza vaccine (QIV) antigen-specific IgG titer in mice infected with influenza virus [80]. Severe influenza virus infection can cause elevated NE and promote psychological symptoms of infection [81].

Further exploration is needed to determine whether monoamine neurotransmitters have anti-influenza virus effects, and the mechanism between their antiviral effects and gut microbiota is not yet clear. Changes in gut microbiota structure may affect neurotransmitter changes, thereby exerting indirect antiviral effects.

4. Regulate gut microbiota and its metabolites to treat influenza

4.1. Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is a new measure to transplant the intestinal flora in the stool of healthy people into the intestine of patients in a certain way, restore the microbial diversity by changing the recipient microflora, and then correct the imbalance of the intestinal flora of patients, so as to treat or assist the treatment of diseases [82]. Fecal microflora can be transported into the digestive tract not only by oral administration and enema but also through nasogastric tube, nasoduodenal tube, endoscopic intestinal tube grafting, or colonoscopy. Studies have shown that IAV mainly disrupts the airway epithelial tight junction, resulting in acute respiratory distress syndrome, and that gastrointestinal symptoms often co-occur with IAV infection, suggesting that the gut-lung axis is involved in the host response to IAV. A significant reduction in SCFAs, especially acetate, was found in IAV-infected patients and mice. At the phylum level, the relative abundance of *Actinomycetes* decreased, while that of *Proteobacteria* increased. At the genus level, the relative abundance of *Bacteroides*, *Bifidobacterium,* and *Ackermannia* was low. In mice after FMT, these conditions were reversed, reducing lung inflammatory damage and confirming that acetate may be an important mediator of the gut-lung axis. Further experiments demonstrated that acetate activated GPR43, restored some IAV-induced airway epithelial barrier function, and reduced TNF-α, IL-6, and IL-1β levels [83]. FMT was able to effectively regulate the antibiotic-induced structural disorder of the intestinal microbiota in influenza-infected mice. Jie Gao et al. [84]found that in antibiotic-treated and IAV-infected mice, intestinal microbiota was disrupted, with the relative abundance of *Enterobacteriaceae* increasing while that of other flora such as *Akkermansiaceae* and *Muribaculaceae* decreasing. After treatment with probiotics and FMT, *Enterobacteriaceae* declined and *Bacteroidaceae* and other bacteria groups recovered. Furthermore, TLR7, MyD88 and NF-κB p65 mRNA were significantly expressed in antibiotic-treated and IAV-infected mice, and all three proteins were down-regulated in the probiotic and FMT groups. However, in $TLR7^{-/-}$ mice, there was no significant difference in expression among antibiotic treatment and IAV-infected mice, probiotics, and FMT groups, which also demonstrated that probiotics and FMT could regulate Th1/Th2 and Th17/Treg imbalances. This suggests that probiotics and FMT regulate the TLR7/NF-κB signaling pathway to regulate the balance of Th1/Th2 and Th17/Treg by restoring the imbalance of intestinal microbiota caused by influenza virus, alleviating intestinal and lung inflammation. Previous studies have found that the activation level of immune cells in mice with humanized microbiota is poor. Therefore, a Gnotobiotic Pig Model was selected to colonize the gut microbiota of obese and healthy children, infected with zoonotic influenza virus strains at 2, 3, and 5 weeks after transplantation. Researchers have found that Gnotobiotic pigs infected with the gut microbiota of obese children have lower levels of *Firmicutes* (*Lactococcus*, *Lactobacillus*, *Turicibacter*, and *Streptococcus*) and *Actinobacteria* (*Bifidobacterium*), and higher levels of *Proteobacteria* (*Klebsiella*), *Bacteroidetes*, and *Verrucomicia* (*Akkermansia*) compared to Gnotobiotic pigs infected with the gut microbiota of healthy children. Further investigation revealed that the Gnotobiotic Pig, which infects the gut microbiota of obese children, promotes immune maturation and activates the expression levels of IL-6, IL-12, TNF-α, and IFN-γ pro-inflammatory factors mediated by influenza virus, particularly in the fifth week. However, the viral load of the two groups of Gnotobiotic Pigs was comparable [85]. In addition, transplanting of bat gut microbiota into H1N1-infected mice, we can see that it regulates the gut microbiota by increasing the richness of *Proteobacteria*, *Lactococcus*, *Enterobacteriaceae,* and *Enterococcusin*, but interestingly, The richness of *Enterobacteriaceae* and *Enterococcus* decreased gradually over time. $CD3^{+}$ and NK cells can also be activated, and also disappear over time to reduce tissue damage and reduce viral titers. This may be related to the presence of high levels of flavonoid and isoflavonoid metabolites in the bat gut flora, which enhance viral tolerance and exert antiviral effects in virus-infected individuals [86].

In viral infections, it is important to mention type I interferons (IFNs), which are key modulators between pathogens and hosts. IFN as the first line of defense against viral infection, by using IAV-infected mouse models, IFN-κb was found to be one of the first type I IFNs to respond to H9N2 infection, and IFN-κb was shown to effectively inhibit the replication of multiple influenza viruses in cultured human lung cells. Therefore, inhibition of the IFN-κ-specific pathway of IAV can be used as evidence for the prevention and treatment of IAV [87]. At the same time, we found that fine-tuning of the IFNs pathway attenuates immune or pathological damage to the host while exerting antiviral protection, such as down-regulation of IFNAR1 prevents early replication of influenza viruses [88]. IFN-I induces transcription of mainly interferon-stimulated genes (ISGs). ISGs encode proteins with multiple antiviral functions. The decrease in interstitial lung cell ISGs induced by antibiotic use increases susceptibility to influenza virus [89]. However, FMT reverses this and increases the IFNs signaling pathway and IFN-driven antiviral status in the interstitium of the lung, thereby enhancing protection against influenza virus infection [90].

