



# Probiotics and MicroRNA: Their Roles in the Host–Microbe Interactions

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Probiotics are widely accepted to be beneficial for the maintenance of the gut homeostasis – the dynamic and healthy interactions between host and gut microorganisms. In addition, emerging as a key molecule of inter-domain communication, microRNAs (miRNAs) can also mediate the host–microbe interactions. However, a comprehensive description and summary of the association between miRNAs and probiotics have not been reported yet. In this review, we have discussed the roles of probiotics and miRNAs in host–microbe interactions and proposed the association of probiotics with altered miRNAs in various intestinal diseases and potential molecular mechanisms underlying the action of probiotics. Furthermore, we provided a perspective of probiotics–miRNA–host/gut microbiota axis applied in search of disease management highly associated with the gut microbiome, which will potentially prove to be beneficial for future studies.

**Keywords:** probiotics, microRNA, gut microbiota, homeostasis, host–microbe interactions

## INTRODUCTION

Trillions of microbes exist in the human gastrointestinal tract, and the number of these microbes greatly exceeds the number of human body cells, which influences the physiological activities of the host throughout the lifespan (Li D. et al., 2016; Chang and Kao, 2019). This complicated ecosystem containing bacteria, fungi, viruses, and protists is called the gut microbiota. Intense exploration for understanding the relationships between host and gut microbiota has never ceased. In particular, the “dysbiosis” of gut microbiota may lead to the occurrence of various diseases of the host, ultimately damaging its health (Li D. et al., 2016; Chang and Kao, 2019). Probiotics, in sufficient doses, can restore the intestinal microecological balance and promote the healthy growth of the host (Hill et al., 2014). The consumption of probiotics is prevalent because they have the potential to become an important intervention strategy to prevent and treat various diseases (Balakrishnan and Floch, 2012; Suez et al., 2019; Yousefi et al., 2019). Although probiotics have great prospects, concerns about security and doubts about their effectiveness are always present. It is important to explain the exact molecular mechanism describing probiotics’ influence on host–microbe interactions, which remains largely unknown so far. MicroRNAs (miRNAs) are

considered to be important regulators in the host gene expression process, and some are found to be significantly related to the microbial community or specific bacteria (Hasan and Yang, 2019). Recent studies have proposed the functional role of miRNAs played in shaping gut microbiota (Moloney et al., 2019; Behrouzi et al., 2020). These host-derived miRNAs were able to enter bacterial cells to cultivate or inhibit specific bacteria (Liu et al., 2016; Spinler et al., 2019). These effects on host-microbe interactions suggested that miRNAs may be important participants in the molecular mechanism of probiotics action.

In this review, we first summarized the interactions between host and gut microbiota and presented a brief overview of probiotic functions and their impact on host-microbe interactions. Then, we highlighted the importance of miRNAs to host gastrointestinal function and described the correlation between miRNA expression levels and gut microbiota profiles. Next, we discussed the current understanding of the host's use of fecal miRNA and plant-derived miRNA in maintaining gut homeostasis. Finally, we proposed the potential molecular mechanism underlying how probiotics maintain gut homeostasis and proposed the concept of probiotics-miRNA-host/gut microbiota axis that can serve as a new direction for future exploration.

