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Mini Review

Radiation and SARS-CoV-2 effects on the microbiota, immune system and health

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This study aims to review the effects of radiation and SARS-CoV-2 infection on the gut microbiota, and the relationship it forms with the immune system and body axes. The intestinal microbiota is established after birth, reaching its greatest diversity in adulthood. It can be altered by factors which will depend on the host and the microorganisms. This work reviews how radiation and SARS-CoV-2 infection impact the microbiota, along with the connections established with body axes and immune system. The gut microbiota has important implications in health due to its role in multiple metabolic, physiological, and immune functions. The interaction with non-pathogenic microorganisms is beneficial; however, can cause diseases like cancer, obesity, diabetes or intestinal bowel disease. Recently, a direct relationship between microbiota and exposure to radiation in cancer patients, SARS-CoV-2 infection or different distal diseases induced via several corporal axes have been described. Microbiota acts as an independent organ, performing physiological, metabolic and immune functions; being beneficial or harmful to host.

Keywords: Dysbiosis, Ionizing radiation, Covid-19, Immune response, Corporal axes

Introduction

The digestive system is a specialized organ that stretches from the lips to the anus and forms a barrier separating the body from the outside environment. The gut microbiota is considered an open ecosystem, consisting of diverse, metabolically active microbial communities that coexist in a specific time and space, playing an important function in the health of the individual. These bacteria function collectively as a metabolic organ within the body, characterized by its adaptability and rapid capacity for renewal. Their intricate polymicrobial ecosystem interacts with both external and internal environments, playing a crucial role in maintaining health. The intestine, in addition to the functions of absorption and digestion, regulates various metabolic, endocrine, digestive and immune processes. The gut microbiota is characterised by its dense population, diverse composition, and complex interactions, with bacteria being the predominant microbial group present. The changes in microbiota alter the physiological status of the organism. These changes include immunity, growth and development[1].

The acquisition of microorganisms that forms the microbiota and the development of the intestinal barrier are gradual processes that begin after birth. In humans, the maternal microbial flora serves as the initial source of bacterial colonization, which is subsequently modified. This effect is modified by the age, sex, nutritional status, the geographic location, or other environmental factors and other situations less frequent such as stress[1].

Knowledge of microbial ecology, including typing, titles, and sources frequently linked to the stages of development, could facilitate the modification of microbiota composition as a means to avoid infection by other pathogenic microorganisms or to improve nutrition.

The beneficial microorganisms found in the gastrointestinal tract are responsible in preventing the colonization of the intestine by harmful microorganisms. They are closely attached to the

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epithelial cells, creating a protective barrier that acts as the first defense line against pathogens, preventing their direct adhesion or integration into the intestinal mucosa. Additionally, the gut microbiota performs essential functions such as protection, metabolism, and nutrition.

The intestinal microbiota provides several benefits to the host's gut physiology. The enzymatic functions of microorganisms are crucial for digestion and help prevent the colonization of harmful pathogens. Its role is essential in shaping the anatomical, physiological, and immune development of the individual. A balanced microbiota composition is important for the correct development and functioning of the immune system. For the prevention and treatment of diseases, it is important to develop new strategies, which must undoubtedly be based on the understanding of the mechanisms involved in microbiota and immune system interactions[3].

This study aims to review the effects of radiation and SARS-CoV-2 infection on the gut microbiota, and the relationship it forms with the immune system and body axes.

Relationship between microbiota and radiation exposure

Radiation exposure is linked to various diseases and can trigger temporary or persistent pathological processes, and in critical cases, it can lead to the death of the patient[4]. Radiation-induced lesions in gastrointestinal tissue present an urgent medical issue that requires effective treatment[5]. Studies in animal models have shown that *Lactobacillus* reduce the damage induced to the gut epithelium, enhancing crypt survival[6].

The role of microorganisms presents in the intestine and their relationship with radiosensitivity is a relatively new field of research that has attracted considerable attention, however there is limited articles providing detailed information on this topic[7]. Advances in DNA and RNA sequencing technologies in recent years have enhanced researchers' ability to explore the gut microbiota's response to various stimuli[8]. Microorganisms residing in the gastrointestinal tract help to maintain gut homeostasis and to improve the overall health. The general state of these microorganisms has been shown to correlate with radiation response during treatment. It was observed that the microbiome of cancer affected patients undergoing radiotherapy has lower diversity and abundance of bacteria in relation to the microbiome of healthy individuals[9-11].