4.2. Microecological preparation

4.2.1. Probiotics

Probiotics, serving as a common gut microbial regulator, affect the gut microbial diversity, structure, and composition. Probiotic treatment is able to alter the metabolic activity of gut microbiota and the metabolites including SCFAs, are closely associated with the host immune response [91,92]. Clinically commonly used probiotics include *Bifidobacterium*, yeast, *bacillus,* and *Lactobacillus* [93]. Upon entering the intestine, probiotics help balance intestinal microorganisms, enhance the barrier function of intestinal epithelial cells, inhibit the growth and adhesion of pathogenic microbes, regulate the immune system, and promote the host's health and growth [94–96]. For instance, *Lactobacillus gasseri* SBT2055 (LG2055) is a probiotic lactic acid bacterium known for its bile tolerance and ability to improve the intestinal environment. LG2055 can inhibit viral replication by upregulating Mx1 expression in macrophages and inducing antiviral genes Mx1 and Oas1a in lung tissues, thereby reducing viral titers and inflammation in the lungs, which is beneficial for treating influenza [97]. Similarly, the oral *Lactobacillus pentosus* b240 strain also has the effect of resistance to influenza

virus, which is achieved by increasing the secretory immunoglobulin A and immunoglobulin G in the body to enhance immunity [98]. *Lactiplantibacillus plantarum* 0111 is a natural strain from the mouse intestine that restores the reduction of *Lactobacillus* and *Faecalibaculum* induced by H9N2 infection and maintains the balance of the intestinal flora. It can stimulate the elevated expression of IFN-β, ISGs, and IgA, enhance the gut microbiota-mediated innate and acquired immune responses, and improve the protection against influenza viruses, and it is very promising to become a probiotic for the prevention and treatment of influenza viruses [99]. In the study of avian influenza viruses, especially in chickens, there is also an inevitable link between changes in gut microbiota and influenza viruses. After infection with H9N2 subtype avian influenza virus, the expression of IgG titer and interferon-γ in spleen cells treated with FMT was significantly increased compared with that of chicken treated with antibiotics alone, and the number of *Firmicutes*, *Bacteroides, Lactobacillus,* and *Alphaproteobacteria* were also significantly increased. This may explain, in part, that changes in the immune response after influenza virus vaccination may be related to the composition of the gut microbiota [100]. A similar conclusion was reached in another study, *Lactobacillus* probiotics can increase the expression of interferon-γ gene in chicken spleen cells and enhance the immunogenicity of H9N2 influenza virus inactivated vaccine [101]. The mechanism varies with different probiotic strains on alleviating influenza virus infection. Studies have found that *Lactobacillus mucosae* 1025 significantly reduced the loss of body weight, pathological symptoms, and viral loading and restored the relative abundance of *Firmicutes* and *Deferribacter*. *Bifidobacterium breve* CCFM1026 significantly reduced the proportion of neutrophils and increased lymphocytes, the expressions of TLR7, MyD88, TRAF6, and TNF-α, and increased *Bacteroidetes*, decreased *Firmicutes* to restore the immune disorders. However, their mixture of MIX decreased viral loading and increased the antiviral protein MxA expression, which was closely associated with the increased butyrate production resulting from gut microbial alteration [102].

4.2.2. Prebiotics

Prebiotics are defined as "non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon" [103], it does not have a direct effect but can promote the growth of probiotics. Prebiotics, which include inulin, fructo-oligosaccharides (FOS), and galacto-oligosaccharides (GOS), have been shown to increase the number of beneficial bacteria such as *Bifidobacterium* and *Lactobacillus* in animal and human gut microbes and improve the immune effect of influenza vaccines [104–106]. GOS/FOS increased the proportion of *Bifidobacterium* and *Lactobacillus* in a murine influenza vaccination model feces in a dose-dependent manner. Dietary intervention with the prebiotic FOS oligofructose mixture has been demonstrated for the first time to enhance the systemic adaptive immune response [107]. Short-chain galacto-oligosaccharides/long-chain fructo-oligosaccharides/2′-fucosyllactose improved influenza vaccine-specific humoral immunity in an early-life dietary intervention in mice and demonstrated that this may be associated with beneficial modulation of the gut microbiota, which provides useful information for the future use of prebiotics in combination for influenza intervention. It is noteworthy that the intervened female mice produced more antibodies than males, and this sex difference may be related to plasma cell differentiation [108]. At the same time, this sex-specific result also provokes us to think about whether there are unknown differences in the intestinal flora of men and women? Is it necessary to consider gender differences in the study design of vaccines? It is worthwhile to carry out further research. Nagafuchi et al. [109] found that elderly people over 60 years old who received enteral nutrition therapy were treated with *Bifidobacterium* growth-stimulating hormone and galactose oligosaccharide for 14 weeks on the basis of their standard enteral nutrition formula treatment, and were vaccinated with trivalent seasonal influenza vaccine (A/H1N1, A/H3N2 and B) at the 4th week after treatment. Antibody titers were measured at week 0, 4, 6, 8 and 12. The results showed that there was no difference in vaccine immune response rate between the two groups, but the number of *Bifidobacterium* in the intestinal tract of the experimental group was significantly higher than that of the control group, and the A/H1N1 antibody titer in the experimental group was maintained longer than that of the control group. It suggests that prebiotics may increase the number of probiotics in the gut, thereby maintaining antibody titers. Similarly, Akatsu et al. [110] conducted a similar trial in elderly Japanese people receiving intestinal nutrition therapy and concluded that prebiotics can affect the gut microbiota and maintain antibody titers. Van den Elsen et al. [108] found that adult mice inoculated with TIV and supplemented with a mixture of lactose oligosaccharide, fucose lactose, galactose, and long-chain fructooligosaccharide could observe an increase in the abundance of *Actinobacteria*, a decrease in *Verrucomicrobia*, *Firmicutes*, and *Proteobacteria*, as well as an increase in vaccine-specific antibody response, such as specific Th cell response and B cell activation in mesenteric lymph nodes, serum levels of IgG, IgG1 and IgG2a were increased.

4.3. Traditional Chinese medicine

Traditional Chinese medicine dosage forms mostly enter the gastrointestinal tract by oral way to prevent and treat diseases [111, 112]. Therefore, intestinal flora also affects the efficacy and adverse reactions of traditional Chinese medicine to a certain extent. Intestinal flora can change the structure of the active ingredients of traditional Chinese medicine through hydrolysis reaction, redox reaction, deacetylation, and other ways to affect the role of traditional Chinese medicine [113]. For example, saponins in ginseng can be reduced to ginsenosides by intestinal flora, thereby improving the efficacy of ginseng [114]. On the one hand, Chinese medicine can prevent and treat diseases by regulating the structure of intestinal flora in disorder under disease conditions, such as increasing the relative abundance of probiotics, and/or reducing the relative abundance of potentially pathogenic bacteria; On the other hand, traditional Chinese medicine can also change the production of metabolites of intestinal flora by affecting the metabolic process of certain specific flora, improve and/or reduce the physiological and pathological process mediated by specific metabolites, such as by increasing the content of SCFAs to regulate host immunity and then play the role of anti-inflammatory and anti-cancer. Therefore, more and more studies on the efficacy of traditional Chinese medicine regard intestinal flora as an important target. Through studying the interaction between traditional Chinese medicine and intestinal flora and its influence on host immune homeostasis, the

mechanism of the efficacy of traditional Chinese medicine is explained.