## INTERACTIONS BETWEEN HOST AND GUT MICROBIOTA

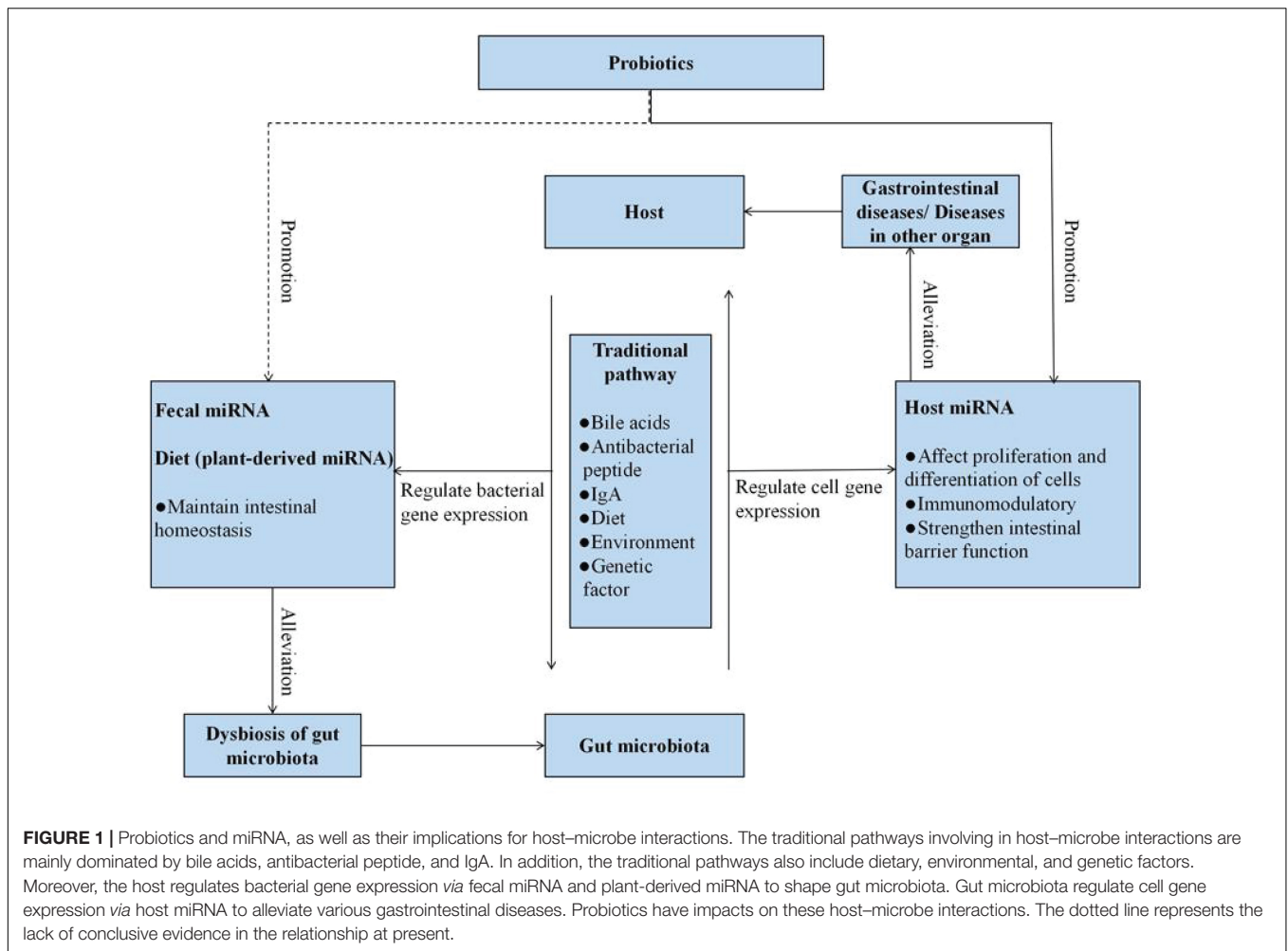
Genes encoded by the gut microbiota are 150 times larger than the human genome, which includes an extremely rich enzyme repository (El Kaoutari et al., 2013; Rooks and Garrett, 2016; Rowland et al., 2018; Zimmermann et al., 2019). Most members of gut microbiota exert harmless or beneficial effects on the host. They provide uncoded human enzymes, participate in human metabolism, and also maintain immune homeostasis through their interactions with host cells (Rooks and Garrett, 2016; Rowland et al., 2018). For example, the bacterial fermentation products of carbohydrates are short-chain fatty acids (SCFAs) that are important energy sources for bacteria itself and host cells (Rowland et al., 2018). SCFAs also have varying regulatory functions on the host, including the enhancement of epithelial barrier function and maintenance of mucosal immunity (Rooks and Garrett, 2016; Rowland et al., 2018). Additionally, bile acids are classical examples of the interactions between host and gut microbiota. The gut microbes modified the bile acids synthesized in the liver into secondary bile acids that modulate multiple host metabolic processes and immune homeostasis (Long et al., 2017; Parasar et al., 2019). In contrast, bile acids are capable of influencing the growth of bacteria, resulting in changes in the structure of the microbial community. The gut microbiota is essential for host metabolism and immune homeostasis, and their components contribute considerably to shaping the host immune system, such as lipopolysaccharide, flagellin, peptidoglycan, etc. (Rooks and Garrett, 2016).

Interactions between the host and gut microbiota promote the establishment of a symbiotic relationship during host development. The optimal operation of a symbiotic relationship

is vital to host health. But, the performance of gut microbiota is affected by various factors, including diet, lifestyle, illness, environment, hygiene, genetics, and antibiotic exposure (Li D. et al., 2016; Cristofori et al., 2018; Celiker and Kalkan, 2020). Although the composition of specific flora may change due to the stimulation of internal and external factors, the structure of the intestinal microbial community remains dynamic and stable (Coyte et al., 2015). Differences in the types of microorganisms are carried by different individuals, but the composition and function of the “core microbiome” are similar and remain relatively stable over time (Lozupone et al., 2012; Coyte et al., 2015; Milani et al., 2017; Gentile and Weir, 2018). This microbial stability is considered to play a critical role in the health of the host. It is worth mentioning that it is regarded as a sign of host intestinal health. Disruption of microbial stability often leads to “dysbiosis,” which induces a range of diseases (Lozupone et al., 2012; Coyte et al., 2015; Li D. et al., 2016; Milani et al., 2017). Moreover, gut microbiota have the ability to trigger responses from a distance by producing metabolites (Agus et al., 2018; Allaire et al., 2018; Gentile and Weir, 2018). The crosstalk between host and gut microbes can be linked to the health status of other body organs (Gresse et al., 2017; Agus et al., 2018; Allaire et al., 2018; Gentile and Weir, 2018; Adak and Khan, 2019; Maslowski, 2019; Zhang et al., 2019). Another aspect of the crosstalk includes the detailed mechanism of host manipulation of the bacterial community that has also received extensive attention (Figure 1). The traditional pathways are mainly dominated by bile acids, antibacterial peptides, and IgA (Brown et al., 2013; Chu and Mazmanian, 2013; Liu, 2016; Parker et al., 2018). Additionally, compelling evidences supported that genetic and environmental factors contributed greatly to the occurrence of dysbiosis, which in turn promoted many diseases, such as obesity and inflammatory bowel disease (IBD; Zhou M. et al., 2017; Cuevas-Sierra et al., 2019; Celiker and Kalkan, 2020). Recent studies have proposed a novel mechanism that the host specifically controls the gut microbiota by promoting the liberation of miRNAs (Liu et al., 2016). Diet and probiotics are also valuable tools available to alter the gut microbiota (Forgie et al., 2019; Tang, 2019).

