



# Utilizing microbiome approaches to assist source tracking, treatment and prevention of COVID-19: Review and assessment



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## ABSTRACT

COVID-19 has been one of the most serious infectious diseases since the end of 2019. However, the original source, as well as the treatment and prevention of causative agent of COVID-19 (namely SARS-CoV-2) are still unclear nearly a year after its publicly report. The microbiome approach, which has emerged in recent years focusing on human-related microbes, has become one of the promising avenues for source tracking, treatment, and prevention of a variety of infectious diseases including COVID-19. In this review, we summarized the microbiome approach as a supplementary approach for source tracking, treatment, and prevention of SARS-CoV-2 infection. We first provided background information on SARS-CoV-2 and microbiome approaches. Then we illustrated current strategies of microbiome methods to assist three aspects of COVID-19 research, namely source tracking, treatment, and prevention, respectively. Finally, we summarized the microbiome approaches and provided perspectives for future studies on faster and more effective SARS-CoV-2 epidemiology and pathogenesis based on microbiome approaches.

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## 1. Background

In December 2019, COVID-19 (or 2019-nCoV) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been one of the most urgent infectious diseases on the globe. Owing to

the high fatality rate, long incubation period, and character of human-to-human transmission of SARS-CoV-2, it has now been reported to infect individuals with all ages and slight predominant in men [1]. The World Health Organization (WHO) has declared COVID-19 a pandemic on March 11, 2020. At the end of August 2020, it has infected more than 24 million people and accounted for more than 820,000 deaths globally, and these numbers continue to increase sharply [2]. The initial mortality rate of

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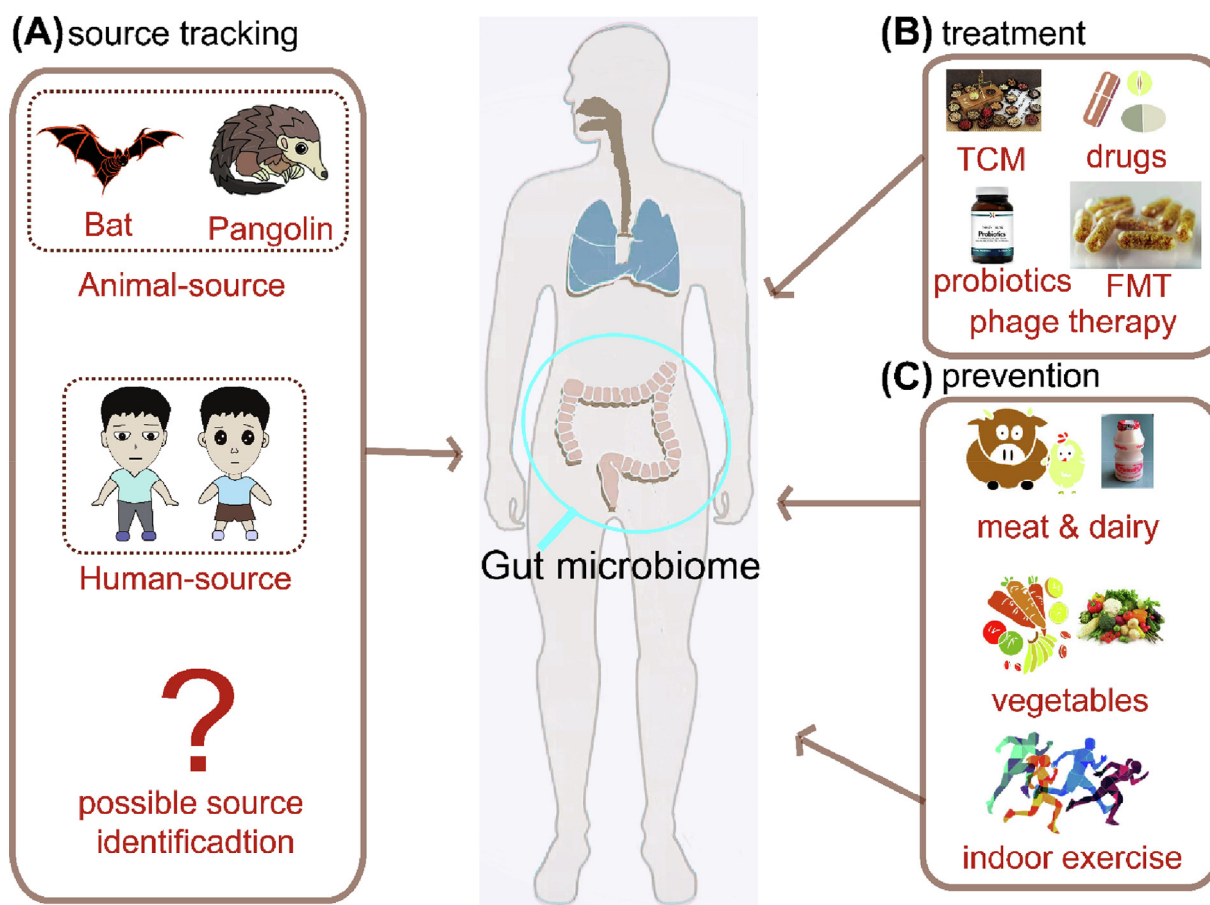
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COVID-19 was around 2% as of Wednesday, January 29, 2020, and the updated mortality rate was 3.4% as of August 28, 2020, estimated by WHO [3]. As to different counties, the actual fatality rate of populations with different age groups are different [4,5]. Several studies have indicated that the high mortality rate in COVID-19 patients with older age and co-morbid diseases, including hypertension, obesity, type 2 diabetes, and other basic metabolic diseases [1,6].