Furthermore, emerging preclinical studies in mouse models are investigating the connection between the intestinal microbiota and radiation resistance. Cui *et al.*[12] studied the role of circadian rhythm in animals treated with radiotherapy and subsequently they compared the microbial composition. They realized that mice with a cycle of 12 h of darkness vs 12 h of light had better survival rates than mice with a different cycle (8 h of darkness vs 16 h of light). These cycles are intimately related to changes in the intestinal bacterial community, which may be part of the antiradiation mechanism. The authors described the correlation between the bacterial community and radiosensitivity in mice treated with antibiotics. The diversity of the intestinal microbiota in irradiated mice differed from that observed in non-treated animals, with a higher rate of survival[12].

Additionally, a direct connection between radiation and the dysbiosis process in microorganisms inhabiting the intestinal epithelium has been confirmed. Notably, bacteria of the *Firmicutes* family (i.e., *Streptococcus* spp.) and the *Bacteroidetes* family (i.e., *Bacteroides* spp.) have been highlighted[13]. Also, patients with pelvic cancer showed that radiation exposure altered the microorganisms in their gastrointestinal tract, resulting in decreased abundance and diversity. An increase in microorganisms belonging to *Clostridium*, *Roseburia*, and *Phascolarctobacterium* species, associated with enteropathy caused by radiation exposure, was reported[14].

All these studies led to a common conclusion: the "malnutrition" of the intestinal microbiota could serve as a reliable biological marker to predict and prevent radiation-induced enteropathies[14,15]. In addition, Barker *et al.*[16] published that exposure to high radiation doses could induce alterations in the gut microbiota, disrupting the natural barrier it forms, which results in increased apoptosis rates of intestinal cells. Moreover, Hao *et al.*[17] conducted an experiment with mice that underwent high doses of radiation, showing that survivors experienced a change in their gut microbiota composition, which alleviated radiation-induced symptoms. Additionally, Touchefeu *et al.*[8] observed that microorganisms like *Lactobacillus casei*, *Bifidobacterium* spp., and *Lactobacillus acidophilus* could induce a reduction of the symptoms induced by radiation toxicity, such as diarrhea.

These findings emphasize the crucial role of the intestinal microbiota as the primary regulator of the

host's defenses against ionizing radiation, protecting the gastrointestinal system[17]. However, the impact of the microbiota on diseases induced by radiation exposure or cancer has not been definitively proven. More studies, both basic research and clinical, are necessary to determine radioresistance-related populations[18].

Microbiota and SARS-CoV-2 infection

A clear association has been observed between the state of the microbiota and the onset of diseases, with a significant relationship identified between them (Fig. 1). The Covid-19 pandemic affected over 124 million individuals globally. While much attention has been given to developing treatments and vaccines, it is equally important to investigate the long-term impacts caused by the virus[19]. Recent research indicates that key gastrointestinal symptoms (abdominal pain, vomiting, diarrhea, and anorexia) may result from Covid-19 infection. This is attributed to the virus's capacity to invade intestinal cells, potentially leading to alterations in the intestinal microbiota[20,21].

The infection of intestinal cells by SARS-CoV-2 reduces the levels of angiotensin-converting enzyme 2 (ACE2), the virus′s primary receptor in the SARS-CoV family, which plays a significant role in managing inflammation. Additionally, ACE2 acts as a cofactor for the amino acid transporter B0AT1. The B0AT1/ACE2 complex plays a crucial role in regulating the diversity and activity of the intestinal microbiota. Disruption of this complex may lead to dysbiosis, triggering immune responses that have a significant impact on the body. Furthermore, patients with diarrhea have shown higher levels of plasma serotonin and fecal calprotectin, suggesting systemic gastrointestinal inflammation triggered by the viral infection. These inflammatory markers, associated with cytokine activity, further support the presence of gastrointestinal inflammation[20,22].

