

### **EXPLORING THE POTENTIAL OF PROBIOTICS AND FECAL MICROBIOTA IN MAINTAINING A HEALTHY GUT MICROBIOTA**

#### **ABSTRACT**

Probiotics are live microorganisms that offer numerous health benefits, particularly in maintaining gut health and reducing the incidence of gastrointestinal diseases. They can be found in fermented dairy products, as well as in the form of pills, capsules, powders and sachets. This paper explores the advantages of using commercial probiotics, including alleviating gastrointestinal pain, preventing gastrointestinal disorders and enhancing immunity. Additionally, probiotics are associated with other axis systems; including gut-skin, gut-lung, gut-heart and gut-metabolism, further highlighting their significance. It is evident that maintaining a balanced gut microbiota is crucial for overall health and any alteration in its composition can lead to the development of local or systemic diseases. In addition, fecal microbiota transplant has also shown promise in treating gastrointestinal disorders in animals. Therefore, this paper emphasizes the role of probiotics and fecal microbiota transplant in preserving gut health and reducing the occurrence of gastrointestinal diseases.

**Keywords:** microbiota, dysbiosis, probiotics, fecal microbiota transplant, gut health

#### **INTRODUCTION**

The term "microbiota" (formerly known as "microflora") refers to communities of bacteria found on mucosal surfaces, with or without microorganisms in the surrounding environment, as well as on other areas of the body like the skin. The gut microbiota, gut microbiome, or gut flora encompass a diverse collection of microorganisms, including bacteria, archaea, fungi and viruses, residing in the digestive tracts of animals. These microorganisms inhabit the gastrointestinal system and contribute to its overall ecosystem [16]. The gut microbiota plays crucial roles in preserving the well-being of the host by supporting host cell differentiation, safeguarding against pathogen colonization and influencing the immune system [7]. Bacterial byproducts or metabolites (short-chain fatty acids (SCFAs), organic salts, amines, alkaloids) can enter the bloodstream and engage in intricate physiological and biochemical processes at various locations, such as interfering with nerve signal transmission and hormone secretion [6]. The presence and composition of gut microbiota play a crucial role in defending against harmful pathogens and facilitating various metabolic processes [14]. The composition and function of gut microbiota can be influenced and altered by factors like antibiotic usage, age, changes in diet, invasion by pathogens, pregnancy, living environment and metabolic disorders [12,13]. When

the gut microbiota is altered, it leads to the proliferation of harmful pathogens and a decrease in diversity of beneficial bacteria, it is referred to as intestinal dysbiosis [13]. During intestinal dysbiosis, both pathogens, which are bacteria capable of harming the host through virulence factors and pathobionts, which are normally harmless bacteria that can become detrimental under specific conditions, experience an increase in their population. This abundance of pathogens and pathobionts disrupts the host's homeostatic and metabolic processes [4]. During a state of dysbiosis, pathogenic bacteria generate inflammatory metabolites, such as proinflammatory compounds, detrimental secondary bile acids like deoxycholic and lithocholic acid, as well as hydrogen sulfide. These substances collectively contribute to the worsening of inflammatory conditions in the gut epithelium [17]. The modified gut microbiota can engage in communication and interaction with the immune system via the release of these detrimental metabolites. As a result, there is an increase in the population of proinflammatory cells, cytokines and metabolites that enter the bloodstream. These substances then reach distant organs such as the brain, lungs, heart and skin, where they contribute to the inflammatory conditions of these organs [13]. There is now strong evidence supporting the crucial role of the gut microbiota in either promoting or alleviating diseases in organs beyond the intestinal tract. The gut microbiota can serve as an alternative mechanism for exacerbating inflammation or improving symptoms in these specific organs.

### **Probiotics and Gut Health**

Probiotics are live microorganisms that, when administered in adequate amounts, confer a health benefit on the host [15]. Probiotic agents commonly used include organisms belonging to the *Lactobacillus* or *Bifidobacterium* genera. However, other organisms such as *Escherichia coli*, *Bacillus subtilis*, *Saccharomyces boulardii* and *Enterococcus faecium* are also utilized as probiotics, among others [19] (Figure 1). They are commonly used to alter the composition of the intestinal microbiota and influence the immune response of the host. Probiotics work in different ways, such as producing substances that fight against harmful microorganisms, helping beneficial bacteria grow, competing with harmful bacteria in the gut, and influencing the immune system. Probiotics are believed to provide benefits through different mechanisms, including the production of antimicrobial peptides, promotion of the growth of beneficial native microorganisms, competition for colonization sites on the intestinal lining and modulation of immune functions [18], produce various antimicrobial substances, for example fatty acids, lactic acid and acetic acid [20] and/or up-regulation of various metabolites [21]. In simple terms, probiotics have the potential to alter the gut bacteria and influence the immune system. However, it is important to note that there is currently a lack of sufficient scientific evidence to substantiate their benefits for various conditions.