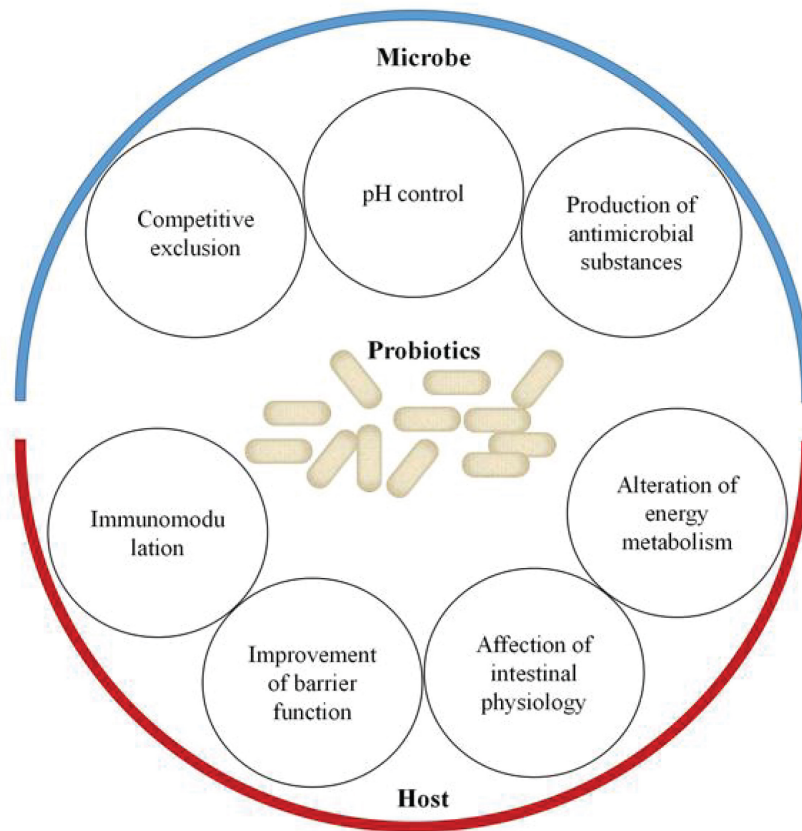
## PROBIOTICS AND THEIR IMPLICATIONS FOR HOST-MICROBE INTERACTIONS

Probiotics are commercial food supplements that are widely used all over the world. It has been generally accepted that they are able to restore the disruption of gut microorganisms. In 2002, probiotics were defined by WHO as live microorganisms that confer a health benefit when administered in adequate amounts (Hill et al., 2014). At present, as shown in Figure 2, various methods, including metagenomics, transcriptomics, and metabolomics, have already been applied to describe the mechanisms of the effects of probiotics on the host-microbe interactions (Bermudez-Brito et al., 2019; Kiousi et al., 2019; Yadav and Pratyosh, 2019; Quigley and Gajula, 2020; Sehrawat et al., 2020). The most commonly beneficial effect of the probiotic administration route is to stabilize the bacterial



community and restore the “signature” of gut microbiota. It mainly stems from their ability to produce bacteriocins, lower pH, and compete with pathogens for space and nutrients (Balakrishnan and Floch, 2012; Cremon et al., 2018; Suez et al., 2019). Competitive exclusion by probiotics is based on the competition for available nutrients and adhesion sites. It has been demonstrated that purified surface adhesion proteins of probiotics can exclude pathogens. Surface adhesins of pathogens and probiotic strains are implicated in mediating the binding of microbes to the host (Du et al., 2010). Probiotics can also change the environment to gain a more favorable competitive advantage. Studies on lactobacilli and bifidobacteria have shown that these two probiotic strains could produce organic acids to lower intestinal pH. Both organic acids and bacteriocins produced by bacteria enable the inhibition of pathogen growth (Dobson et al., 2012). On the other hand, probiotic bacteria (e.g., *Lactobacillus* and *Bifidobacterium*) have been revealed to improve barrier function. The ability of probiotics to upregulate expression levels of mucus-secretion genes may be one of the mechanisms of improving barrier function and excluding pathogens (Khoruts, 2018; Bermudez-Brito et al., 2019; Sanders et al., 2019; Yan and Polk, 2020). Furthermore, probiotic strains have been reported

to directly exert immune and anti-inflammatory effects on the host. Probiotics may affect the immune system by changing the levels of metabolites, components, and DNA. They have been shown to activate immune cells, increase the production of immunoglobulins, and regulate cytokines (Khoruts, 2018; Sanders et al., 2019; Liwinski and Elinav, 2020; Yan and Polk, 2020). Several studies have demonstrated that these probiotic-derived factors can suppress intestinal inflammation *via* targeting toll-like receptor (TLR) signaling (Gómez-Llorente et al., 2010). Additionally, probiotics could also alter energy metabolism and impact intestinal physiology by releasing metabolites including the SCFAs, oligosaccharides, vitamins, amino acids, and secondary bile acids (Gura, 2014; Lee et al., 2018; Bermudez-Brito et al., 2019; Kiouisi et al., 2019; Quigley and Gajula, 2020; Sehrawat et al., 2020). For instance, a recent study found that the SCFAs produced by *Lactobacillus casei* and *Bifidobacterium breve* could potentially be an essential regulatory effector of intestinal epithelial cell (IEC) proliferation (Matsuki et al., 2013). Currently, nutritional programs have received increasing attention; probiotic administration manipulates the gut microbiota to prevent or attenuate metabolic-related diseases (e.g., hypertension and hyperglycemia) (LeBlanc et al., 2017).