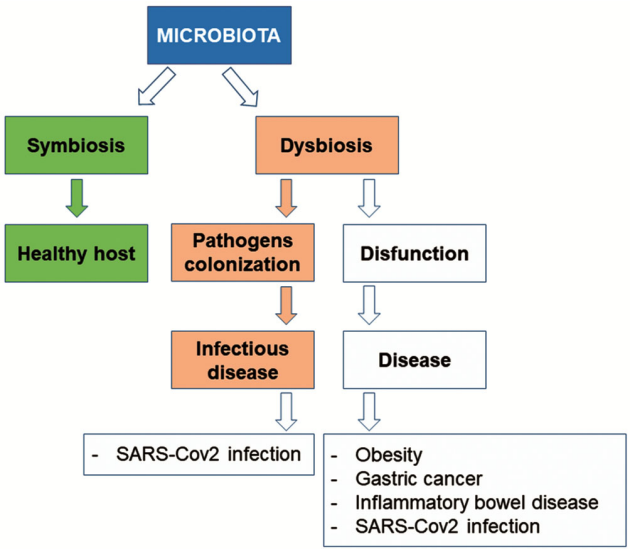

Fig. 1 — Relationship between microbiota and disease.

Tian *et al.*[19] reported significant differences in the microbiota diversity between individuals recovered from SARS-CoV-2 infection and healthy ones. Analysis of stool samples using sequencing technology of 16S RNA, revealed notable modifications in the intestinal microbiota of recovered patients. The microorganisms in the gastrointestinal tract of these individuals were categorized as: (i) opportunistic pathogens (i.e., *Aspergillus niger*), and (ii) native microorganisms (*Actinobacteria*), which were found at significantly reduced levels[19-24].

The above results suggest that SARS-CoV-2 infection affects the respiratory system and causes imbalances in the intestinal microbiota[21,25]. Additionally, other authors suggest that this dysbiosis may be permanent, underlining the need for regular monitoring of the microbiota composition in patients who have recovered from Covid-19. In this case, the exact mechanisms connecting the gastrointestinal issues with the virus infection remain unclear. Thus, further research in this field is vital, as it could help in preventing and managing serious gastrointestinal diseases[26].

Immune system and microbiota relationship

Throughout evolution, the microbiome has established a mutually beneficial relationship with the gastrointestinal environment. The intestinal mucosa, which contains the largest immune system component in vertebrates, interacts with the gut microbiome. Ensuring its correct balance and stability is vital for the overall homeostasis and defense of the host[27].

Studies involving germ-free (GF) mice have highlighted the microbiome′s role in the development, evolution and maturation of mucosal immunity. These mice exhibited lower mRNA expression of Ang4, indicating the vital role the gut microbiota plays in mucosal immunity. Additionally, GF mice had smaller Peyer′s patches compared to conventional mice, emphasizing the gut mucosa′s importance as a primary site for microbiome-host interactions[28,29].

The dynamic interactions between the microbiome and external factors influence both mucosal and systemic immunity. Diet and exogenous substances

significantly influence the gut microbiome. For instance, diets rich in fatty acids and sugars alter microbiome diversity and composition in mice, affecting the synthesis of short-chain fatty acids (SCFAs) (i.e., succinate, acetate, butyrate, and propionate) by various gut bacteria[30-32]. Four groups of bacteria have been identified in healthy individuals: Bacteroidetes, Proteobacteria, Firmicutes, and Actinobacteria[33].

Various studies have demonstrated that lipopolysaccharides (LPS) lead to a significant decrease in GM-CSF and IL-6 synthesis in *Lactobacillus kefir* treated mice, indicating its critical role in inflammatory bowel conditions[34]. *Bacteroides fragilis*, a symbiotic bacterium, inhibits IL-17 production and promotes the function of regulatory T cells (TREGs), which in turn produce anti-inflammatory polysaccharide A[35,36]. Polysaccharide A regulates CD4+T cell conversion to Foxp3+TREGs in a TLR2-dependent manner[36]. These TREGs induce IL-10 production, an anti-inflammatory cytokine that helps mitigate inflammation[37]. Colonization of *Clostridium coli* clusters IV and XIVa increases TGFβ1 levels inducing IL-10 expression in Foxp3+TREGs. Segmented Filamentous Bacteria (SFB), (i.e., *Candidatus savagella*) are associated with intestinal inflammation (Fig. 2)[38,39].

Inflammatory bowel disease (IBD) is a complex disease influenced by the genetic, environment, and microbial molecules, which can trigger an abnormal immune response leading to intestinal inflammation[27]. Advances in the technology of next-generation sequencing (NGS) have contributed to valuable insights into both the human genome and the microbiome, helping to identify microorganisms involved in disease pathogenesis[40,41]. Consequently, manipulating the intestinal microbiome has emerged as a potent strategy for preventing and treating inflammation, with fecal microbiota transplantation being an effective approach for managing IBD[42].