### **Fecal microbiota transplantation**

Fecal microbiota transplant is a procedure that involves the transfer of fecal material from a healthy donor to a recipient's gastrointestinal tract (GIT). The purpose of the transplant is to introduce a diverse and healthy community of bacteria and microorganisms into the recipient's gut, with the aim of restoring or improving the balance of their gut microbiota [10]. Fecal transplants have primarily been used to treat conditions such as *C. difficile* infection, which is characterized by severe recurrent diarrhea and is often resistant to antibiotics. The process typically involves a healthy donor providing a stool sample, which is then processed to isolate the fecal microbes [2]. These microbes are usually transferred to the recipient through various administration methods, including colonoscopy, enema, or oral capsules [1,22].

Fecal Microbiota Transplant (FMT) has also shown promise in treating gastrointestinal disorders in animals. Similar to humans, animals can experience imbalances in their gut microbiota, leading to conditions such as diarrhea, inflammatory bowel disease and antibiotic-associated diarrhea [8]. The goal of FMT is to introduce a healthy and diverse community of microorganisms, restoring the balance of the recipient's gut microbiota and improving their gastrointestinal health. Studies have demonstrated the effectiveness of FMT, particularly in cases of enteropathogenic infections and antibiotic-associated diarrhea in various animal species [5]. The potential mechanisms of FMT include competitive niche exclusion and the production of antimicrobials (Figure 2). In competitive niche exclusion, certain strains of fecal donors may outcompete the pathogenic strains present in the recipient's intestines by successfully occupying the same niches. By doing so, the donor fecal material displaces the resident microbial communities of the recipient [11]. Another mechanism is the production of antimicrobials, which can be seen as a competition-based strategy as well. In this mechanism, the donor microbiota produces antimicrobial substances that inhibit the growth and survival of pathogenic microorganisms in the recipient's gut. This competition between the antimicrobial-producing donor strains and the pathogenic strains helps restore a healthier microbial balance in the recipient's gut [3]. The use of antibiotics leads to a reduction in the diversity of the gut microbiome, further disrupting its balance. This disruption creates an opportunity for pathogenic bacteria like *Clostridial difficile* to colonize the gut. Paradoxically, the treatment for *C. difficile* infection often involves the use of antibiotics like metronidazole. While these antibiotics can eliminate *Clostridial difficile*, but spores of clostridia may persist in the gut. This not only increases the risk of recurrence of infection, but also poses a threat of contamination in soil, food and water through feces. Restoring a healthy gut microbiota can be therefore achieved by transferring fecal bacteria from a healthy donor into the gastrointestinal tract of the patient.

While FMT holds promise for treating animal gastrointestinal disorders, further research is necessary to establish standardized protocols, determine optimal donor selection and evaluate long-term effects.

## CONCLUSION

This paper presents a comprehensive overview of the significance of probiotics and fecal transplantation in preserving gut health. Recognizing the significance of probiotics in different axis systems and their influence on overall well-being, researchers and healthcare experts can explore their potential as therapeutic interventions for various conditions. However, additional research is required to unravel the mechanisms of action and optimize the utilization of probiotics and fecal transplant to maximize their advantages in enhancing gut health and preventing neurodegenerative disorders.

## REFERENCES

- [1] Allegretti JR, Korzenik JR, Hamilton MJ. Fecal microbiota transplantation via colonoscopy for recurrent *C. difficile* Infection. *J Vis Exp*. 2014 Dec 8;(94):52154.
- [2] Baunwall SMD, Lee MM, Eriksen MK, Mullish BH, Marchesi JR, Dahlerup JF, Hvas CL. Faecal microbiota transplantation for recurrent *Clostridioides difficile* infection: An updated systematic review and meta-analysis. *EClinicalMedicine*. 2020 Nov 23;29-30:100642.
- [3] Baktash, A.; Terveer, E.M.; Zwartink, R.D.; Hornung, B.V.H.; Corver, J.; Kuijper, E.J.; Smits, W.K. Mechanistic Insights in the Success of Fecal Microbiota Transplants for the Treatment of *Clostridium difficile* Infections. *Front. Microbiol*. 2018, 9, 1242.
- [4] Casadevall, A.; Pirofski, L.A. Host-pathogen interactions: Redefining the basic concepts of virulence and pathogenicity. *Infect. Immun*. 1999, 67, 3703–3713
- [5] Chaitman J, Jergens AE, Gaschen F, Garcia-Mazcorro JF, Marks SL, Marroquin-Cardona AG, Richter K, Rossi G, Suchodolski JS, Weese JS. Commentary on key aspects of fecal microbiota transplantation in small animal practice. *Vet Med (Auckl)*. 2016 May 31;7:71-74.
- [6] Festi, D. et al. Gut microbiota and metabolic syndrome. *World J. Gastroenterol*. 20(43), 16079–16094. <https://doi.org/10.3748/wjg.v20.i43.16079> (2014).
- [7] Gershuni, V. M. & Friedman, E. S. The microbiome-host interaction as a potential driver of anastomotic leak. *Curr. Gastroenterol. Rep*. 21(1), 4 (2019).
- [8] Honneffer JB, Minamoto Y, Suchodolski JS. Microbiota alterations in acute and chronic gastrointestinal inflammation of cats and dogs. *World J Gastroenterol*. 2014;20(44):16489–16497.
- [9] Juul FE, Garborg K, Bretthauer M, Skudal H, Øines MN, Wiig H, Rose Ø, Seip B, Lamont JT, Midtvedt T, Valeur J, Kalager M, Holme Ø, Helsingen L, Løberg M, Adami HO. Fecal Microbiota Transplantation for Primary *Clostridium difficile* Infection. *N Engl J Med*. 2018 Jun 28;378(26):2535-2536. doi: 10.1056/NEJMc1803103. Epub 2018 Jun 2.