It's well-known that the human microbiome is a hub linking with almost all organs, and the gut microbiome is associated with many diseases, such as inflammatory bowel diseases (IBD), hypertension, and type 2 diabetes, etc. [7]. The alterations of gut microbiota lead to the dysbiosis of the human gut microbiome and the disorder of gut homeostasis, which affects the phenotype of the host [8,9]. Several studies have reported the clinical symptoms of COVID-19 patients and these results indicated that gastrointestinal symptoms were common in COVID-19 patients [10–12]. Among the gastrointestinal symptoms, such as diarrhea, abdominal pain, or vomiting, caused by SARS-CoV-2 during the early phases of the COVID-19 [13]. Of course, it should be noted that diarrhea is not common in COVID-19 patients (2%–20%) [14,15]. However, the COVID-19 patients with gastrointestinal symptoms is dangerous. And gastrointestinal symptoms might be one of the important factors for the high mortality rate of COVID-19 patients [16], especially for patients with older age and basic metabolic diseases, including hypertension and type 2 diabetes, etc. Thus, we proposed that microbiome approaches might be used to assist the treatment and prevention of COVID-19.

At present, physicians and scientists from various countries have devoted efforts to the treatment of COVID-19 patients and tackle key problems in urgent scientific research, including the development of diagnosis and treatment plans, the discovery of specific drugs, the development of SARS-CoV-2 vaccines, etc. [17]. Among these issues, the source tracking of SARS-CoV-2 pathogen, treatment and prevention of infection by the pathogen have drawn great interests [18]. As to the source tracking of SARS-CoV-2, the transmissions of SARS-CoV-2 from animals to humans and humans to humans in a population were introduced in this review. On one hand, by using microbiome approaches, several studies have shown that the host of SARS-CoV-2 might be pangolins [19–21] or directly from bat [16]. On the other hand, the microbiome approaches, coupled with artificial intelligence (AI) technologies, is also a very effective method for tracking the source of SARS-CoV-2 [22]. Therefore, we proposed that utilizing microbiome approaches to assist SARS-CoV-2 source tracking of COVID-19. Secondly, it has already found that maintaining a healthy human gut microbiota is important to the treatment and prevention of COVID-19 [23,24]. However, despite these advancements in utilizing microbiome approaches for better source tracking, treatment, and prevention of COVID-19, there is still a lack of systematic review on how these tasks could be done for solving the emergent COVID-19 crisis based on microbiome approaches.

Therefore, in this review, we provided a holistic view on how microbiome approaches could assist in SARS-CoV-2 source tracking, treatment and prevention of COVID-19 (Fig. 1). We first provided background information on SARS-CoV-2 and microbiome



**Fig. 1. Microbiome approach is a potential venue for the fight against SARS-CoV-2.** (A): The possible origin of SARS-CoV-2, including bat, pangolin, etc. (B): Microbiome approach provides insights into the treatment of SARS-CoV-2. (C): Maintaining a healthy human gut microbiome with microbiome approaches, including dietary habits and indoor exercise, might be used as a potential venue for the prevention of SARS-CoV-2.

approaches, respectively. Secondly, we illustrated current strategies of microbiome methods to assist three aspects of SARS-CoV-2, namely source tracking, treatment and prevention, respectively. We summarized the promise of microbiome approaches on SARS-CoV-2, and provided perspectives for future studies on faster and more effective SARS-CoV-2 epidemiology and pathogenetics based on microbiome approaches. We also tested several machine learning source-tracking methods for deducting possible sources of samples containing SARS-CoV-2. Results have shown that the source-tracking of samples containing SARS-CoV-2 could reach accuracies higher than 96% based on microbiome data. Together, we summarized that microbiome approaches could assist in SARS-CoV-2 source tracking, treatment and prevention of COVID-19.