Recently, some authors have pinpointed a crucial gene in the development of IBD: *CARD9*, a member of the caspase recruitment domain family, which mediates intracellular signaling to induce inflammation. In *CARD9* knockout mice, changes in the gut microbiome were observed, along with increased susceptibility to intestinal fungal infections, suggesting *CARD9*'s role in IBD-related malnutrition. Exposure to feces in patients with mild to moderate colitis induces increased synthesis of IL-22 by IL-C3 cells. This fact highlights the role of the intestinal microbiota. Additionally, the inhibition of MiR-19b and SOCS3 induces the regulation of cytokines production by the intestinal epithelial cells, and hence the suppression of inflammation, preventing eosinophilic colitis (EC)[43-45].

Alterations in microbiota diversity were observed in individuals with IBD, marked by a reduction in beneficial bacteria (*Bacteroides* and *Sclerotium*) and an increment in dangerous microorganisms (*Actinomycetes* and *Proteus*). This loss of microbial diversity affects the microbiota's ability to adapt to

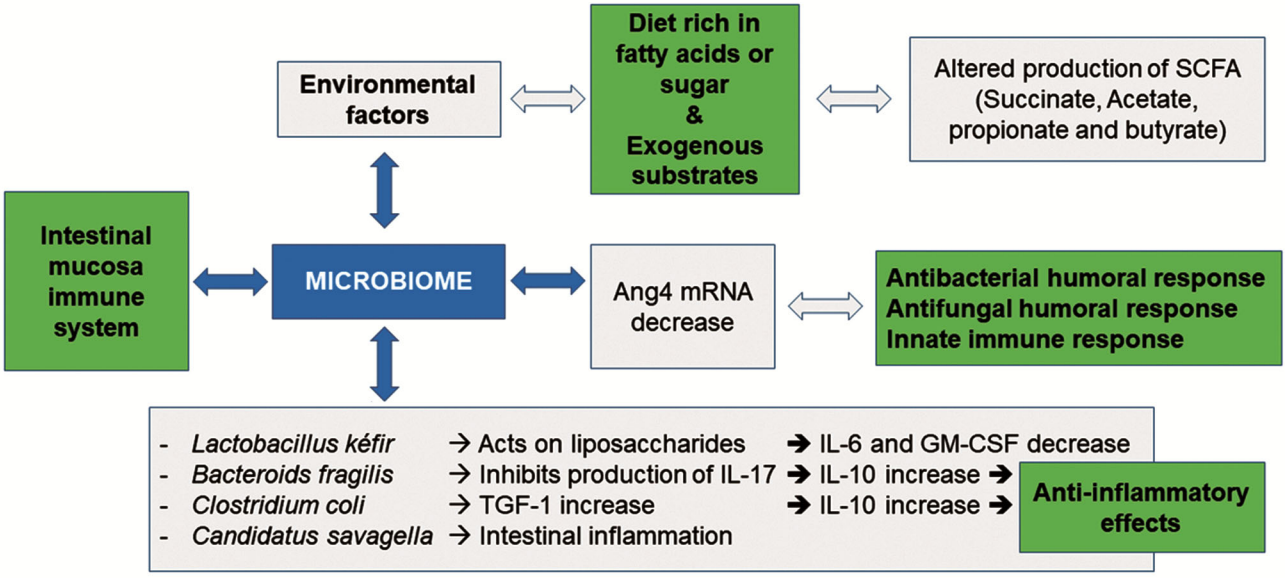

Fig. 2 — Microbiota and immune system relationships.

