ECRONICON OPEN ACCESS

EC GASTROENTEROLOGY AND DIGESTIVE SYSTEM

Research Article

Colorectal Cancer and Microbiome Link-Up

Álvaro Zamudio Tiburcio[1]*, Héctor Bermúdez Ruiz[2] and Silverio Alonso López[3]

[1]Department of Gastroenterology, Intestinal Microbiota Transplantation Medical Specialties Naples Unit, Mexico

[2]Endoscopy Service, Oncology Hospital, National Medical Center, XXI Century, Mexican Social Security Institute, Hospital Trinidad, Mexico City, Mexico

[3]Department of Urologist, Chairman Medical Specialties Naples in Mexico City, Mexico

***Corresponding Author:** Álvaro Zamudio Tiburcio, Department of Gastroenterology, Intestinal Microbiota Transplantation Medical Specialties Naples Unit, Mexico.

Received: October 26, 2022; **Published:** September 28, 2022

Abstract

Due to the multiple coincidences that we have observed in the relationship between colorectal cancer and the microbiome, we analyzed numerous articles, in order to pour out and consider all those positive aspects that this transcendental interrelationship has, most of the times beneficial for the carrier patient of cancer pathology. We consider what the microbiome is importance it currently has, not only in the management of colorectal cancer, but also in other eventualities. We take a deep look at how this important and forgotten organ, the microbiome, acts in malignant processes, especially in colorectal cancer, through specific functions that this much-cited new organ has. We see how the action of the microbiota is reinforced, by using probiotics, prebiotics and synbiotics, for a variable time. As well as its mechanism of action, without neglecting its negative effects. Finally, we consider the microbiota administration methodology, through the different current procedures and which of them is more useful and less harmful. We conclude that adding the microbiota to conventional treatments is not only useful, but also necessary in the management of colorectal cancer.

Keywords: *Colorectal Cancer (CRC); Microbiome (Micb); Microbiota (Mic); Probiotic, Prebiotics and Synbiotics (Biot); Intestinal Microbiota Transplantation (IMT)*

Introduction

Since Joshua Lederberg created the term Microbiome (Micb) on April 1, 2001, pointing to it as the ecological community of commensal, symbiotic and pathogenic microorganisms that share our body space and have been ignored as determinants of health or disease, more than 100,000 articles about it, determining the importance of this new super organ [1]. It is made up of more than 1,000 different species of microorganisms and includes 100 trillion bacteria, quadrillions of viruses, archaea, parasites and fungi. *Bacteroidetes* and *Firmicutes* are the most abundant bacteria in the human intestine. There are other bacterial species that belong mostly to members of the *Actinobacteria, Proteobacteria, Fusobacteria, Cyanobacteria, Verrucomicrobia* and *Verrucomicrobia* phyla [2]. The microbiota (Mic), intestinal is the most important component of the Mic (refers to the microorganisms found within a specific environment) in greater numbers in the colon and rectum (Extraordinary diversity of genomes) [3]. Currently the Micb can be synthesized like microorganisms and their genes.

The risk of colorectal cancer (CRC) be increased by changing the environment of the Micb and altering the composition of the intestinal Mic, a state called intestinal dysbiosis [4]. The most important thing about this super-organ is the number of functions it carries out, ranging from immunological to metabolic, many of which have an impact on preventing cancers from proliferating, just as they do with CRC. Emphasizing neurological development, through the brain-gut axis [5]. Below are the different functions of the Micb, we underline them and then we analyze those that have to do with the CRC.