Flavonoids are a group of natural substances with different phenolic structures, which are widely found in fruits, vegetables, wine, flowers, and tea [115]. It has been reported that flavonoids affect viral adsorption, entry, replication viral protein translation, the formation of some viral envelope glycoprotein complexes, and the release of viruses [116–119]. Flavonoids have immunomodulatory effects [120]. In addition, human gut microbes can produce DAT from flavonoid and amino acid metabolism [121–123]. It has been confirmed that Clostridium orbiscindens can effectively degrade flavonoid compounds and convert them to DAT, thereby preventing influenza through type I IFN signaling [120]. Houttuynia cordata polysaccharides (HCP) could improve the disturbance of intestinal flora caused by swine flu virus infection, increase *Bacteroidetes*, *f_Muribaculaceae, Akkermansiaceaemetabolize*, reduce *Proteobacteria* more acetate content, and regulate Th17/Treg rebalancing, thus reducing pulmonary and intestinal injury [124]. This provides a new idea for the targeted regulation of intestinal flora by macromolecular polysaccharides in the treatment of influenza. Molecular Mechanisms of FMT, Microbial Preparation, and Traditional Chinese Medicine on Influenza (Table 1).

5. Application of machine learning in influenza

In recent years, with the rapid development of artificial intelligence, its application in the medical field has attracted much attention and gradually increased. Machine learning, a core part of artificial intelligence, is an algorithm that trains models by utilizing large data sets, adjusts algorithm parameters to optimize models, and predicts unknown data based on these models [125]. Therefore, the application of machine learning to influenza provides a powerful aid for disease monitoring and prediction, diagnosis and classification, vaccine development, and personalized treatment [126,127]. Machine learning can use historical flu data and other relevant variables to predict the time and location of future flu outbreaks. By using 2008–2014 influenza data, developing four machine learning models, and using an integrated approach to integrate predictions, all models were found to provide accurate, real-time predictions of influenza-like illness within four weeks, helping the public sector to take preventive and control measures in advance [128]. In addition, clinical data, metabolomics, laboratory test results, and imaging data can also be analyzed to predict the positive rate of influenza patients and the most prevalent types of influenza viruses in the season, thereby improving the accuracy of the clinician's diagnosis of influenza [129,130]. Getting vaccinated against influenza is an important method for preventing the occurrence of influenza, reducing the severity of the disease, and limiting its related serious complications. A study has found that using machine learning models to analyze the human H3N2 sequences of all hemagglutinin and neuraminidase from 1980 to 2020 can

Table 1
Molecular mechanisms of FMT, microbial preparation, and traditional Chinese medicine on influenza.

Therapy method	Models	Molecular mechanisms	Refs.
FMT	Human bronchial epithelial cells and Male C57BL/6 J mice	SCFAs↓, acetate↓, TNF-α↓, L-6↓, IL-1β↓, Viral load↓, TJ↑, *Actinomycetes*↓, *Proteobacteria*↑, *Bacteroides*↓, *Bifidobacterium*↓, *Ackermannia*↓	[83]
FMT and Probiotics (Bifidobacterium and Lactobacillus triple live bacteria tablets)	Female C57BL/6 wild-type and $Tlr7^{-/-}$ mice	Lung indexes↓, Viral load↓, *Enterobacteriaceae*↓, *Bacteroidaceae*↑, TLR7↓, MyD88↓, NF-κB p65↓, Th1/Th2↑, Th17/Treg↑	[84]
FMT	Gnotobiotic Pig and MDCK cells	Viral load↓, IL-6↑, IL-12↑, TNF-α↑, IFN-γ↑, *Firmicutes* (*Lactococcus*, *Lactobacillus*, *Turicibacter*, *Streptococcus*) ↓, *Actinobacteria* (*Bifidobacterium*) ↓, *Proteobacteria* (*Klebsiella*) ↑, *Bacteroidetes*↑, *Verrucomicia* (*Akkermansia*) ↑	[85]
FMT	Female C57BL/6 mice	Proteobacteria↑, Lactococcus↑, Enterobacteriaceae↑, Enterococcus↑, $CD3^+$ cells↑, NK cells↑, Viral load↓, CXCL10↑, IFN-α↑, IFN-β↑, IL-10↑, IL-12p70↑, TNF-α↑	[86]
Probiotics (*Lactobacillus gasseri* SBT2055)	Male C57BL/6N mice, MDCK cells and RAW264.7 cells	PR8 Viral load↓, IL-6↓, LDH↓, IFN-β↑, Mx1↑	[97]
Probiotics (*Lactobacillus pentosus* b240)	MDCK cells and Female BALB/c/Cr Slc mice	Viral load↓, IgA↑, IgG↑, CTLL-2↑	[98]
Probiotics (Lactiplantibacillus plantarum 0111*)*	MDCK cells and Female C57B/6 mice	IL-6↓, TNF-α↓, *Lactobacillus*↑, *Faecalibaculum*↑ IFN-β↑, $CD3^+$ T cells↑, $CD4^+$ T cells↑, IgA↑	[99]
FMT and Probiotics (*Lactobacilli*)	Specific pathogen free layer chickens and MDCK cells	*Firmicutes*↑, *Bacteriodetes*↑, *Alphaproteobacteria*↑, *Lactobacillus*↑, IgG↑, IgM↑, IFN-γ↑, Hemagglutination inhibition↑, Virus neutralization antibody titers↑	[100]
Probiotics (*Lactobacilli s*)	Specific pathogen free layer chickens	Hemagglutination inhibition↑, Virus neutralization antibody titers↑, IgM↑, Igγ↑	[101]
Probiotics (*Lactobacillus mucosae* 1025, *Bifidobacterium breve CCFM1026*)	Female ICR mice	Viral load↓, TLR7↑, MyD88↑, TRAF6↑, TNF-α↑, Firmicutes↑, Deferribacteres↑, Butyrate↑	[102]
Prebiotics (scGOS, lcFOS and the human milk specific oligosaccharide 2′-FL)	BALB/c mice	IgG↑, IgG1↑, IgG2a↑, *Actinobacteria*↑, *Verrucomicrobia*↓, *Firmicutes*↓, *Proteobacteria*↓, $CD138^+$↑	[108]
Prebiotics (BGS and GOS)	Elderly patients	*Bifidobacterium*↑, Hemagglutination inhibition↑	[109]
Prebiotics (BGS and GOS)	Elderly patients	Prealbumin↑, *Bacteroides*↑, *Clostridium coccoides*↑, *Lactobacillus*↑, Antibody titers↑	[110]
FMT and Houttuynia cordata polysaccharides	Male BALB/c mice	Th17↑, Treg↑, *Bacteroidetes*↑, *f_Muribaculaceae*↑, *Akkermansiaceae*↑, *Proteobacteria*↓, Acetate↑	[124]