## 2. Development history and phylogenetic origin of SARS-CoV-2

Since December 2019, the Chinese CDC officials of Wuhan, China reported several cases of unexplained pneumonia with unknown origin. The causative agent was identified as a novel coronavirus, initially referred to as 2019-nCoV, and the researchers of China sequenced the genome of this novel coronavirus and publicly shared its genome sequence on January 11, 2020. Subsequently, WHO renamed 2019-nCoV as SARS-CoV-2, and this respiratory illness called Coronavirus Disease 2019 (COVID-19). And WHO called COVID-19 a public health emergency and declared it a pandemic on March 11, 2020 [25]. Owing to the high case fatality rate, long incubation period, and character of human-to-human transmission of SARS-CoV-2, it has spread rapidly and has caused major outbreaks worldwide and become one of the most urgent infectious diseases on the globe [26]. Until now, the COVID-19 is affecting more than 210 countries and territories worldwide, posing a great threat to the global public and health and causing tremendous economic losses [27]. At the end of August 2020, SARS-CoV-2 has infected more than 24 million people around the world and accounted for more than 820,000 deaths, and the numbers are still increasing sharply [2].

SARS-CoV-2, the causative agent of COVID-19, was affiliated with Coronaviridae family and betacoronavirus genus. Coronavirus is known for its positive-sense, single-stranded RNA viruses and its hosts can be mammalian and avian. Among the known coronaviruses, SARS-CoV, MERS-CoV, HKU1, NL63, OC43, and 229E have been shown to infect humans. SARS-CoV-2 is the seventh coronavirus known to infect humans. Among these seven coronaviruses, HKU1, NL63, OC43, and 229E are associated with the mild seasonal symptoms of humans, whereas SARS-CoV-2, as well as SARS-CoV and MERS-CoV, can cause severe and emerging disease of humans [28]. The genetic analysis of SARS-CoV-2 showed that its 30 kb genome consists of six major open reading frames and encodes proteases, a RNA-dependent RNA polymerase, and several structural proteins [16,29]. The virion of SARS-CoV-2 consists of a helical capsid and an envelope, which formed by membrane and envelope proteins, coating with trimeric spike (S) proteins [16,29]. The spike protein of SARS-CoV-2 has a functional polybasic cleavage site [30] and the receptor-binding domain in the spike protein is the most fickle part of the genome of SARS-CoV-2 [31]. It has been reported that SARS-CoV-2 binds to its functional ACE2 on the plasma membrane of type 2 pneumocytes and intestinal epithelial cells, causing the humoral immune response and facilitating viral entry [29,30,32]. The transmission routes of SARS-CoV-2 are diverse, including direct droplet transmission and faecal-oral transmission, etc. Faecal excretion, environmental contamination and fomites are also contributed to the transmission of SARS-CoV-2 [33]. It should be noted that COVID-19 patients shed SARS-CoV-2 virus in their stools for a while after clinical

recovery, and these fecal samples are a potential source of SARS-CoV-2 transmission, which makes the transmission of SARS-CoV-2 more complicated and the clinical observation time longer [34].

To date, the origin of the SARS-CoV-2 is still unclear. The genetic analyses of SARS-CoV-2 and several studies with microbiome approaches have reported bat as the natural reservoir of coronaviruses [28] and SARS-CoV-2 entered the humans from wild animals, with possible candidates such as pangolins [19,20] and bat [16].

## 3. Microbiome approaches

The microbiome is a novel research field related to biochemical cycles, environmental protection, and human health, etc. [35–37]. In particular, the human microbiome has recently emerged as a key factor in human physiology and disease. Humans can be considered as “superorganisms”, which consists of about 10% human cells and 90% microorganism cells [38]. A majority of human microbiota was colonized in the gastrointestinal tract and evolved alongside humans [39,40]. The microbes of the human gut microbiome affect nearly all aspects of human biology through the interactions between gut microbes and hosts [41]. Under normal circumstances, the human gut microbiome is in a state of homeostasis. The alterations of the human gut microbiome caused by environmental factors, drugs, dietary shifts, and other factors result in the dysbiosis of human gut microbiota and effects on human health [8,9]. And increasing evidence indicated that the disorder of human gut microbiome homeostasis is associated with human diseases, for example, hypertension, obesity, type 2 diabetes, etc. [42,43].