Microbiome functions:

1. Absorbs and produces vitamins
2. Adjusts the immune system
3. Provides substrates for enterocytes, preventing diseases by opportunistic pathogens
4. Helps assimilate nutrients
5. Collaborates with neurological function, through the gut-brain axis
6. Confers resistance to inflammatory processes
7. Digests certain food compounds
8. Avoid dying from skin and mucosal diseases, caused by opportunistic pathogens
9. Maintains intestinal balance
10. Keeps the intestinal barrier intact
11. Multiplies the ability to digest carbohydrates
12. Grants resistance to infections
13. Prevents the development of neoplasms
14. Produces anti-inflammatories
15. Promotes endocrine functions
16. Protect life
17. Regulates the energy balance
18. Regulates metabolism
19. It is a source of folates (Vitamin B-9)
20. Metabolic contributions to short chain fatty acids, such as butyrate

21. Intervenes in the decomposition of food carcinogens
22. Keeps the intestine in a state of controlled inflammation
23. Compete for the nutrients available in ecological niches
24. It is involved in the formation of memory mechanisms of systemic immunity, such as oral tolerance
25. Promotes the development and homeostasis of the immune system
26. Secret small cationic antimicrobial peptides (Defensins). Key mechanism for host defense
27. Preserves the viability of stem cells
28. Secrete antimicrobial substances (bacteriocins).

Function number 2. Adjusts the immune system. It seems to play a significant role in the immune balance and the prevention of inflammation, maintaining metabolic homeostasis and determining the appearance and development of pathologies such as cancer, allergies, intestinal and cardiovascular diseases and obesity. Intestinal Mic provides essential health benefits to its host, particularly by regulating immune homeostasis. Furthermore, it has recently become obvious that disturbances of these gut microbial communities can cause immune dysregulation, leading to autoimmune disorders [6].

Function number 3. Provides substrates for enterocytes, preventing diseases due to opportunistic pathogens. The indigenous microorganisms co-evolved with the host in a symbiotic relationship. In addition to metabolic benefits, symbiotic bacteria provide the host with various functions that promote immune homeostasis, immune responses, and protection against pathogen colonization [7].

Function number 5. Collaborates with the neurological function, through the gut-brain axis. The intestinal Mic is home to approximately 100 trillion microorganisms, which are linked to health and disease, including central nervous system malignancies; although this emerging evidence should be better contextualized [8].

Function number 6. Confers resistance to inflammatory processes. There are effects of Micb on innate and adaptive immunological people from epithelial cells and antigen presenting cells, to innate lymphoid cells and regulatory T cells [9].

Function number 9. Maintains intestinal balance. The maintenance of the oxygen balance, the production of short-chain fatty acids (SCFA) and the maintenance of intestinal health generate balance in the intestine. The most important SCFAs is butyric, which has an anti-inflammatory effect, helps in the synthesis of various neurotransmitters and modulates the gut-microbiota-brain axis [10].

Function number 10. Keeps the intestinal barrier intact. The composition of intestinal Mic affects the development of the immune system and modulates immune mediators, which in turn affect the intestinal barrier [11].

Function number 13. Prevents the development of neoplasms. Lymphocytes play an important role in the reaction to bacterial colonization, mainly by eliciting a safe reaction to obstruction or initiation. Most of the immunologically occupying cells take place in the invulnerable framework of the mucosa and are continuously mobilized by dendritic cells or other antigen-introducing cells that collect intestinal samples. Therefore, Micb is a key contributor to the development of lymphomas and specific alterations, its composition mitigates the risk [12].

Function number 14. Produces anti-inflammatories. Metabolic processes in bacteria, including some SCFAs, may play a role in the inhibition of inflammatory processes [13].

Function number 18. Regulates metabolism. Intestinal Micb can exert a profound influence on host metabolism by altering the composition of the bile acid pool, by altering bile acid synthesis and reuptake [14].

Function number 19. It is a source of folates (Vitamin B-9). Antifolate chemotherapy agents, such as methotrexate and fluorouracil, reduce the proliferation of neoplastic cells by inhibiting DNA synthesis [15].

Function number 20. Metabolic contributions to short chain fatty acids, such as butyrate. SCFAs, the main metabolites produced in the colon by bacterial fermentation, are considered to play a key role in neuroimmunoendocrine regulation [16].

Function number 21. Intervenes in the decomposition of food carcinogens. Lung dysbiosis and/or gut microbiome dysbiosis are related to dietary patterns [17].