↑: Indicates upward adjustment; ↓:Indicates downward adjustment or reduction.

predict upcoming influenza viruses and guide the confirmation of candidate vaccines for seasonal influenza viruses next year [131]. At present, with the continuous improvement of data acquisition and processing capabilities, the application of machine learning in influenza has broad prospects, which can help us to monitor influenza, diagnose influenza, select vaccine strains, and manage public health, and is worthy of further research. We can strengthen the following aspects: (1) Build a more comprehensive and accurate influenza prediction model by combining genomic data, clinical data, and environmental data, and realize multi-modal data fusion and analysis; (2) Use machine learning algorithms to dynamically update influenza transmission models to provide real-time influenza risk assessment and early warning services; Strengthen interdisciplinary cooperation in the fields of computer science, epidemiology, public health and clinical medicine to jointly promote the application and development of machine learning in influenza disease.

6. Conclusions

The gut microbiota, a complex and extensive community, significantly influences various biological systems, including the immune system and metabolic functions. Recent studies increasingly highlight a potential link between the gut microbiome and influenza, suggesting that the gut microbiota may impact the pathogenicity of influenza viruses, presenting a novel therapeutic target. This paper systematically reviews the effects of gut microbiota and its metabolites on the treatment and intervention of influenza. The protective effects of the intestinal flora and its metabolites against influenza suggest that FMT, microbiological preparations, and traditional Chinese medicine could play crucial roles in the adjunctive treatment of influenza and other severe respiratory infections. However, current research is limited. The concept of a 'normal' intestinal flora requires quantitative indicators, the relationships within the microbiota remain unclear, the specific roles of individual strains need clarification, and the underlying mechanisms of the "microbiota-gut-lung axis" demand a deeper investigation. Additionally, the overuse of antibiotics disrupts the gut microbiota and weakens mucosal immunity, posing challenges in balancing these factors, which necessitates further scholarly exploration.

In conclusion, the gut microbiota exhibits therapeutic potential for influenza, which can be addressed by regulating the intestinal microecology. Future studies should focus on identifying key strains, specific metabolites, and immune regulation mechanisms within the gut microbiota to precisely target microbiota interventions for preventing and treating influenza and other respiratory viral infections.

Ethics approval

Not applicable. Review and/or approval by an ethics committee was not needed for this study because this study involved a comprehensive analysis of existing literature and did not involve any primary data collection or experiments that would require ethical considerations.

Consent for publication

All the authors agreed to be published.

Availability of data and materials

Not applicable. No data was used for the research described in the article.

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CRediT authorship contribution statement

Cheng Luo: Writing – original draft, Conceptualization, Investigation, Visualization. **Yi Yang:** Supervision. **Cheng Jiang:** Visualization. **Anqi Lv:** Conceptualization. **Wanzhao Zuo:** Conceptualization. **Yuanhang Ye:** Writing – review & editing. **Jia Ke:** Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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References