Currently, the methods used in microbiome research include metagenomics, meta-proteomics, meta-transcriptome, etc. With the launch of several international projects on the human gut microbiome, it has become a research hotspot and promoted the most significant paradigm shift in modern medicine. On the basis of theories of the microbiome, several treatment methods are gradually applied in the treatment of diseases related to gut microbes. For instances, faecal microbiota transplantation (FMT), which transfer of pre-screened stool from healthy donors into the gut of patients, is applied to restore the gut microbiota to a pre-morbid state [44], and probiotics and prebiotics, which are microbiota-management tools, are applied to improve host health [45]. There is already abundant evidence showing that the human microbiome, especially the human gut microbiome, has profound effects on the infection and progression of SARS-CoV-2 from multiple aspects [46–48].

## 4. Microbiome approaches for assisting the source tracking of SARS-CoV-2

Source tracking of pathogenic bacteria and/or virus is undoubtedly important and is of great significance for understanding the origin, transmission, and pathogenesis of an unknown disease. Moreover, many tools have been developed to solve the source tracking of pathogens. For microbial communities, Source Tracker [22] and FEAST [49] are the two most widely used tools. Source Tracker is a Bayesian approach that can predict the source of microbial community based on its proportions [22]. FEAST is an Expected-Maximization method for the same purpose with higher accuracy and accelerated speed. While specifically for virus identification and source tracking, PHASTEST and PHASTER [50] are tools suitable for prophage or virus discovery from samples of interests. Both PHASTER and PHASTEST are significant upgrades to the popular tool PHAST for identification and annotation of prophage and virus sequences on the basis of metagenomic data [51].

Several studies have proven that microbiome approaches can assist the source tracking of SARS-CoV-2 [19,20]. It is well known that coronaviruses are common in mammals, while birds and bats may be the reservoir host for various coronaviruses [19,52]. Xiao et al. used the whole genome sequence of SARS-CoV-2 (2019-nCoV, GenBank accession No. MN908947) in a Blast search of SARS-CoV-2-like sequences in all available viromic, metagenomic, and transcriptomic data of mammals and birds. They obtained 34 highly related contigs affiliated with pangolin viral metagenomes and then focused on the source tracking of SARS-CoV-2 in wild pangolin. Hence, they conducted the SARSr-CoV analysis in the lung tissues from 4 Chinese pangolins and 25 Malayan pangolins by using RT-PCR and the isolation of a coronavirus from lung tissues of pangolins is highly related to SARS-CoV-2. These results suggested that pangolin has the potential to act as the intermediate host of SARS-CoV-2 (Fig. 1A) [19]. On the basis of published data from pangolin lung tissues contributed by Liu et al. [53], Zhang et al. re-investigated these data using microbiome approaches and detected the occurrence of a Pangolin-CoV (an SARS-CoV-2-like CoV) in dead Malayan pangolins [20]. The genomic and evolutionary analysis was conducted among Pangolin-CoV, BatCoV RaTG13, and SARS-CoV-2. The results showed that Pangolin-CoV is the second closely related to SARS-CoV-2 aside from BatCoV RaTG13 and is 91.02% similar to SARS-CoV-2 at the whole-genome level, which suggest that pangolin species are a natural reservoir of SARS-CoV-2-like CoVs (Fig. 1A) [20]. Still, applying these methods for source tracking of SARS-CoV-2 has a certain deviation. For example, virus invasion can regulate the intestinal ecosystem and symbiotic flora, whether it promotes stimulation or suppression. In addition, if the traceability strategy depends on specific bacteria in the gut, it will lead to a high degree of heterogeneity. Due to different research settings, the patient's stool sample testing tools are inconsistent, which can also lead to deviations in the results. In addition, the sample size is not large because the number of published studies on fecal SARS-CoV-2 may be limited.

In general, the natural reservoirs of SARSr-CoVs are wild animals, such as bats, camels, and pangolins (Fig. 1A). Although possible candidate for SARS-CoV-2 origin is still under debate, it is highly likely that microbiome approaches not only are effective

and important tools for exploring the natural origin of SARS-CoV-2, but also are outstanding tools to monitor surveillance in real-time and keep better health pursuits overall, not just during outbreaks (Fig. 1A).