- [10] Kelly CR, Kahn S, Kashyap P, et al. Update on fecal microbiota transplantation 2015: indications, methodologies, mechanisms and outlook. *Gastroenterology*. 2015;149(1):223–237.
- [11] Kelly, C.R.; Khoruts, A.; Staley, C.; Sadowsky, M.J.; Abd, M.; Alani, M.; Bakow, B.B.; Curran, P.; McKenney, M.J.; Tisch, N.A.; et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridial difficile Infection. *Ann. Intern. Med.* 2016, 165, 609–616.
- [12] Lehtimäki, J.; Sinkko, H.; Hielm-Björkman, A.; Laatikainen, T.; Ruokolainen, L.; Lohi, H. Simultaneous allergic traits in dogs and their owners are associated with living environment, lifestyle and microbial exposures. *Sci. Rep.* 2020, 10, 21954.
- [13] Levy, M.; Kolodziejczyk, A.A.; Thaiss, C.A.; Elinav, E. Dysbiosis and the immune system. *Nat. Rev. Immunol.* 2017, 17, 219–232
- [14] Li, Q.; Larouche-Lebel, E.; Loughran, K.A.; Huh, T.P.; Suchodolski, J.S.; Oyama, M.A. Gut Dysbiosis and Its Associations with Gut Microbiota-Derived Metabolites in Dogs with Myxomatous Mitral Valve Disease. *mSystems* 2021, 6, e00111-21.
- [15] Mary Ellen Sanders, Probiotics: Definition, Sources, Selection, and Uses, *Clinical Infectious Diseases*, Volume 46, Issue Supplement\_2, February 2008, Pages S58–S61
- [16] Moszak, M; Szulińska, M; Bogdański, P (15 April 2020). "You Are What You Eat-The Relationship between Diet, Microbiota, and Metabolic Disorders-A Review". *Nutrients*. 12 (4): 1096.
- [17] Rath, S.; Rud, T.; Karch, A.; Pieper, D.H.; Vital, M. Pathogenic functions of host microbiota. *Microbiome* 2018, 6, 174.
- [18] Schmitz S, Suchodolski J. Understanding the canine intestinal microbiota and its modification by pro-, pre- and synbiotics - what is the evidence? *Vet Med Sci.* 2016 Jan 11;2(2):71-94.
- [19] Sullivan, G. Thorton, G. C. O'Sullivan, and J. K. Collins, "Probiotic bacteria: myth or reality?" *Trends in Food Science & Technology*, vol. 3, pp. 309–314, 1992.
- [20] Saarela M., Mogensen G., Fonden R., M€atto J. & Mattila- €Sandholm T. (2000) Probiotic bacteria: safety, functional and technological properties. *Journal of Biotechnology* 84, 197–21
- [21] Soo I., Madsen K.L., Tejpar Q., Sydora B.C., Sherbaniuk R., Cinque B. et al. (2008) VSL#3 probiotic upregulates intestinal mucosal alkaline sphingomyelinase and reduces inflammation. *Canadian Journal of Gastroenterology* 22, 237–2

[22] Youngster I, Russell GH, Pindar C, Ziv-Baran T, Sauk J, Hohmann EL. Oral, capsulized, frozen fecal microbiota transplantation for relapsing *Clostridium difficile* infection. *JAMA*. 2014 Nov 5;312(17):1772-8. Erratum in: *JAMA*. 2015 Feb 17;313(7):729.