Function number 22. It keeps the intestine in a state of controlled inflammation. Alterations in intestinal Mic, arrests in the intestinal barrier and changes in metabolites are evidence of the relationship between intestinal Mic and intestinal inflammation [18].

Function number 23. Competes for the nutrients available in the ecological niches. Rolf Freter proposed the nutrient niche theory, in which he proposes that a microorganism can only live if it is able to use one or several niches and in this way harmful microbes will be prevented from settling in them, developing diseases, such as CRC [19].

Function number 24. It is involved in the formation of memory mechanisms of systemic immunity, such as oral tolerance. This function is performed by the Micr through complex mechanisms, using the training and development of the main components of the host's innate and adaptive immune system [20].

Function number 25. Promotes the development and homeostasis of the immune system. Intestinal Mic regulates adaptive and innate immune homeostasis, which can affect the development of autoimmune diseases, not only intestinal but also systemic [21].

Function number 26. Secretes small cationic antimicrobial peptides (defensin). Host defense peptides have been implicated as antifungal therapy [22].

Function number 27. Preserves the viability of stem cells. The importance of intestinal Micr in diseases caused by stem cells has been pointed out [23].

Function number 28. It can secrete antimicrobial substances (bacteriocin). The antagonism is often due to the production of antimicrobials versus other organisms that occupy the same environmental niche [24].

Probiotics, prebiotics and synbiotics (Biot)

Probiotics: Live microorganisms that, when administered in adequate quantity, confer health benefits to the host. They are effective in the prevention and treatment of many intestinal diseases such as inflammatory bowel disease, diarrhea, irritable bowel syndrome, gluten intolerance, gastroenteritis, *Helicobacter pylori* infection and CRC; even though further studies are suggested [25]. In relation to CRC, the use of probiotics may be beneficial. Classic examples are the use of *Lactobacillus, Bifidobacterium, Enterococcus* and *Lactococcus*. And not only that, the use of preventive probiotics tends to promote a balanced Mic, as well as sufficient immunological surveillance, to prevent CRC [26]. Probiotics play a crucial role in modulating the immune response, and it is worth remembering that 80% of immune cells are

associated with the intestinal membrane [27]. One of the reasons for the increased incidence of CRC is the prevalence of chronic inflammatory disorders of the gastrointestinal epithelium, mainly represented by ulcerative colitis and Crohn's disease [28]. Recently, probiotic-derived factors, including proteins and other molecules released from live probiotics, have been.

Prebiotics: They are indigestible food ingredients (by the host) that have a beneficial effect through their selective metabolism in the intestinal tract. Current studies have suggested that prebiotics also have a protective effect against colon carcinogenesis, due to the production of SCFA after fermentation by intestinal Mic and the alteration of gene expression in tumor cells [29]. These ingredients must not be hydrolyzed or absorbed in the upper gastrointestinal tract and be selective for one or a limited number of potentially beneficial bacteria, such as those that reside in the colon. Prebiotics, being non-digestible, have been associated with improved intestinal function and metabolism of the distal colon, including reduced risk of CRC. Fewer tumors have been observed in rats treated with carcinogens when fed cereal bran [30]. Most of the protective effects of prebiotics on CRC have been emphasized in those containing Oligo-fructose, such as fructo-oligo-saccharides and inulin [31]. Prebiotics, which can help maintain gut microbial homeostasis and mitigate dysbiosis, could be beneficial in preventing inflammation and CRC. These nutrients can hinder the effects of dysbiosis by promoting the growth of beneficial bacteria involved in SCFA production, anti-inflammatory immunity, intestinal epithelial barrier maintenance, pro-apoptotic mechanisms and other cellular mechanisms [32].