We assessed the source tracking of COVID-19 patients with machine learning methods on the basis of datasets of microbial communities of COVID-19 patients and healthy individuals. We have applied several source tracking methods on gut microbial communities from known COVID-19 patients and healthy individual samples, aiming for evaluating the ability of these methods on source tracking using microbial community data. The sequencing data of gut microbial communities of healthy individuals were obtained from several published studies and manually selected with the criteria of no 'disease' in their description (Supplementary Table S1). While the sequencing datasets of fecal samples of COVID-19 patients were obtained from a previous study, which focused on the alterations of gut microbiota of COVID-19 patients during time of hospitalization [54]. The median age of these 15 COVID-19 patients was 55 and among these COVID-19 patients, 7 were antibiotics-naïve (COVID-19[abx-]) and 8 received empirical antibiotics (COVID-19[abx+]) at baseline. And the median duration of hospitalization was 21 ± 2.4 days (mean ± SE) [54]. To frankly reflect the difficulties in identifying a few COVID-19 patients from thousands of healthy individuals, we adopted the following setting: 1,000 samples from healthy individuals, plus 15 samples from COVID-19 patients, and the training/testing settings have been repeated 15 times. Four source tracking methods, including FEAST, Jensen-Shannon divergence (JSD), Meta-Prism (<https://github.com/HUST-NingKang-Lab/metaPrism>) and Random Forest, have been utilized for differentiating samples from COVID-19 patients out of many healthy samples.

Based on the composition of gut microbial community of COVID-19 patients and healthy individuals, the assessment results with these methods shown that machine learning method is a potential method for tracking the COVID-19 patients depend on the gut microbial communities (Fig. 2). Firstly, the microbial community structures of gut microbiome of COVID-19 patients and healthy individuals have largely different that was consistent with a previous, which has reported that the differences of gut micro-

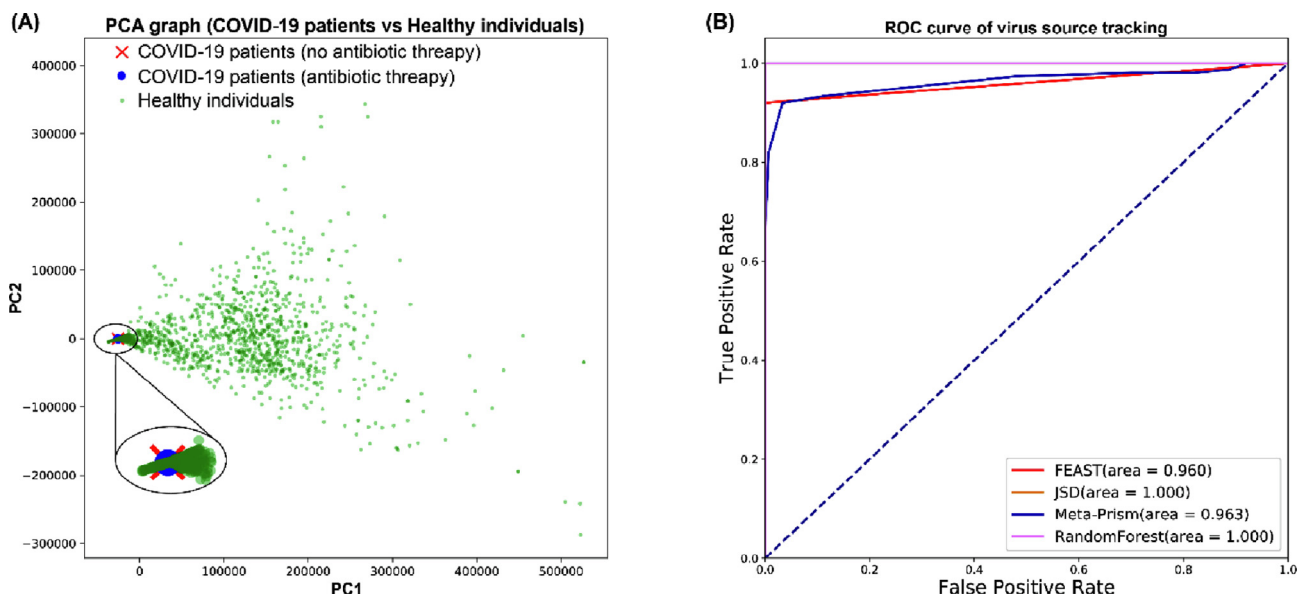


Fig. 2. Source tracking methods could successfully identify COVID-19 patients with high accuracy. (A) PCA cannot completely differentiate samples from COVID-19 patients (patients who with and without antibiotic treatment) and healthy individuals. (B) Microbial community-based source tracking methods such as FEAST could successfully source track COVID-19 patients with accuracies higher than 96%.



biota among healthy individuals, COVID-19 patients, and H1N1 patients [55], though classification methods such as PCA cannot completely differentiate samples from these two groups. Secondly, microbial community-based source tracking methods such as FEAST could successfully source track COVID-19 patients with accuracy higher than 96%. The microbial community-based source tracking methods could thus enable the fast and accurate COVID-19 patient identification purely based on the non-invasive approach using gut microbiota.