**FIGURE 2 |** Effects of probiotics on the host–microbe interactions. Probiotics support the stability of the bacterial community and restore the “signature” of gut microbiota through competitive exclusion, pH control, and production of antimicrobial substances. On the other hand, probiotics promote health benefits for the host through improvement of barrier function, immunomodulation, affection of intestinal physiology, and alteration of energy metabolism.

As probiotics can prevent and/or treat various diseases, their consumption is becoming more and more common all over the world. The growing industry shows that probiotics have a huge market prospect and the global market is expected to reach \$65 billion by 2024 (Abid and Koh, 2019). Of note, both current research and application have found some limitations of probiotics. The action level of probiotics depends on different conditions, including the strains, individuals, types of administration, or location within the intestines (Markowiak and Ślizewska, 2017; Kothari et al., 2019; Langella and Chatel, 2019; Salvucci, 2019; Wan et al., 2019). Although compelling evidence has been obtained in clinical trials, the exact molecular mechanism of probiotics that confer beneficial effects on the host remains unclear. Of late, new possibilities have been observed in different studies exploring the interaction between miRNA and microbiota and the responses of miRNA to probiotic intervention.

## WHAT IS miRNA?

MicroRNAs are endogenous, small, non-coding RNAs that are 19–25 nucleotides in length (Yu et al., 2016). They are first

synthesized in the nucleus, transported into the cytoplasm, and processed into mature miRNAs (Yu et al., 2016; Bartel, 2018). Mature miRNAs are loaded onto the miRNA-induced silencing complex (miRISC) and bound to the 3′ untranslated region (3′ UTR) of mRNA to mediate post-transcriptional gene silencing (Yu et al., 2016; Bartel, 2018).

Despite complexity was added in terms of gene regulation, interest has surged in the function of miRNA molecules to mediate gene silencing to repress protein synthesis. Since the first miRNA, *lin-4*, was discovered in the 90s in *Caenorhabditis elegans*, hundreds of different miRNAs were found to play critical roles in healthy and pathological cell processes, including cellular differentiation, proliferation, signal transduction, and apoptosis (Fischer, 2015; Mohr and Mott, 2015; Yu et al., 2016; Rupaimoole and Slack, 2017; Bartel, 2018). Insights into the ability of miRNAs had made them into promising therapeutic tools (miRNA mimics) or targets (miRNA inhibitors) in cancer and other diseases (Link et al., 2010; Kalla et al., 2015; Rupaimoole and Slack, 2017; Tili et al., 2017; Hossian et al., 2019; Chen et al., 2020).

An early encouraging work demonstrated that miRNAs could be isolated from circulating body fluids (Weber et al., 2010; Lu and Rothenberg, 2018; Lee, 2019). They exist and transfer

stably outside the cell and in feces through vesicles. Exosomes (30–100 nm nanosized vesicles) derived from multiple cell types are capable of encapsulating protein and RNA molecules (Turchinovich et al., 2011; Celluzzi and Masotti, 2016; Yu et al., 2016; Bartel, 2018; Moloney et al., 2019). miRNA molecules have been observed to complete the intercellular communication in this way while preventing endogenous degradation (Turchinovich et al., 2011; Celluzzi and Masotti, 2016; Yu et al., 2016; Bartel, 2018; Moloney et al., 2019). miRNAs dysregulation observed in tissues and serum associated with disease activity was considered as a potential biomarker for clinical diagnosis (Link et al., 2010; Kalla et al., 2015; Rupaimoole and Slack, 2017; Tili et al., 2017; Hossian et al., 2019; Chen et al., 2020), but several issues have impeded the application of circulating miRNAs in clinical diagnosis (Wang et al., 2018; Saliminejad et al., 2019). In the host's gastrointestinal tract, fecal miRNA can be influenced by the alteration of gut microbial composition, which provides a new perspective to identify intestinal and microbiota healthiness (Carter et al., 2017; Horne et al., 2019; Tarallo et al., 2019; Sarshar et al., 2020).

## THE IMPLICATIONS OF miRNA FOR THE HOST

MicroRNAs play an important role in the host's gastrointestinal function. Numerous studies have revealed that miRNAs can participate in many aspects of intestinal functions, including proliferation and differentiation of cells, architecture, and barrier function of the host intestines (Zou et al., 2018; Ding et al., 2019). In 2010, McKenna et al. (2010) determined the complete miRNA transcriptome of the mouse intestinal epithelium cells. They found that miR-192 and let-7 presented high expression levels and observed reduction in goblet cells, increased apoptosis, and intestinal inflammation in the mice deficient of all miRNAs in the intestine. Part of the reason for the proliferation and differentiation of IECs is the precise regulation of key transcription factors, such as SOX9 (Peck et al., 2016). miR-30 could indirectly regulate SOX9 protein and thus mediate IEC homeostasis (Suez et al., 2019). Recent study showed that miR-381-3p directly suppressed nuclear receptor-related protein 1 (*nurr1*) translation (Liu et al., 2018). By inhibiting miR-381-3p, *nurr1*-mediated IEC proliferation and barrier function were enhanced.