[1] M. Javanian, M. Barary, S. Ghebrehewet, et al., A brief review of influenza virus infection, J. Med. Virol. 93 (8) (2021) 4638–4646.
[2] L.V. Patrono, B. Vrancken, M. Budt, et al., Archival influenza virus genomes from Europe reveal genomic variability during the 1918 pandemic, Nat. Commun. 13 (1) (2022) 2314.
[3] A. Madsen, Y.N. Dai, M. McMahon, et al., Human antibodies targeting influenza B virus neuraminidase active site are broadly protective, Immunity 53 (4) (2020) 852–863.e7.
[4] B.M. Hause, E.A. Collin, R. Liu, et al., Characterization of a novel influenza virus in cattle and Swine: proposal for a new genus in the Orthomyxoviridae family, mBio 5 (2) (2014) e14–e31.
[5] C.R. Parrish, P.R. Murcia, E.C. Holmes, Influenza virus reservoirs and intermediate hosts: dogs, horses, and new possibilities for influenza virus exposure of humans, J. Virol. 89 (6) (2015) 2990–2994.
[6] E.C. Hutchinson, Influenza virus, Trends Microbiol. 26 (9) (2018) 809–810.
[7] D.M. Morens, J.K. Taubenberger, Making universal influenza vaccines: lessons from the 1918 pandemic, J. Infect. Dis. 219 (Suppl_1) (2019) S5–S13.
[8] F. Krammer, G. Smith, R. Fouchier, et al., Influenza, Nat Rev Dis Primers 4 (1) (2018) 3.
[9] L.R. Clayville, Influenza update: a review of currently available vaccines, P T 36 (10) (2011) 659–684.
[10] J. Alvarez, R.J. Fernandez, F. Guarner, et al., Gut microbes and health, Gastroenterol. Hepatol. 44 (7) (2021) 519–535.
[11] H.T. Groves, S.L. Higham, M.F. Moffatt, et al., Respiratory viral infection alters the gut microbiota by inducing inappetence, mBio 11 (1) (2020).
[12] I. Sekirov, S.L. Russell, L.C. Antunes, et al., Gut microbiota in health and disease, Physiol. Rev. 90 (3) (2010) 859–904.
[13] E.G. Avery, H. Bartolomaeus, A. Maifeld, et al., The gut microbiome in hypertension: recent advances and future perspectives, Circ. Res. 128 (7) (2021) 934–950.
[14] C. Campbell, P.T. Mckenney, D. Konstantinovsky, et al., Bacterial metabolism of bile acids promotes generation of peripheral regulatory T cells, Nature 581 (7809) (2020) 475–479.
[15] Y. Saiman, T.D. Shen, P.J. Lund, et al., Global microbiota-dependent histone acetylation patterns are irreversible and independent of short chain fatty acids, Hepatology 74 (6) (2021) 3427–3440.
[16] J.A. Foster, N.K. Mcvey, Gut-brain axis: how the microbiome influences anxiety and depression, Trends Neurosci. 36 (5) (2013) 305–312.
[17] K.F. Budden, S.L. Gellatly, D.L. Wood, et al., Emerging pathogenic links between microbiota and the gut-lung axis, Nat. Rev. Microbiol. 15 (1) (2017) 55–63.
[18] K.C. Bauer, P.T. Littlejohn, V. Ayala, et al., Nonalcoholic fatty liver disease and the gut-liver Axis: exploring an undernutrition perspective, Gastroenterology 162 (7) (2022) 1858–1875.
[19] P.J. Ma, M.M. Wang, Y. Wang, Gut microbiota: a new insight into lung diseases, Biomed. Pharmacother. 155 (2022) 113810.
[20] L. Wang, Y. Cai, J. Garssen, et al., The bidirectional gut-lung Axis in chronic obstructive pulmonary disease, Am. J. Respir. Crit. Care Med. 207 (9) (2023) 1145–1160.
[21] C. Luo, Y. Ye, A. Lv, et al., The impact of Astragaloside IV on the inflammatory response and gut microbiota in cases of acute lung injury is examined through the utilization of the PI3K/AKT/mTOR pathway, PLoS One 19 (7) (2024) e0305058.
[22] S. Yildiz, B. Mazel-Sanchez, M. Kandasamy, et al., Influenza A virus infection impacts systemic microbiota dynamics and causes quantitative enteric dysbiosis, Microbiome 6 (1) (2018) 9.
[23] T. Hagan, M. Cortese, N. Rouphael, et al., Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans, Cell 178 (6) (2019) 1313–1328.
[24] J.Z. Oh, R. Ravindran, B. Chassaing, et al., TLR5-mediated sensing of gut microbiota is necessary for antibody responses to seasonal influenza vaccination, Immunity 41 (3) (2014) 478–492.
[25] L.V. Hooper, D.R. Littman, A.J. Macpherson, Interactions between the microbiota and the immune system, Science 336 (6086) (2012) 1268–1273.
[26] L.B. Thackray, S.A. Handley, M.J. Gorman, et al., Oral antibiotic treatment of mice exacerbates the disease severity of multiple flavivirus infections, Cell Rep. 22 (13) (2018) 3440–3453.
[27] O.H. Robak, M.M. Heimesaat, A.A. Kruglov, et al., Antibiotic treatment-induced secondary IgA deficiency enhances susceptibility to Pseudomonas aeruginosa pneumonia, J. Clin. Invest. 128 (8) (2018) 3535–3545.
[28] T.J. Schuijt, J.M. Lankelma, B.P. Scicluna, et al., The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia, Gut 65 (4) (2016) 575–583.
[29] A.L. Steed, G.P. Christophi, G.E. Kaiko, et al., The microbial metabolite desaminotyrosine protects from influenza through type I interferon, Science 357 (6350) (2017) 498–502.
[30] J. Qin, R. Li, J. Raes, et al., A human gut microbial gene catalogue established by metagenomic sequencing, Nature 464 (7285) (2010) 59–65.
[31] H. Jiang, M. Cai, B. Shen, et al., Synbiotics and gut microbiota: new perspectives in the treatment of type 2 diabetes mellitus, Foods 11 (16) (2022).
[32] V. Tremaroli, F. Backhed, Functional interactions between the gut microbiota and host metabolism, Nature 489 (7415) (2012) 242–249.
[33] P.B. Eckburg, E.M. Bik, C.N. Bernstein, et al., Diversity of the human intestinal microbial flora, Science 308 (5728) (2005) 1635–1638.
[34] M.M. El, A.A. Al-Hussaini, S.A. Al, et al., Intestinal microbiota profile in healthy Saudi children: the bacterial domain, Saudi J. Gastroenterol. 28 (4) (2022) 312–317.
[35] B. Abdullah, S. Daud, M.S. Aazmi, et al., Gut microbiota in pregnant Malaysian women: a comparison between trimesters, body mass index and gestational diabetes status, BMC Pregnancy Childbirth 22 (1) (2022) 152.
[36] R.P. Dickson, B.H. Singer, M.W. Newstead, et al., Enrichment of the lung microbiome with gut bacteria in sepsis and the acute respiratory distress syndrome, Nat Microbiol 1 (10) (2016) 16113.
[37] Q. Zhang, J. Hu, J.W. Feng, et al., Influenza infection elicits an expansion of gut population of endogenous Bifidobacterium animalis which protects mice against infection, Genome Biol. 21 (1) (2020) 99.
[38] E. Deriu, G.M. Boxx, X. He, et al., Influenza virus affects intestinal microbiota and secondary Salmonella infection in the gut through type I interferons, PLoS Pathog. 12 (5) (2016) e1005572.
[39] H.T. Groves, L. Cuthbertson, P. James, et al., Respiratory disease following viral lung infection alters the murine gut microbiota, Front. Immunol. 9 (2018) 182.
[40] H. Li, X. Liu, F. Chen, et al., Avian influenza virus subtype H9N2 affects intestinal microbiota, barrier structure injury, and inflammatory intestinal disease in the chicken ileum, Viruses 10 (5) (2018).
[41] K.L. Stefan, M.V. Kim, A. Iwasaki, et al., Commensal microbiota modulation of natural resistance to virus infection, Cell 183 (5) (2020) 1312–1324.
[42] M.L. Watzenboeck, B. Drobits, S. Zahalka, et al., Lipocalin 2 modulates dendritic cell activity and shapes immunity to influenza in a microbiome dependent manner, PLoS Pathog. 17 (4) (2021) e1009487.
[43] L.C. Gierse, A. Meene, D. Schultz, et al., Influenza A H1N1 induced disturbance of the respiratory and fecal microbiome of German Landrace pigs - a multi-omics characterization, Microbiol. Spectr. 9 (2) (2021) e18221.
[44] K.M. Maslowski, A.T. Vieira, A. Ng, et al., Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43, Nature 461 (7268) (2009) 1282–1286.
[45] A. Trompette, E.S. Gollwitzer, K. Yadava, et al., Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis, Nat Med 20 (2) (2014) 159–166.
[46] V. Sencio, A. Gallerand, M.M. Gomes, et al., Influenza virus infection impairs the gut's barrier properties and favors secondary enteric bacterial infection through reduced production of short-chain fatty acids, Infect. Immun. 89 (9) (2021) e73420.
[47] D. Gowda, Y. Li, G.S. B, et al., Determination of short-chain fatty acids by N,N-dimethylethylenediamine derivatization combined with liquid chromatography/mass spectrometry and their implication in influenza virus infection, Anal. Bioanal. Chem. 414 (22) (2022) 6419–6430.
[48] J. Niu, M. Cui, X. Yang, et al., Microbiota-derived acetate enhances host antiviral response via NLRP3, Nat. Commun. 14 (1) (2023) 642.