## 5. Microbiome approaches for facilitating the treatment of COVID-19 patients

Among the symptoms of COVID-19, several publications have indicated that gastrointestinal symptoms were common in COVID-19 patients [10–12], which might be due to ACE2 was considered intestine-specific [56]. In particular, diarrhea, a common gastrointestinal symptom, was presented in COVID-19 patients, and more patients with diarrhea showed severe symptoms of COVID-19 than those without diarrhea [12]. In general, the occurrence of gastrointestinal symptoms indicated the alteration of the human microbiota, especially human gut microbiota. A recent meta-analysis has reported that up to 20% COVID-19 patients have gastrointestinal symptoms [57], which are accompanied by intestinal damage or inflammation. The loss of gut microbes and intestinal barrier integrity can activate innate and adaptive immune and lead to systemic inflammation [13]. Taken together, a combined gastrointestinal symptom can potentially initiate a systemic inflammation that can create even more harm than the SARS-CoV-2 itself. It is necessary and essential to investigate the correlations among gastrointestinal symptoms, gut microbes, and the infection and treatment of SARS-CoV-2.

To date, a growing number of studies have explored the link and correlation between SARS-CoV-2 and human microbiota, especially at the clinical side. Shen et al. investigated the interactions between SARS-CoV-2 and other microbiota in the lung by using metatranscriptome sequencing, and their results showed that the microbial diversity was significantly lower in COVID-19 patients than in healthy human and the composition of the microbial community of COVID-19 patients were similar to those in community-acquired pneumonia [58]. Zhang et al. proposed a clinical trial plan to change the dysbiosis of human gut microbiota in COVID-19 patients and the goal of this clinical trial is to evaluate the outcome of Washed Microbiota Transplantation combined with standard therapy for COVID-19 patients (Clinical trial NCT04251767, Fig. 1B). Patel et al. proposed that oral microbiota is involved in the pathogenesis of respiratory diseases, such as those implicated in COVID-19, and are associated with chronic inflammatory systemic diseases including type 2 diabetes, hypertension, and cardiovascular disease [59], and these diseases are frequently reported comorbidities associated with an increased risk of severe complications and death from COVID-19 [60]. An increasing number of studies have revealed that modulating the composition of human gut microbiota can reduce enteritis and ventilator-associated pneumonia [61,62]. These results suggested that the microbiome approaches, such as FMT, could be used for facilitating the treatment of COVID-19 patients.

Additionally, previous studies have investigated the relationship between anti-virus chemical drugs and gut microbiome and found that a very complex relationship exists between chemical drugs and gut microbiome, both positively and negatively (Fig. 1B) [63]. The human gut microbiome is a complex ecosystem and there is a complex bidirectional interaction between the human gut microbiome and non-antibiotic drugs. Briefly, on the one hand, the taxonomical and functional compositions of gut

microbiome can be influenced by drugs. On the other hand, the gut microbiome can influence the response of individuals to a drug by enzymatically transforming the structure and bioavailability of drugs [64]. Among the treatment of COVID-19 patients, it has already been suggested by Lanjuan Li that the effects of gut microbiome should be considered when treatment based on anti-virus chemical drugs is applied [65]. Although there are no specific chemical drugs to treat COVID-19, we believed that the concert effects of chemical drugs and gut microbiome should be focused [66].