Synbiotics: Mixture of probiotics and prebiotics that contain live microorganisms and substrates used selectively by host microorganisms that confer health benefits. They exert a synergistic effect in improving colon carcinogenesis [33]. They theoretically have a synergistic protective effect against the development and progression of CRC through mechanisms that include decreased intestinal inflammation, enhanced immune function and antitumor activity, binding to potential food carcinogens and reduction of bacterial enzymes that hydrolyze pre-carcinogenic compounds [34]. Furthermore, the importance of tailor-made Biot in cancer treatment by bio-anti-mutagenic and de-mutagenic activity has been elaborated [35]. Recently, synbiotics have been proposed as a new preventive and therapeutic option. Epidemiological studies have indicated that the consumption of large amounts of fermented milk products containing *Lactobacilli* or *Bifidobacterium* is associated with a lower incidence of CRC [36]. Although there are detractors, about it. Among the mechanisms that have been suggested: Alteration of the metabolic activities of the intestinal Mic, alteration of the physicochemical conditions in the colon, union of potential carcinogens, production of SCFA, production of antitumor or anti-mutagenic compounds, elevation of the capacity of the hosts and immune response that alters host physiology.

Microbiota transplant: Fecal microbiota transplantation, bacteriotherapy, or gut microbiota transplantation (IMT), is the infusion or grafting of filtered liquid feces from a healthy donor into the intestine of a recipient to cure a specific disease. The IMT method has been extensively reviewed, including comparing it with the Biot effect [37]. An imbalance in intestinal Mic promotes the progression of colorectal carcinogenesis through multiple mechanisms, including inflammation, activation of carcinogens and tumorigenic pathways, as well as host DNA damage and TP53 mutation, most frequently. To improve the above, TMI has been used, which is one of the most recent processes in the therapeutic armamentarium. And modulator of the intestinal Mic; even though more studies are needed to evaluate the long-term effects. The abundance of *Fusobacterium nucleatum, Bacteroides fragilis, Escherichia coli, Enterococcus faecalis*, *Helicobacter hepaticus, Peptostreptococcus anaerobius, Helicobacter pylori, Streptococcus bovis* and *Porphyromonas gingivalis* has been associated with the development of CRC. Each individual has their own Mic, which is related to lifestyle, antibiotic intake, diet and personal hygiene. There are limited data on the use of fecal microbiota transplantation in the treatment of CRC. However, there are studies that have confirmed the impact of TMI, for example, on the immune response. Further trials should focus on evaluating the efficacy of fecal microbiota transplantation, for example, in reducing the severity gastrointestinal side effects associated with cancer treatment. In addition, there is a clear need to assess the safety of fecal microbiota transplantation with respect to its long-term effects and clinical outcome of CRC patients [38]. One of the experts in fecal microbiota transplantation, Dr. Thomas Julius Borody, states: "The fecal microbiota transplantation is one of the most effective methods to manipulate the gastrointestinal Micb" [39]. Intestinal dysbiosis appears in numerous conditions, including CRC [40].

Administration route: It varies between institutions and can be nasoduodenal, trans-colonic or by enema. Some patients may not find it pleasant to have stool through the upper intestine; the occasional complication such as vomiting would be avoided by lower gastro-intestinal infusion and the infusion of Mic from the lower colon into the upper gastro-intestinal tract may disturb the local microbial balance. Colonoscopy offers the advantage of allowing direct evaluation of the colonic mucosa, diagnosing coexisting pathologies and treating them. The use of bowel preparation can help remove the abnormal Mic from the host and facilitate implantation of the donor Mic. Enema administration is effective, cheap, safe and carries less procedural or institutional admission costs [41].