With the increasing recognition of the importance of miRNAs in the host's gastrointestinal tract function, the association between miRNAs and a wide variety of intestinal diseases have received more and more attention (Tables 1, 2). For example, colorectal cancer (CRC) is one of the most common malignant tumors. Multiple signaling pathways (WNT, EGFR, TGF- $\beta$ , etc.) in CRC are regulated by miRNAs (Balacescu et al., 2018). They have been identified as oncomiRs and tumor suppressor miRNAs (Yamamoto and Mori, 2016; Balacescu et al., 2018; Shirafkan et al., 2018). Their deregulation contributes to the development, progression, and metastasis of CRC (Yamamoto and Mori, 2016; Balacescu et al., 2018; Shirafkan et al., 2018; To

et al., 2018). Natural endogenous and stability make numerous of them therapeutic targets and potential biomarkers for CRC (Yamamoto and Mori, 2016; Shirafkan et al., 2018; To et al., 2018). The exploitation of favorable miRNAs delivery systems is likely to expand the options for CRC treatment. Similarly, many miRNAs could interfere in the pathogenesis of IBDs by regulating multiple pathways (Cao et al., 2017; Schönauen et al., 2018; Boros and Nagy, 2019; Feng et al., 2019). They were observed to play important roles in inflammation, fibrosis, autophagy, and cellular proliferation (Yamamoto and Mori, 2016; Balacescu et al., 2018; Shirafkan et al., 2018; To et al., 2018; Feng et al., 2019). According to Tian et al. (2019), miRNA 31 (miR31) expression was altered in inflamed mucosa of IBD patients *via* the NF- $\kappa$ B and STAT3 signaling pathways. This miRNA has the function of relieving inflammation and promoting epithelial cell regeneration. A microsphere delivery system has been developed based on this characteristic of miR31, which provided a new proposal for the treatment of IBD.

Notably, microbiota-derived extracellular vesicles (EVs) also play a major role in intercellular communication and signal transduction between gut microbiota and host cells. EVs included outer membrane vesicles (OMVs) and membrane vesicles (MVs) that are, respectively, liberated by Gram-negative and Gram-positive bacteria. Various RNA species (e.g., mRNAs, miRNAs, tRNAs) are biologically active components of EVs, which may impact gene expression when being delivered to host cells (Ahmadi Badi et al., 2017; Felli et al., 2017; Macia et al., 2019; Sarshar et al., 2020). In a fascinating study, Fábrega et al. confirmed the role of OMVs in signal transduction between gut microbiota and host. OMVs produced by the probiotic *Escherichia coli* strain Nissle (EcN) 1917 induced the expression and secretion of several cytokines and chemokines in the *ex vivo* model (Fábrega et al., 2016). Overall, intestinal bacteria utilized OMVs as a significant strategy to communicate with the host and influence host responses.

## THE CORRELATION BETWEEN HOST MIRNA EXPRESSION LEVELS AND GUT MICROBIOTA PROFILES

In addition to participating in the regulation of intestinal function, the close relationship between miRNAs and gut microbiota has also been confirmed (Masotti, 2012; Belcheva, 2017; Hoban et al., 2017; Yuan et al., 2018). A potential mechanism by which gut microbiota affect host physiology is to modulate host gene expression through miRNAs. Dalmaso et al. (2011) demonstrated that nine miRNAs were differently expressed in the colonized mice relative to germ-free mice. They confirmed that the potential targets of miRNAs overlapped with the dysregulated host genes during microbial colonization. Commensal bacteria might affect more host genes at the post-transcriptional level than expected. Singh et al. (2012) investigated the influence of endogenous microbiota on the overall expression of cecal miRNA *in vivo* by using germ-free and conventional mice. The result supported that cecal miRNA expression levels were modified by endogenous microbiota. The

**TABLE 1** | Circulating miRNAs and their possible/identified targets in different gastrointestinal disorders.

Circulating miRNAs	Diseases	Up/down	Potential/identified target genes	Roles	References
miR-25-3p	CRC	Up	KLF2, KLF4	Promoting CRC vascular permeability and angiogenesis	Zeng et al., 2018
miR-106b-3p	CRC	Up	DLC-1	Promoting CRC metastasis	Liu et al., 2020
miR-1229	CRC	Up	HIPK2	Promoting CRC angiogenesis	Hu et al., 2019
miR-590-5p	CRC	Down	NF90	Inhibiting CRC angiogenesis and metastasis	Zhou Q. et al., 2016
miR-622	CRC	Down	CXCR4, K-Ras	Inhibiting CRC angiogenesis and metastasis	Fang et al., 2016, 2019
miR-382	CRC	Down	NR2F2	Inhibiting CRC cell growth and invasion	Zhou B. et al., 2016
miR-409-3p	CRC	Down	Beclin-1	Inhibiting autophagy	Tan et al., 2016
miR-223	IBD	Up	CLDN8	Dysfunction of the intestinal epithelial barrier	Wang et al., 2016
miR-21	IBD	Up	RhoB	Dysfunction of the intestinal epithelial barrier	Yang et al., 2013
miR-320	IBD	Down	NOD2	Disruption of immune homeostasis	Pierdomenico et al., 2016
miR-31	IBD	Up	IL6st, IL7r, IL17ra	Suppressing inflammation	Tian et al., 2019

Up and down indicate upregulated and downregulated circulating miRNA expression levels in diseased tissues compared with normal tissues, respectively. Roles, roles of miRNAs in the pathogenesis of gastrointestinal disorders; CRC, colorectal cancer; IBD, inflammatory bowel disease.