[49] A. Trompette, E.S. Gollwitzer, C. Pattaroni, et al., Dietary fiber confers protection against flu by shaping Ly6c(-) patrolling monocyte hematopoiesis and CD8(+) T cell metabolism, Immunity 48 (5) (2018) 992–1005.
[50] Q. Liang, Q. Zhao, X. Hao, et al., The effect of Flammulina velutipes polysaccharide on immunization analyzed by intestinal flora and proteomics, Front. Nutr. 9 (2022) 841230.
[51] M. Neinast, D. Murashige, Z. Arany, Branched chain amino acids, Annu. Rev. Physiol. 81 (2019) 139–164.
[52] M.M. Adeva-Andany, L. Lopez-Maside, C. Donapetry-Garcia, et al., Enzymes involved in branched-chain amino acid metabolism in humans, Amino Acids 49 (6) (2017) 1005–1028.
[53] S. Everman, L.J. Mandarino, C.C. Carroll, et al., Effects of acute exposure to increased plasma branched-chain amino acid concentrations on insulin-mediated plasma glucose turnover in healthy young subjects, PLoS One 10 (3) (2015) e120049.
[54] F.T. Fellendorf, M. Platzer, R. Pilz, et al., Branched-chain amino acids are associated with metabolic parameters in bipolar disorder, World J Biol Psychiatry 20 (10) (2019) 821–826.
[55] Y. Sun, Z. He, J. Li, et al., Gentamicin induced microbiome adaptations associate with increased BCAA levels and enhance severity of influenza infection, Front. Immunol. 11 (2020) 608895.
[56] H.P. Hsia, Y.H. Yang, W.C. Szeto, et al., Amino acid substitutions affecting aspartic acid 605 and valine 606 decrease the interaction strength between the influenza virus RNA polymerase PB2 '627' domain and the viral nucleoprotein, PLoS One 13 (1) (2018) e191226.
[57] M. Borghi, M. Puccetti, M. Pariano, et al., Tryptophan as a central hub for host/microbial symbiosis, Int. J. Tryptophan Res. 13 (2020) 520714955.
[58] I. Cervenka, L.Z. Agudelo, J.L. Ruas, Kynurenines: tryptophan's metabolites in exercise, inflammation, and mental health, Science 357 (6349) (2017).
[59] Z.S. Donati, F. Ferrini, D. Agostini, et al., Nutraceuticals and physical activity as antidepressants: the central role of the gut microbiota, Antioxidants 11 (2) (2022).
[60] B. Lamas, J.M. Natividad, H. Sokol, Aryl hydrocarbon receptor and intestinal immunity, Mucosal Immunol. 11 (4) (2018) 1024–1038.
[61] S.J. Cho, K.S. Hong, E. Schenck, et al., Decreased Ido1-dependent tryptophan metabolism in aged lung during influenza, Eur. Respir. J. 57 (5) (2021).
[62] Y.T. Lin, C.F. Lin, T.H. Yeh, Influenza A virus infection induces indoleamine 2,3-dioxygenase (Ido) expression and modulates subsequent inflammatory mediators in nasal epithelial cells, Acta Otolaryngol. 140 (2) (2020) 149–156.
[63] A. Bertolini, R. Fiorotto, M. Strazzabosco, Bile acids and their receptors: modulators and therapeutic targets in liver inflammation, Semin. Immunopathol. 44 (4) (2022) 547–564.
[64] A. Wahlstrom, S.I. Sayin, H.U. Marschall, et al., Intestinal crosstalk between bile acids and microbiota and its impact on host metabolism, Cell Metab. 24 (1) (2016) 41–50.
[65] M. Nagai, M. Moriyama, C. Ishii, et al., High body temperature increases gut microbiota-dependent host resistance to influenza A virus and SARS-CoV-2 infection, Nat. Commun. 14 (1) (2023) 3863.
[66] X. Sun, X. Hu, Q. Zhang, et al., Sodium taurocholate hydrate inhibits influenza virus replication and suppresses influenza a Virus-triggered inflammation in vitro and in vivo, Int. Immunopharm. 122 (2023) 110544.
[67] Y. Kim, K.O. Chang, Inhibitory effects of bile acids and synthetic farnesoid X receptor agonists on rotavirus replication, J. Virol. 85 (23) (2011) 12570–12577.
[68] H. Yan, B. Peng, Y. Liu, et al., Viral entry of hepatitis B and D viruses and bile salts transportation share common molecular determinants on sodium taurocholate cotransporting polypeptide, J. Virol. 88 (6) (2014) 3273–3284.
[69] L. Luo, W. Han, J. Du, et al., Chenodeoxycholic acid from bile inhibits influenza A virus replication via blocking nuclear export of viral ribonucleoprotein complexes, Molecules 23 (12) (2018).
[70] C. Carre, G. Wong, V. Narang, et al., Endoplasmic reticulum stress response and bile acid signatures associate with multi-strain seroresponsiveness during elderly influenza vaccination, iScience 24 (9) (2021) 102970.
[71] H. Li, P. Wang, L. Huang, et al., Effects of regulating gut microbiota on the serotonin metabolism in the chronic unpredictable mild stress rat model, Neuro Gastroenterol. Motil. 31 (10) (2019) e13677.