Potential complications: IMT can be safe and well tolerated with few serious adverse events, although it is often given to patients with significant comorbidities [42]. Commonly reported immediate adverse events after IMT include abdominal discomfort, bloating, flatulence, diarrhea, constipation, vomiting and transient fever [43]. Most of these symptoms are self-limited and disappear within 2 days after transplant. However, little information is available on long-term immunological effects, including the development of latent infections. In addition, diseases or conditions related to changes in intestinal Mic may occur, such as obesity, diabetes, atherosclerosis, IBD [44]. Although little has been said about the usefulness of the Biot, after the IMT. It is a fact that they can protect even more from a bad evolution, as occurs in inflammatory bowel disease, where they are provided a month or more after the transplant and improve the barrier function of the intestinal mucosa, the function of the immune system and they promote the secretion of anti-inflammatory factors, inhibiting the growth of harmful bacteria in the intestine [45]. However, the same Biot are not exempt from complications, since they can appear with probiotics: allergic reactions, mild gastric discomfort, diarrhea, flatulence and occasionally infections [46]. With prebiotics: Abdominal discomfort, abdominal swelling and flatulence, while the patient adapts. If the patient has irritable bowel syndrome, it´s recommended to be very careful [47]. Finally, with synbiotics, the following may appear: Alterations similar to the use of probiotics or prebiotics, since they are a mixture of both [48]. Future: Richards K and her group encapsulated three different *E. coli* phyla, using membrane emulsification processes [49]. The ability to safely administer IMT to patients will depend on standardized and highly specialized laboratories for stool preparation. Next-generation Mic-based drugs are likely to become the preferred option. We can alter the Micb through diet, so it should be insisted on. Blocking a specific bacterial enzyme could be healthy.

Conclusion [50-52]

- Laboratories will require expertise in collecting and managing medical and lifestyle data from donors; proper sample collection, preparation and storage procedures; careful selection of donor material and standardized methods for reporting adverse events. Well-designed clinical trials of IMT will help validate the role of Mic in disease and identify the specific bacteria or metabolites responsible for this effect. These trials could also guide the development of bacteriotherapy.
- If a disease is driven by a single microorganism, vaccination against it could have beneficial effects.
- A strategy that repairs the leak in the intestinal wall could be effective.
- Gut Mic will advance asthma research and treatment for the foreseeable future.
- Ultimately, it is conceivable that after any use of antibiotics, oral FMT becomes routine to ecologically conserve our GI Micb.

Conflicts of Interest

The authors declare that do not have affiliation or participation in organizations with financial interests.

Ethical Approval

This report does not contain any study with human or animal subjects carried out by the authors.

Informed Consent

The authors obtained informed written consent from the patients, in order to develop this article.

Bibliography

1. Lederberg J and McCray A. "Ome sweet 'omics: -- A genealogical treasury of words". *The Scientist* 15.7 (2001): 8.
2. Thursby E and Juge N. "Introduction to the human gut microbiota". *Biochemical Journal* 474.11 (2017): 1823-1836.
3. Hillman ET., *et al*. "Microbial Ecology along the Gastrointestinal Tract". *Microorganisms in Environmental* 32.4 (2017): 300-313.
4. Martinez JE., *et al*. "Unhealthy Lifestyle and Gut Dysbiosos: A Better Understanding of the Effects of Poor Diet and Nicotine on the Intestinal". *Frontiers in Endocrinology Gut Endocrinology* (2021).
5. Anadure RK., *et al*. "The Gut-brain Axis". February 2019/02/16. In book: API Textbook of Medicine Publisher: API (2019): 1-5.
6. Jung Wu H and Wu E. "The role of gut microbiota in immune homeostasis and autoimmunity". *Gut Microbes* 3.1 (2012): 4-14.
7. Pickard JM., *et al*. "Gut Microbiota: Role in Pathogen Colonization, Immune Responses and Inflammatory Disease". *The Annual Review of Immunology* 279.1 (2017): 70-89.
8. Longsha Liu., *et al*. "Microbiota and the gut-brain-axis: Implications for new therapeutic design in the CNS. EBio Medicine". *Part of the LANCET Discovery Medicine* 77 (2022): 103908.
9. Blander JM., *et al*. "Regulation of inflammation by microbiota interactions with the host". *Nature Immunology* 18.8 (2017): 851-860.
10. Takiishi T., *et al*. "Intestinal barrier and gut microbiota: Shaping our immune responses throughout life". *Tissue Barriers* 5.4 (2017): e1373208.
11. Vacca I. "The microbiota maintains oxygen balance in the gut". *Nature Reviews Microbiology* 15 (2017): 574-575.
12. Mamgain G., *et al*. "The Role of Microbiota in the Development of Cancer Tumour Cells and Lymphoma of B and T Cells". *Cureus* 13.10 (2021): e19047.
13. Bander ZA., *et al*. "The Gut Microbiota and Inflammation: An Overview". *International Journal of Environmental Research and Public Health* 17.20 (2020): 7618.
14. Martin AM., *et al*. "The Influence of the Gut Microbiome on Host Metabolism Through the Regulation of Gut Hormone Release". *Frontiers in Physiology Clinnical and Translational Physiology* (2019).
15. Hubner RA and Houlston RS. "Folate and colorectal cancer prevention". *British Journal of Cancer* 100 (2009): 233-239.
16. Silva YP., *et al*. "The role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication". *Frontiers in Endocrinology Neuroendocrine Science* (2020).