**TABLE 2** | Fecal miRNAs and bacteria correlated with them in different gastrointestinal disorders.

Fecal miRNAs	Diseases	Up/down	Correlated microbiome taxa	References
miRNA-135b	CRC	Up	–	Wu et al., 2014
miR-21	CRC	Up	–	Link et al., 2010
miR-106a	CRC	Up	–	Link et al., 2010
miR-182	CRC	Up	<i>Blautia</i>	Yuan et al., 2018
miR-139	CRC	Down	<i>Blautia</i>	Yuan et al., 2018
miR-155	IBD	Up	–	Schönauen et al., 2018
miR-223	IBD	Up	–	Schönauen et al., 2018
miR-199a	IBD	Up	–	Ji et al., 2018
miR-223-3p	IBD	Up	–	Ji et al., 2018
miR-1226	IBD	Down	–	Ji et al., 2018
miR-515-5p	IBD	Down	–	Ji et al., 2018

Up and down indicate upregulated and downregulated fecal miRNA expression levels in diseased tissues compared with normal tissues, respectively. Correlated microbiome taxa, bacteria significantly correlated with fecal miRNAs; CRC, colorectal cancer; IBD, inflammatory bowel disease.

authors also discovered the proteins encoded by 34 putative miRNA targets involved in controlling intestinal barrier and immune regulation. Also, Xue et al. (2011) reported a study focusing on the roles of commensal bacteria in the regulation of intestinal gene expression. They found that commensal bacteria downregulated dendritic cell miR-10a expression *via* TLR–TLR ligand interactions through a MyD88-dependent pathway. IL-12/IL-23p40, a key molecule for innate immune responses to commensal bacteria, was identified as a target gene for miR-10a. Compared with the control mice, colitis mice have higher levels of IL-12/IL-23p40 and lower levels of intestinal miR-10a. Surprisingly, gut microbiota are also reported to influence host miRNA expression in other tissues and organs (Zhou G. et al., 2017; Allegra et al., 2020). Both the two studies have identified the effects of gut microbiota on the miRNA expression in the hippocampus and white adipocytes in mice, respectively (Chen J.J. et al., 2017; Virtue et al., 2019). An additional researcher claimed that after viral infection, the expression of miRNAs in the lungs of antibiotic-treated mice was altered, resulting in a reduction in host antiviral immunity (Pang et al., 2018). Accordingly, the aforementioned findings indicated that

miRNA could impact the host through participating in signal transmission, maintaining intestinal homeostasis.

## INTERACTIONS BETWEEN HOST miRNAs AND BACTERIAL PATHOGENS

miRNAs have also been recognized for their important role in the interactions between host and bacterial pathogens, either as an indispensable part of the host response to fight infection or as a molecular strategy utilized by bacterial pathogens to cause the dysregulation of host miRNA expression for their own benefit (Aguilar et al., 2019a,b). For example, miR-301b is involved in the augmentation of pro-inflammatory response during infection by *Pseudomonas aeruginosa* (Li X. et al., 2016). A target of miR-301b is c-Myb that can increase the expression of anti-inflammatory cytokines IL-4 and TGF- $\beta$ 1. miR-301b suppresses anti-inflammatory response by targeting c-Myb in response to *P. aeruginosa* infection. Wang et al. (2017) observed that miR-143-3p expression was significantly upregulated in *Helicobacter pylori*-positive gastric cancer tissues. miR-143-3p targets AKT2,

which induced cell apoptosis and negatively regulated tumor growth, migration, and invasion. Bacterial pathogens have evolved the ability to regulate host miRNAs to resist autophagy, thereby promoting the survival and reproduction of bacteria. miR-23a-5p was shown to facilitate bacterial survival and inhibit *Mycobacterium tuberculosis*-induced autophagy in macrophages by impacting the TLR2/MyD88/NF- $\kappa$ B pathway (Gu et al., 2017). miRNAs have emerged as important participants in the interactions between host and bacterial pathogens, which suggests an underlying mechanism that miRNAs are transmitted between host and bacteria.