Moreover, there is growing evidence that the clinical efficacy of traditional Chinese medicine (TCM) may be related to human gut microbiota (Fig. 1B) [67]. In terms of the treatment of COVID-19, although the interferons can be systemically injected by the gut after gut being hijacked by SARS-CoV-2 and provided implications for the treatment of COVID-19 patients [24,68], although there is no specific drug has been discovered for COVID-19 until now. An increasing number of clinical practices showed that TCM plays a significant role in the prevention and treatment of COVID-19. TCM has its own characteristics and thousands of years of experience in adjusting the body and strengthening the resistance to epidemics. For the COVID-19 patients with mild and common symptoms, the early intervention of TCM can effectively prevent the disease from turning into severe and critical disease, while in patients with severe symptoms, the use of TCM can win time for rescuing them [69,70]. The TCM, such as *qingfei paidu* decoction (QPD), *gancaoganjiang* decoction, *lianhuaqingwen* exerts, has been promoted as a general prescription in the diagnosis and treatment plan of COVID-19 in China on February 2020, which has clearly demonstrated the effectiveness of TCM [71], the biological benefits of whose appear to involve the modulation of gut microbiota balance [72]. *Lianhuaqingwen* exerts has been widely used in the clinical treatment of COVID-19 [70] and has been demonstrated that plays an important role in fighting against COVID-19 both in China and Italy and other counties [73]. These results indicated that TCM plays a more important role in the fight against the COVID-19 for both China and other counties and international communities. Moreover, as to the beneficial effects of TCM for COVID-19 patients, previous studies have reported TCM show the beneficial effects such as decrease of mortality and relief of symptom, and etc. [74], and previous studies have proven that TCM could bring benefits to maintain the homeostasis of the human gut microbiota [75,76], and in turn, the gut microbiome can exert the pharmacological effects of the TCM on hosts [67,77]. It should be noted that TCM is a resource for drug discovery against SARS-CoV-2 and its beneficial effects is not conclusive and more-high-quality clinical studies are required.

Furthermore, gut microbiome intervention, probiotic treatment and phage therapy have shown great potential for the fight against COVID-19. Chinese researchers have suggested that gut microbiological regulators can be used to maintain the balance of gut microbial community in severe and critical cases of COVID-19 patients in the latest version of “Diagnosis and treatment of novel coronavirus pneumonia” [72]. Previous studies have demonstrated that the composition of gut microbiota is closed related to human health, gut microbiota acts as a protective mediator during hosts infected by microbes and gut microbiota can be used as a target to reduce the symptoms of pneumonia [61,78]. Probiotic bacteria (Fig. 1B), such as *Lactobacillus* and *Bifidobacterium*, numerous studies have proven that it can enhance the immune system and reduce serum lipids to maintain the health of hosts [79,80]. Phage therapy (Fig. 1B), as a promising treatment, has been widely used in clinical treatment to reduce pathogenic bacteria and acts as a new method to modulate the diversity of gut microbiota [81,82]. In clinical treatment, the content of certain probiotic microbiota was decreased, including *Lactobacillus* and *Bifidobacterium*, and the

gut microbiota was dysbiosis in COVID-19 patients [72]. At present, although there is no direct evidence that the regulation of gut microbes plays a therapeutic role in clinical treatment in COVID-19 patients, we speculated that gut microbiota should be focused during the treatment of COVID-19 with TCM. Therefore, we proposed that microbiome approaches have advantages of enhancing the clinical efficacy of TCM and may be new therapeutic options in the prevention and treatment of COVID-19, which brings new hope for control of COVID-19.

Together, we believed that microbiome approaches could facilitate the treatment of COVID-19 by either chemical and TCM treatment, FMT, probiotic treatment, phage therapy for better treatment effects.

## 6. Microbiome approaches for complement the prevention of COVID-19

As to the prevention of COVID-19, we have already known that the best way is to inject the SARS-CoV-2 vaccine. However, to date, SARS-CoV-2 vaccines are still in development and testing phases [83]. The SARS-CoV-2 vaccine produced by China shows promise in monkeys and it has entered early clinical trials in human volunteers April 24, 2020 [84]. Therefore, before injecting the SARS-CoV-2 vaccine, the best way to avoid spreading the SARS-CoV-2 is cutting your chances of catching it and keeping personal protection, such as reducing non-essential social contact and regularly washing your hands, etc. Besides, to prevent SARS-CoV-2 infection, healthy individuals need to build up defenses from the inside by both strengthening the immune system and maintaining a healthy gut microbiome, which was due to there are links between the gut microbiome and inflammation. Intriguingly, Tim Spector from King's College London has already highlighted that healthy gut microbiome plays an important and essential role in mounting a response to the coronavirus [23]. The possibility that SARS-CoV-2 can interact with certain microbes in the intestine makes the integrity of the intestinal microbiome interfered by SARS-CoV-2, leading to intestinal malnutrition in the host. An important step in understanding the impact of the gut on SARS-CoV-2 is to identify the main gut microbiome that interacts with the virus. Moreover, since SARS-CoV-2 infection is thought to occur through respiratory droplets, measures to reduce the number of infected virus particles in the oral mucosa may help reduce the risk of transmission [85,86]. In addition, oral rinses that could damage or destroy the lipid envelope may have the potential to reduce the viral load of SARS-CoV-2 in the mouth and oropharynx [85,87]. Evidence showed that oral hygiene can impact the oral microbiota and then could be a way to prevent the spread of SARS-CoV-2 [88]. For example, the use of oral rinses and interdental brushes to maintain oral hygiene and reduce the viral load of SARS-CoV-2 and the potential risk of a bacterial superinfection.