## Figures

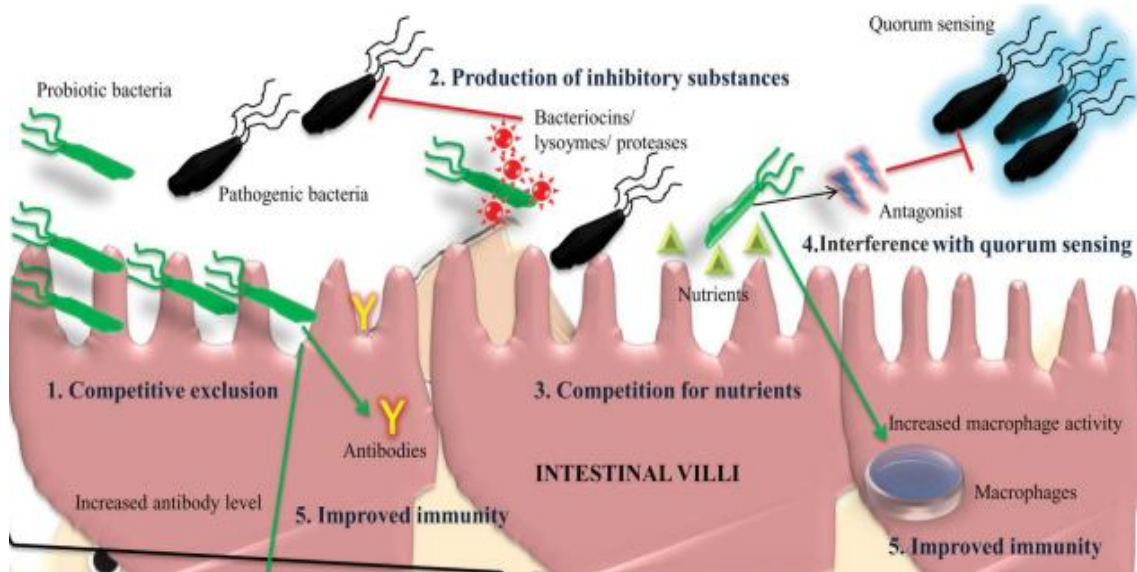


Figure 1. Mechanism of action of probiotics; immune modulation, competition with pathogens, enhancement of barrier function, production of antimicrobial compounds and modulation of microbial composition and activity.

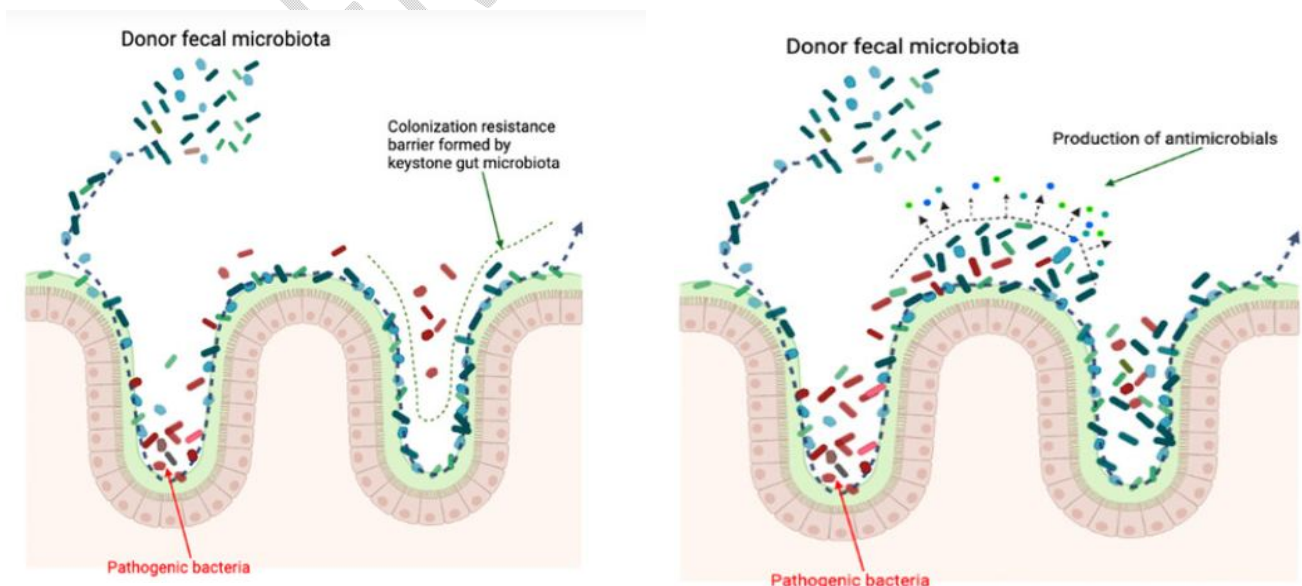


Figure 2. Potential mechanisms of Fecal Microbiota Transplantation (FMT); Competitive Inhibition and production of Antimicrobials

UNDER PEER REVIEW