## FECAL miRNA AND PLANT-DERIVED miRNA AS USEFUL TOOLS FOR MAINTAINING GUT HOMEOSTASIS

Actually, a bidirectional relationship exists between gut microbiome and miRNAs. An analysis of miRNA sequencing in human CRC tumor and normal tissues identified 76 differentially expressed miRNAs that are correlated with the abundance of microbes in the tumor microenvironment, including Firmicutes, Bacteroidetes, and Proteobacteria (Yuan et al., 2018). Moloney et al. (2018) proved that the expression of murine miRNAs produced by IECs in feces was influenced by the gut microbiota (Gu et al., 2017). They discovered that the relative abundance of the phyla Bacteroidetes and Firmicutes was significantly correlated with the level of miR-141-3p and phyla Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria were significantly correlated with the level of miR-200a-3p. As a valuable tool, host miRNAs play significant roles in maintaining intestinal homeostasis (Link et al., 2010; Moloney et al., 2018; Yuan et al., 2018). Recent studies have illustrated the mechanism by which the host could foster favorable microbiota *via* fecal miRNA (Liu et al., 2016; Jiayi et al., 2019). An important work from Liu et al. introduced that fecal miRNAs are mainly derived from IECs and Hopx+ cells (Liu et al., 2016). miRNAs present in the feces have the ability to enter bacterial cells and specifically regulate gene transcripts, thereby affecting the growth of bacteria. miRNA mimics synthesized for oral administration could act on gut bacteria. Moreover, they found that IEC miRNA-deficient mice suffered from dysbiosis and that the fecal miRNA transplantation from wild-type mice restored the intestinal bacterial community. Recently, Liu and Weiner (2016) also reported that fecal miR-30d upregulated the expression of a lactase in *Akkermansia muciniphila* and increased this bacterial abundance in the gut, which suppressed multiple sclerosis in mouse model through the expansion of regulatory T cells (Liu and Weiner, 2016).

Dietary intervention is widely known as an important means for the host to maintain intestinal homeostasis (Liu et al., 2019). Another source of miRNAs that the host can utilize is plant-derived miRNAs. These miRNAs from food can also enter bacteria and regulate gene expression. Teng et al. revealed that miRNAs encapsulated in plant-derived exosome-like nanoparticles (ELNs) were taken up by gut

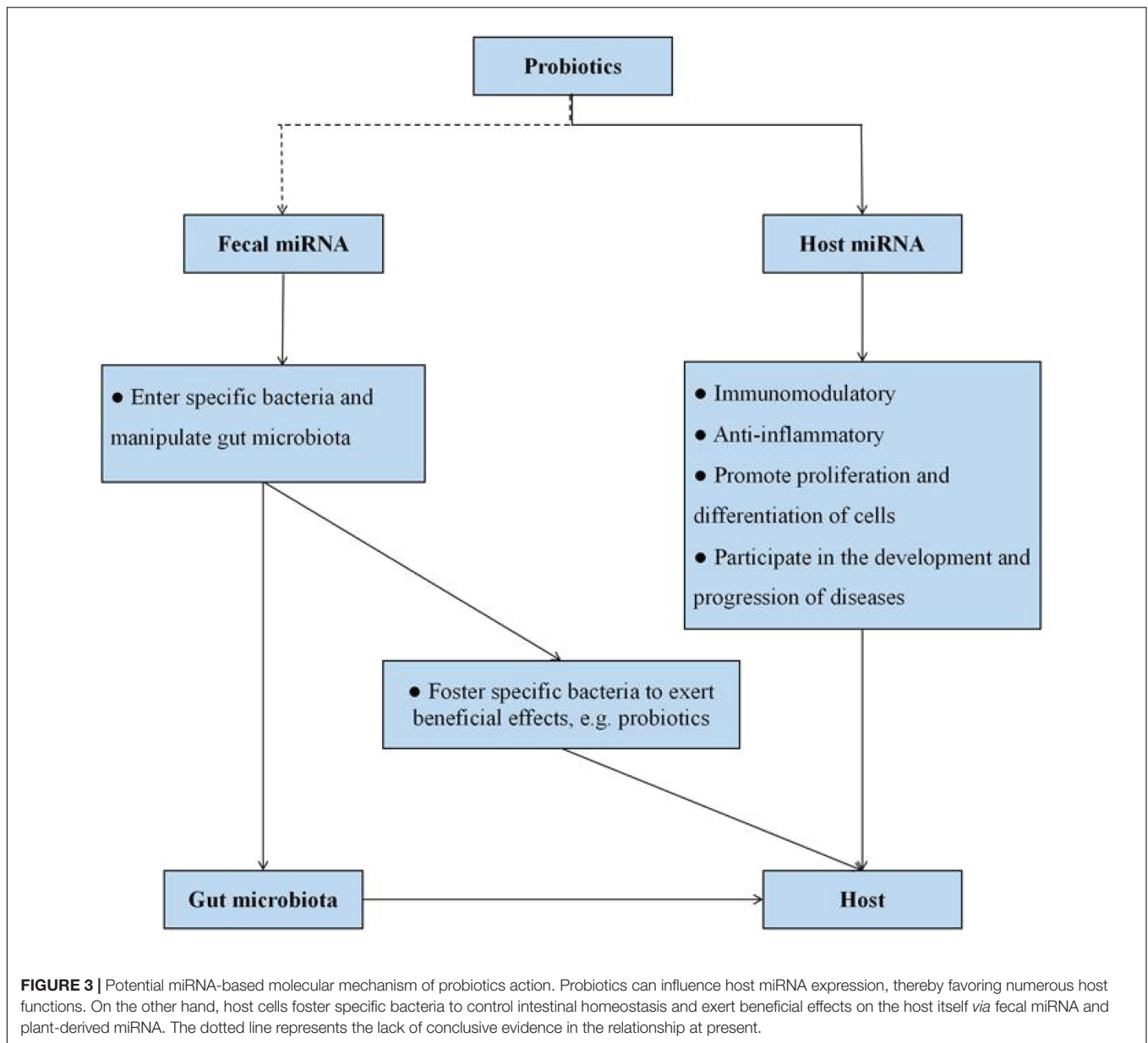
bacteria, subsequently bound to bacterial mRNAs, and modified the composition of gut microbiota (Nagai et al., 2016). The priority for specific gut bacteria to absorb plant-derived ELNs depended on the lipid type of the outer membrane of ELNs. More importantly, miRNAs within ginger ELNs could enter *Lactobacillus rhamnosus* GG (LGG) and induce the IL-22 expression *via* the activation of the AHR pathway to enhance LGG-mediated inhibition of mouse colitis (Spinler et al., 2019). This result indicated that probiotics may be manipulated by miRNA originating from the host or diet.