[72] R. Yaghoubfar, A. Behrouzi, F. Ashrafian, et al., Modulation of serotonin signaling/metabolism by Akkermansia muciniphila and its extracellular vesicles through the gut-brain axis in mice, Sci. Rep. 10 (1) (2020) 22119.
[73] J.L. Moreno, M. Kurita, T. Holloway, et al., Maternal influenza viral infection causes schizophrenia-like alterations of 5-HT(2)A and mGlu(2) receptors in the adult offspring, J. Neurosci. 31 (5) (2011) 1863–1872.
[74] G. Sharma, S.D. Champalal, F.L. Hwei, et al., Reduction of influenza virus-induced lung inflammation and mortality in animals treated with a phosophodisestrase-4 inhibitor and a selective serotonin reuptake inhibitor, Emerg. Microb. Infect. 2 (8) (2013) e54.
[75] C. Gonzalez-Arancibia, J. Urrutia-Pinones, J. Illanes-Gonzalez, et al., Do your gut microbes affect your brain dopamine? Psychopharmacology (Berl) 236 (5) (2019) 1611–1622.
[76] Y. Wang, Q. Tong, S.R. Ma, et al., Oral berberine improves brain dopa/dopamine levels to ameliorate Parkinson's disease by regulating gut microbiota, Signal Transduct. Targeted Ther. 6 (1) (2021) 77.
[77] D. Dodd, M.H. Spitzer, W. Van Treuren, et al., A gut bacterial pathway metabolizes aromatic amino acids into nine circulating metabolites, Nature 551 (7682) (2017) 648–652.
[78] A. Fukushima, A. Fukui, Y. Takemura, et al., The anti-influenza drug oseltamivir evokes hypothermia in mice through dopamine D(2) receptor activation via central actions, J. Pharmacol. Sci. 136 (1) (2018) 39–41.
[79] B.J. Zheng, K.W. Chan, Y.P. Lin, et al., Delayed antiviral plus immunomodulator treatment still reduces mortality in mice infected by high inoculum of influenza A/H5N1 virus, Proc. Natl. Acad. Sci. U.S.A. 105 (23) (2008) 8091–8096.
[80] B. Bufan, N. Arsenovic-Ranin, I. Zivkovic, et al., B-cell response to seasonal influenza vaccine in mice is amenable to pharmacological modulation through beta-adrenoceptor, Life Sci. 301 (2022) 120617.
[81] P.J. Fitzgerald, Serious infection may systemically increase noradrenergic signaling and produce psychological effects, Med. Hypotheses 139 (2020) 109692.
[82] L. Zheng, Y.Y. Ji, X.L. Wen, et al., Fecal microbiota transplantation in the metabolic diseases: current status and perspectives, World J. Gastroenterol. 28 (23) (2022) 2546–2560.
[83] L. Hu, L. Sun, C. Yang, et al., Gut microbiota-derived acetate attenuates lung injury induced by influenza infection via protecting airway tight junctions, J. Transl. Med. 22 (1) (2024) 570.
[84] J. Gao, H. Chen, L. Xu, et al., Effects of intestinal microorganisms on influenza-infected mice with antibiotic-induced intestinal dysbiosis, through the TLR7 signaling pathway, Front Biosci (Landmark Ed) 28 (3) (2023) 43.
[85] S. Renu, L. Deblais, V. Patil, et al., Gut microbiota of obese children influences inflammatory mucosal immune pathways in the respiratory tract to influenza virus infection: optimization of an ideal duration of microbial colonization in a gnotobiotic pig model, Microbiol. Spectr. 10 (3) (2022) e0267421.
[86] B. Liu, X. Chen, L. Zhou, et al., The gut microbiota of bats confers tolerance to influenza virus (H1N1) infection in mice, Transbound Emerg Dis 69 (5) (2022) e1469–e1487.
[87] Y. He, W. Fu, K. Cao, et al., IFN-κ suppresses the replication of influenza A viruses through the IFNAR-MAPK-Fos-CHD6 axis, Sci. Signal. 13 (626) (2020) eaaz3381.
[88] K.M. Shepardson, K. Larson, L.L. Johns, et al., IFNAR2 is required for anti-influenza immunity and alters susceptibility to post-influenza bacterial superinfections, Front. Immunol. 9 (2018) 2589.
[89] A. Garcia-Sastre, C.A. Biron, Type 1 interferons and the virus-host relationship: a lesson in detente, Science 312 (5775) (2006) 879–882.
[90] K.C. Bradley, K. Finsterbusch, D. Schnepf, et al., Microbiota-driven tonic interferon signals in lung stromal cells protect from influenza virus infection, Cell Rep. 28 (1) (2019) 245–256.
[91] R. Blumberg, F. Powrie, Microbiota, disease, and back to health: a metastable journey, Sci. Transl. Med. 4 (137) (2012) 137r.
[92] P.M. Smith, M.R. Howitt, N. Panikov, et al., The microbial metabolites, short-chain fatty acids, regulate colonic Treg cell homeostasis, Science 341 (6145) (2013) 569–573.