17. Nigro E., *et al*. "Food, Nutrition, Physical Activity and Microbiota: Which Impact on Lung Cancer?" *International Journal of Environmental Research and Public Health* 5 (2021): 2399.

18. Lobionda S., *et al*. "The Role of Gut Microbiota in Intestinal Inflammation with Respect to Diet and Extrinsic Stressors". *Microorganisms* 7.8 (2019): 271.

19. Pereira FC and Berry D. "Microbial nutrient niches in the gut". *Environmental Microbiology* 19.4 (2017): 1366-1378.

20. Zheng D., *et al*. "Interaction between microbiota and immunity in health and disease". *Cell Research* 30.6 (2020): 492-506.

21. Wu HJ and Wu E. "The role of gut microbiota in immune homeostasis and autoimmunity". *Gut Microbes* 3.1 (2012): 4-14.

22. Basso V., *et al*. "Host Defense Peptides as Templates for Antifungal Drug Development". *Journal of Fungi* 6.4 (2020): 241.

23. Staffas A., *et al*. "The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease". *Blood* 129.8 (2017): 927-933.

24. Garcia-Gutierrez E., *et al*. "Gut microbiota as a source of novel antimicrobials". *Gut Microbes* 10.1 (2019): 1-21.

25. Mara CD., *et al*. "Probiotic: effectiveness nutrition in cancer treatment and prevention". *Nutricion Hospitalaria* 33.6 (2016): 1430-1437.

26. Shida K and Nomoto K. "Probiotics as efficient immunopotentiators: Translational role in cancer prevention". *Indian Journal of Medical Research* 138.5 (2013): 808-814.

27. Fields H. "The Gut: Where Bacteria and Immune System Meet. Johns Hopkins". *Medicine* (2015).

28. Kim ER and Chang DK. "Colorectal cancer in inflammatory bowel disease: The risk, pathogenesis, prevention and diagnosis". *World Journal of Gastroenterology* 20.29 (2014): 9872-9881.

29. Liong MT. "Roles of Probiotics and Prebiotics in Colon Cancer Prevention: Postulated Mechanisms and In-vivo Evidence". *International Journal of Molecular Sciences* 9.5 (2008): 854-863.

30. Topping DL and Clifton PM. "Short-chain fatty acids and human colonic functions: roles of resistant starch and nonstarch polysaccharides". *Physiology Reviews* 81 (2001): 1031-1063.

31. Femia AP., *et al*. "Antitumorigenic activity of the prebiotic inulin enriched with oligofructose in combination with the probiotics Lactobacillus rhamnosus and Bifidobacterium lactis on azoxymethane-induced colon carcinogenesis in rats". *Carcinogenesis* 23 (2002): 1953-1960.

32. Mahdavi M., *et al*. "Preventing Colorectal Cancer through Prebiotics". *Microorganisms* 9.6 (2021): 1325.

33. Gavresea F., *et al*. "Beneficial effect of synbiotics on experimental colon cancer in rats". *Turkish Journal of Gastroenterology* 29.4 (2018): 494-501.