In summary, these data demonstrated that the fecal miRNA and plant-derived miRNA contribute to the modification of the gut microbiome.

## EXPLORATION OF miRNA-BASED MOLECULAR MECHANISM OF PROBIOTICS ACTION

Host–microbiota interactions play a vital role in intestinal homeostasis, and miRNAs have been considered to be key molecular regulators for mediating such interactions (Behrouzi et al., 2020). The addition of probiotics can also interfere with these interactions and influence the expression of miRNAs (Teng et al., 2018). For instance, miRNAs involved in the alleviation of cecal inflammation are induced by probiotic *Lactobacillus plantarum* Z01 (Rodríguez-Nogales et al., 2018a). In IBD, probiotic EcN 1917 was reported to have the ability to regulate the miRNA expression levels that participated in the inflammatory response in colitic mice (Chen Q. et al., 2017). Similarly, *Bacillus coagulans* R11 may alter the structure of the bacterial community by influencing the host fecal miRNAs (Rodríguez-Nogales et al., 2018b). The ability to regulate miRNA expression by probiotics is of great significance for maintaining the intestinal microenvironment homeostasis. Notably, there is a highly complex relationship between miRNAs and intestinal diseases. However, few reports are available about the roles of miRNAs in shaping the gut microbiota as a therapy of diseases. Moreover, the capacity of the host to regulate gut microbiota in a miRNA-dependent manner remains poorly understood and may even be restricted. Considering that a health benefit was delivered to the host *via* the ingestion of probiotics, the effects of miRNAs may be strengthened by these beneficial microorganisms.

As mentioned above, miRNAs have emerged as important mediators of interactions between host and gut microbiota. Furthermore, probiotics have the ability to modulate miRNA expression levels, and we speculated that the potential mechanism of probiotics acting on the host may be associated with the modification of miRNAs (Figures 1, 3). Probiotics drive intestinal cells to produce miRNAs with important regulatory functions (such as intestinal anti-inflammatory effects) to act on host cells. On the other hand, probiotics impact the releases of fecal miRNAs from IECs, thereby prompting fecal miRNAs to penetrate into specific bacteria and regulate gene expression, with consequences for restoring the “signature” of gut microbiota.



Additionally, side effects of probiotics should not be ignored. Although probiotics are widely used and have considerable potential as preventive or therapeutic options against various gastrointestinal disorders, there are still a few reports indicating the potentially negative effects of probiotics. In fact, the reason for these conflicting clinical results is that the health benefits provided by probiotics to the host depend on many factors, including the strains, individuals, types of administration, or location within the intestines. At present, there is no sufficient and convincing evidence to demonstrate the mechanism of probiotics resulting in negative consequences in the host. The exact mechanisms of both positive and negative effects of probiotics should be further investigated and perfected. Here, this review aimed to open up a new direction for studying the molecular pathways involved in the probiotic mode of

action. More explorations and evidence for the research about elucidating the probiotic mechanisms of action are desirable.

## FUTURE PERSPECTIVES

In recent years, significant breakthroughs have been made in miRNA-based research field, especially in regard to the applications that provided opportunities for the treatment of numerous gastrointestinal diseases including CRC, IBD, etc. (Soroosh et al., 2018; Konno et al., 2019; Tian et al., 2019; Xing et al., 2019). Notably, a single miRNA can target multiple mRNAs, and one mRNA can become the target of numerous miRNAs. A wide range of miRNAs from mammalian cells constitute a complex regulatory network. In this context, it is particularly



important to clarify the real targets with therapeutic effects. They will be valuable tools for the treatment and intervention of patients with various diseases. miRNA-based therapeutics are able to deliver miRNA mimics or anti-miRs to target tissues and target cells through advanced technologies. Several pathways have shown promise to enable this strategy to become a clinical reality. Simultaneously, the administration of fecal miRNA mimics or anti-miRs *in vivo* makes manipulation of the gut microbiota feasible. However, this concept is still relatively novel in the field, and the investigation of manipulating bacterial communities has just begun. Growing valuable insights will promote the cross-kingdom communication between host and gut microorganism to become a subject of intense exploration.

To date, accumulating evidence supported that miRNAs play central roles in mediating host–microbe interactions and can be used as biomarkers of intestinal and microbiota healthiness. Considering that probiotics are likely to be the regulators or amplifiers of miRNA expression levels, we believe that miRNA may be an important part of the molecular mechanism underlying how probiotics maintain gut homeostasis. In this point, the probiotics–miRNA–host/gut microbiota axis can serve as a new direction for the next phase of research but

with the caveat that this molecular mechanism of probiotics remains to be fully understood. Further work is needed to delineate the precise mechanism of how probiotics control miRNA expression levels and to obtain more knowledge about subsequently how these prominently expressed miRNAs mediate host–microbe interactions.

## AUTHOR CONTRIBUTIONS

YZh, YZe, and XN contributed to the topic conception. YZh wrote the main manuscript text. YZe designed the figures. YZh and MZ revised the manuscript. All authors read and approved the final manuscript.

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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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