The microbiome approaches can provide the guidance of maintaining the healthy status of the human gut microbiome (Fig. 1C). It's well-known that the makeup of human gut microbiota was affected by dietary factors and environmental factors, and the healthy human gut microbial community is characterized by stability, plasticity, and resilience [89]. Diet is related to changes in the microbiome diversity. For example, a high-fat diet increases the abundance of *Prevotella*. Consuming foods rich in *Lactobacillus* species can produce lactic acid in the body, and the subsequent pH changes in the body will affect the status of different microorganisms or viruses. Although there is no study has been reported on SARS-CoV-2 directly or indirectly interacting with microbes, there have been many reports that some drugs and foods can enhance the health of the host by improving the intestinal barrier against pathogens and inflammatory agents. The strategy of nutri-

tion and diet aimed at restoring the beneficial microbiota may reduce the host's viral infection. Therefore, keeping healthy eating habits is very important to maintain the homeostasis of gut microbiota and then enhance the immune functions of the hosts (Fig. 1C) [24]. Such as, increasing the consumption of high-fiber plant-based foods, natural yogurt and artisan cheeses, which consists of live probiotics, and fermented vegetable-based foods (Fig. 1C) is important to improve the diversity of gut microbiota and reduce inflammation [90,91]. Healthy dietary habit provides nutrition and benefits to restore the human gut microbiota and strengthen the host immune system against SARS-CoV-2 [92].

Besides, performing a moderate amount of indoor exercise (Fig. 1C), especially when people are required to stay at home, should be encouraged [93]. This is not only because the moderate amount of exercise helps to improve the physical fitness of hosts, but also because an increasing number of studies have indicated that keeping a moderate amount of exercise is a benefit to maintain the homeostasis of the gut microbiome (Fig. 1C) [94,95]. Therefore, we believed that the microbiome is a potential venue against SARS-CoV-2 and the microbiome approaches can be used as complement methods for the prevention of COVID-19.

## 7. Conclusion

COVID-19 is a sudden and serious infectious disease and no specific drugs or vaccines are available for the treatment and prevention of the disease until now. In this review, we summarized the background information on SARS-CoV-2 and microbiome approaches and proposed that the microbiome approach is a potential venue against novel coronavirus SARS-CoV-2, serving as one of the promising avenues for source tracking, treatment, and prevention of varieties of infectious diseases including COVID-19.

In this review, we provided a holistic view which clearly demonstrated that: the human microbiome is not only a hub that is linked with almost all organs, but also a key player that stands at every venue against SARS-CoV-2. Microbiome approaches provide the ability to identify and respond to a variety of known and unknown pathogens including viruses, and provide perspectives for future studies on faster and more effective SARS-CoV-2 epidemiology and pathogenesis.

We have also tested several machine learning source-tracking methods for deducting possible sources of samples containing SARS-CoV-2. The tests were based on microbiome data from different cohorts. Results have shown that based on microbiome data, the source tracking of COVID-19 patients could reach accuracies higher than 90%. These results once again verified the strong correlation of gut microbiome with phenotypes of COVID-19 patients, and proven the effectiveness of microbiome approaches in assisting source tracking, treatment and prevention of COVID-19.

By accumulating and updating current tools and databases related to the microbiome, we are confident that we could quickly obtain an in-depth understanding of SARS-CoV-2 and for better real-time surveillance of SARS-CoV-2, and provide insights of drugs and vaccines developed for the pandemic.

## CRedit authorship contribution statement

**Maozhen Han:** Writing - original draft, Visualization, Writing - review & editing, Funding acquisition. **Yuguo Zha:** Writing - review & editing, Visualization. **Hui Chong:** Writing - review & editing, Visualization. **Chaofang Zhong:** Writing - review & editing, Visualization. **Kang Ning:** Writing - review & editing, Supervision, Funding acquisition.

## 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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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.csbj.2020.11.027>.

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