34. Raman M., *et al*. "Potential of probiotics, prebiotics and synbiotics for management of colorectal cancer". *Gut Microbes* 4.3 (2013): 181-192.

35. Longoria-García S., *et al*. "Prebiotics, Probiotics, Synbiotics and Functional Foods in Control and Treatment of Type II Diabetes Mellitus and Colorectal Cancer. Probiotics and Prebiotics in Human Nutrition a Health. Edited By Venketeshwer Rao and Leticia Rao". *Intech Open* (2016).

36. Fotiadis CL Stoidis CN., *et al*. "Role of probiotics, prebiotics and synbiotics in chemoprevention for colorectal cancer". *World Journal of Gastroenterology* 14.42 (2008): 6453-457.

37. Kaźmierczak-Siedlecka K., *et al*. "Therapeutic methods of gut microbiota modification in colorectal cancer management – fecal microbiota transplantation, prebiotics, probiotics, and synbiotics". *Gut Microbes* 11.6 (2020): 1518-1530.

38. Dai Z., *et al*. "The role of Microbiota in the development of colorectal cancer". *International Journal of Cancer* 45.8 (2018): 2032-2041.

39. Borody TJ., *et al*. "Fecal microbiota transplantation as a New therapy: from Clostridioides difficile infection to inflammatory bowel disease, irritable bowel syndrome, and colon cancer". *Current Opinion in Pharmacology* 49 (2019): 43-51.

40. Choi HH and Cho YS. "Fecal Microbiota Transplantation, Effectiveness, and Future Perspectives". *Clinical Endoscopy* 49.3 (2016): 257-265.

41. Borody T., *et al*. "Fecal Microbiota Transplantation in ulcerative colitis: review of 24 years experience". *The American Journal of Gastroenterology* 1 (2012): S665.

42. Van Beurden YH., *et al*. "Complications, effectiveness, and long term follow-up of fecal microbiota transfer by nasoduodenal tube for treatment of recurrent Clostridium difficile infection". *United European Gastroenterology Journal* 5.6 (2017): 868-879.

43. Gaonkar P. Safety and Potential Risks with Fecal Microbiota Transplantation (2021).

44. Zhang Z., *et al*. "Impact of Fecal Microbiota Transplantation on Obesity and Metabolic Syndrome-ASystematic Review". *Nutrients* 11.10 (2019): 2291.

45. Shen ZH., *et al*. "Relationship between intestinal microbiota and ulcerative colitis: Mechanisms and clinical application of probiotics and fecal microbiota transplantation". *World Journal of Gastroenterology* 24.1 (2018): 5-14.

46. Doron S and Snydman DR. "Risk and Safety of Probiotics". *Clinical Infectious Diseases* 60.2 (2015): S129-S134.

47. Markowiak P and Śliżewska K. "Effects of Probiotics, Prebiotics, and Synbiotics on Human Health". *Nutrients* 9.9 (2017): 1021.

48. Flesch AG., *et al*. "The Therapeutic Use of Synbiotics". *Arquivos Brasileiros de Cirurgia Digestiva* 27.3 (2014): 206-209.

49. Richards K and Maik DJ. "Microencapsulation of Bacteriophages Using Membrane Emulsification in Different pH-Triggered Controlled Release Formulations for Oral Administration". *Pharmaceuticals* 14.5 (2021).

50. Giles EM., *et al*. "The future of faecal transplants". *Nature Reviews Microbiology* 17 (2019): 719.

51. Rosenbaum JT. "Just another crappy commentary: the future of fecal microbiota transplantation". *Expert Review of Clinical Immunology* 15.10 (2019): 987-989.

52. Kang Y and Cai Y. "Future prospect of faecal microbiota transplantation as a potential therapy in asthma". *Allergologia and Immunopathology* (2021).

Volume 9 Issue 10 October 2022