[93] B. Foligne, C. Daniel, B. Pot, Probiotics from research to market: the possibilities, risks and challenges, Curr. Opin. Microbiol. 16 (3) (2013) 284–292.
[94] S. Hu, L. Wang, Z. Jiang, Dietary additive probiotics modulation of the intestinal microbiota, Protein Pept. Lett. 24 (5) (2017) 382–387.
[95] R.V. Bubnov, M.Y. Spivak, L.M. Lazarenko, et al., Probiotics and immunity: provisional role for personalized diets and disease prevention, EPMA J. 6 (1) (2015) 14.
[96] Y. Wang, B. Wang, X. Zhan, et al., Effects of glucose oxidase and its combination with B. amyloliquefaciens SC06 on intestinal microbiota, immune response and antioxidative capacity in broilers, Animal 16 (3) (2022) 100473.
[97] Y. Nakayama, T. Moriya, F. Sakai, et al., Oral administration of Lactobacillus gasseri SBT2055 is effective for preventing influenza in mice, Sci. Rep. 4 (2014) 4638.
[98] N. Kobayashi, T. Saito, T. Uematsu, et al., Oral administration of heat-killed Lactobacillus pentosus strain b240 augments protection against influenza virus infection in mice, Int. Immunopharm. 11 (2) (2011) 199–203.
[99] J.H. Xing, C.W. Shi, M.J. Sun, et al., Lactiplantibacillus plantarum 0111 protects against influenza virus by modulating intestinal microbial-mediated immune responses, Front. Microbiol. 13 (2022) 820484.
[100] A. Yitbarek, J. Astill, D.C. Hodgins, et al., Commensal gut microbiota can modulate adaptive immune responses in chickens vaccinated with whole inactivated avian influenza virus subtype H9N2, Vaccine 37 (44) (2019) 6640–6647.
[101] N. Alqazlan, J. Astill, K. Taha-Abdelaziz, et al., Probiotic lactobacilli enhance immunogenicity of an inactivated H9N2 influenza virus vaccine in chickens, Viral Immunol. 34 (2) (2021) 86–95.
[102] W. Lu, Z. Fang, X. Liu, et al., The potential role of probiotics in protection against influenza a virus infection in mice, Foods 10 (4) (2021).
[103] R.K. Buddington, C.H. Williams, S.C. Chen, et al., Dietary supplement of neosugar alters the fecal flora and decreases activities of some reductive enzymes in human subjects, Am. J. Clin. Nutr. 63 (5) (1996) 709–716.
[104] N. Manhart, A. Spittler, H. Bergmeister, et al., Influence of fructooligosaccharides on Peyer's patch lymphocyte numbers in healthy and endotoxemic mice, Nutrition 19 (7–8) (2003) 657–660.
[105] M. Roller, G. Rechkemmer, B. Watzl, Prebiotic inulin enriched with oligofructose in combination with the probiotics Lactobacillus rhamnosus and Bifidobacterium lactis modulates intestinal immune functions in rats, J. Nutr. 134 (1) (2004) 153–156.
[106] K.S. Swanson, C.M. Grieshop, E.A. Flickinger, et al., Effects of supplemental fructooligosaccharides and mannanoligosaccharides on colonic microbial populations, immune function and fecal odor components in the canine, J. Nutr. 132 (6 Suppl 2) (2002) 1717S–1719S.
[107] A.P. Vos, M. Haarman, A. Buco, et al., A specific prebiotic oligosaccharide mixture stimulates delayed-type hypersensitivity in a murine influenza vaccination model, Int. Immunopharm. 6 (8) (2006) 1277–1286.
[108] L. Van den Elsen, S. Tims, A.M. Jones, et al., Prebiotic oligosaccharides in early life alter gut microbiome development in male mice while supporting influenza vaccination responses, Benef. Microbes 10 (3) (2019) 279–291.
[109] S. Nagafuchi, T. Yamaji, A. Kawashima, et al., Effects of a formula containing two types of prebiotics, bifidogenic growth stimulator and galacto-oligosaccharide, and fermented milk products on intestinal microbiota and antibody response to influenza vaccine in elderly patients: a randomized controlled trial, Pharmaceuticals 8 (2) (2015) 351–365.
[110] H. Akatsu, S. Nagafuchi, R. Kurihara, et al., Enhanced vaccination effect against influenza by prebiotics in elderly patients receiving enteral nutrition, Geriatr. Gerontol. Int. 16 (2) (2016) 205–213.
[111] J. Wu, Z. Wei, P. Cheng, et al., Rhein modulates host purine metabolism in intestine through gut microbiota and ameliorates experimental colitis, Theranostics 10 (23) (2020) 10665–10679.
[112] W.F. Zuo, Q. Pang, L.P. Yao, et al., Gut microbiota: a magical multifunctional target regulated by medicine food homology species, J. Adv. Res. 52 (2023) 151–170.
[113] T.L. Lin, C.C. Lu, W.F. Lai, et al., Role of gut microbiota in identification of novel TCM-derived active metabolites, Protein Cell 12 (5) (2021) 394–410.
[114] T. Niu, D.L. Smith, Z. Yang, et al., Bioactivity and bioavailability of ginsenosides are dependent on the glycosidase activities of the A/J mouse intestinal microbiome defined by pyrosequencing, Pharm. Res. (N. Y.) 30 (3) (2013) 836–846.
[115] K. Wen, X. Fang, J. Yang, et al., Recent research on flavonoids and their biomedical applications, Curr. Med. Chem. 28 (5) (2021) 1042–1066.
[116] C.S. Lima, M. Mottin, L.R. de Assis, et al., Flavonoids from Pterogyne nitens as Zika virus NS2B-NS3 protease inhibitors, Bioorg. Chem. 109 (2021) 104719.
[117] J.F. Shimizu, C.S. Lima, C.M. Pereira, et al., Flavonoids from pterogyne nitens inhibit hepatitis C virus entry, Sci. Rep. 7 (1) (2017) 16127.
[118] P. Sithisarn, M. Michaelis, M. Schubert-Zsilavecz, et al., Differential antiviral and anti-inflammatory mechanisms of the flavonoids biochanin A and baicalein in H5N1 influenza A virus-infected cells, Antiviral Res 97 (1) (2013) 41–48.
[119] S.L. Badshah, S. Faisal, A. Muhammad, et al., Antiviral activities of flavonoids, Biomed. Pharmacother. 140 (2021) 111596.
[120] V. Izzi, L. Masuelli, I. Tresoldi, et al., The effects of dietary flavonoids on the regulation of redox inflammatory networks, Front Biosci (Landmark Ed) 17 (7) (2012) 2396–2418.
[121] F. Saura-Calixto, J. Perez-Jimenez, S. Tourino, et al., Proanthocyanidin metabolites associated with dietary fibre from in vitro colonic fermentation and proanthocyanidin metabolites in human plasma, Mol. Nutr. Food Res. 54 (7) (2010) 939–946.
[122] L. Schoefer, R. Mohan, A. Schwiertz, et al., Anaerobic degradation of flavonoids by Clostridium orbiscindens, Appl. Environ. Microbiol. 69 (10) (2003) 5849–5854.
[123] M.A. Lambert, C.W. Moss, Production of p-hydroxyhydrocinnamic acid from tyrosine by Peptostreptococcus anaerobius, J. Clin. Microbiol. 12 (2) (1980) 291–293.
[124] C. Shi, L. Zhou, H. Li, et al., Intestinal microbiota metabolizing Houttuynia cordata polysaccharides in H1N1 induced pneumonia mice contributed to Th17/Treg rebalance in gut-lung axis, Int. J. Biol. Macromol. 221 (2022) 288–302.
[125] L.K. Borkenhagen, M.W. Allen, J.A. Runstadler, Influenza virus genotype to phenotype predictions through machine learning: a systematic review, Emerg. Microb. Infect. 10 (1) (2021) 1896–1907.
[126] S.A.W. Shah, D.P. Palomar, I. Barr, L.L.M. Poon, A.A. Quadeer, M.R. McKay, Seasonal antigenic prediction of influenza A H3N2 using machine learning, Nat. Commun. 15 (1) (2024) 3833.
[127] J. Li, S. Zhang, B. Li, et al., Machine learning methods for predicting human-adaptive influenza A viruses based on viral nucleotide compositions, Mol. Biol. Evol. 37 (4) (2020) 1224–1236.
[128] H.Y. Cheng, Y.C. Wu, M.H. Lin, et al., Applying machine learning models with an ensemble approach for accurate real-time influenza forecasting in taiwan: development and validation study, J. Med. Internet Res. 22 (8) (2020) e15394.
[129] M. Hayati, P. Biller, C. Colijn, Predicting the short-term success of human influenza virus variants with machine learning, Proc. Biol. Sci. 287 (1924) (2020) 20200319.
[130] C.A. Hogan, P. Rajpurkar, H. Sowrirajan, et al., Nasopharyngeal metabolomics and machine learning approach for the diagnosis of influenza, EBioMedicine 71 (2021) 103546.
[131] M. Hayati, B. Sobkowiak, J.E. Stockdale, C. Colijn, Phylogenetic identification of influenza virus candidates for seasonal vaccines, Sci. Adv. 9 (44) (2023) eabp9185.