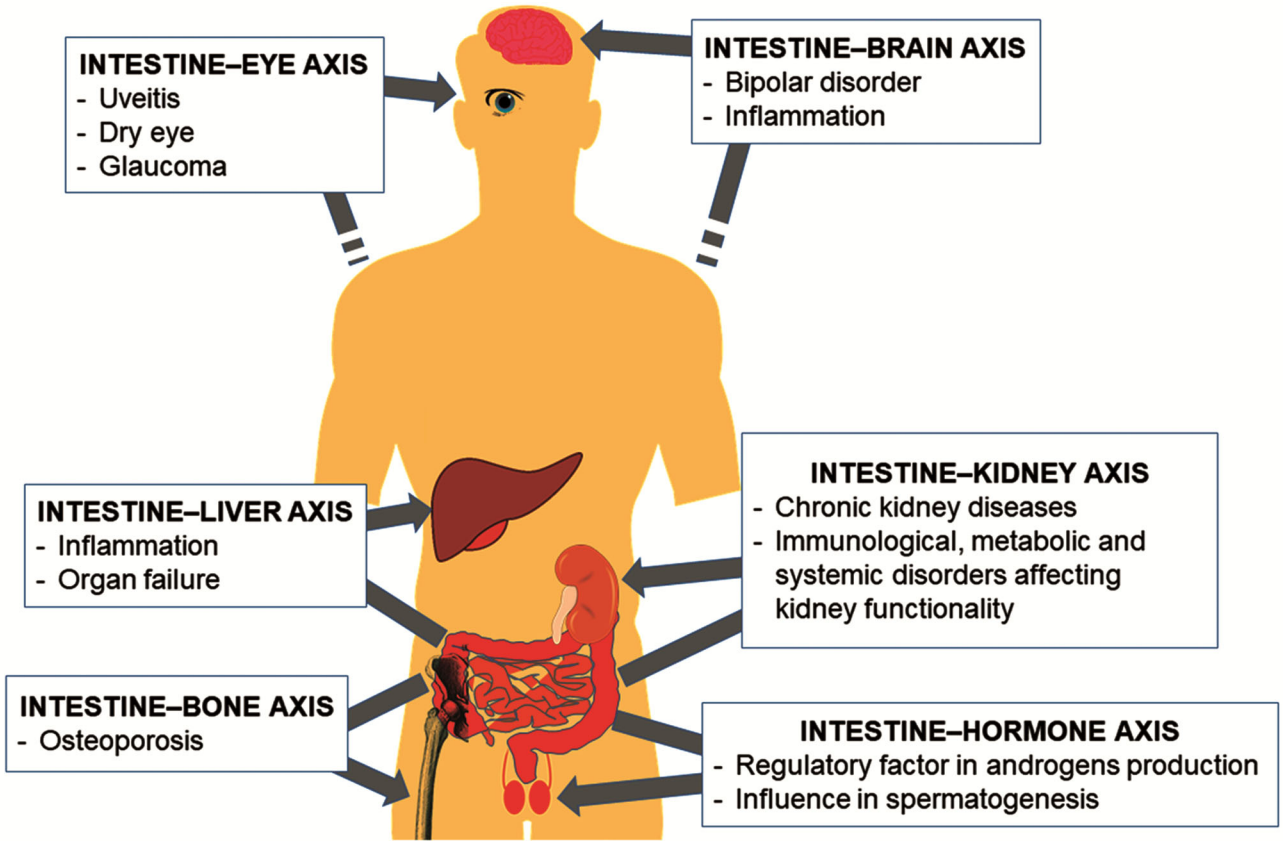

Fig. 3 — Microbiota and corporal axes.

environmental changes due to the presence of disruptors. Since the gut microbiota produces immunogenic substances, bacterial products are important in the inflammation regulation presents in IBD patients[46-48]. Lipopolysaccharides located on the membrane of gram-negative bacteria stimulate the immune response in the intestine. These immunogenic molecules may breach the intestinal barrier when it is compromised, leading to further harm. *Bacteroides fragilis*, a bacterium present in the gut, develops a crucial role in immune regulation[36].

Disruptions to the microbiome can also trigger autoimmune diseases. Research has demonstrated that certain molecules (anti-double-stranded DNA antibodies, antinuclear antibodies, rheumatoid factors (in lupus erythematosus), or citrullinated protein antibodies (in rheumatoid arthritis), appears before the onset of these diseases. The microbiome, particularly *Porphyromonas gingivalis*, is believed to be implicated in the origin and evolution of autoimmune diseases. Recent studies found a reduction in the ratio of ciliates to *Bacteroides* in the intestines of patients with Sweet′s syndrome (STE), suggesting impaired mucosal immune function. Furthermore, analysis of 16S RNA revealed an increase in *Lactobacillus* in the microbiota of rheumatoid arthritis affected patients, with elevated levels of *Prevotella* in those undergoing long-term treatment, with notable decrease in purine synthesis[49,50].

Microbiota and corporal axes

The gut microbiota, a complex ecosystem interacting with the host, plays a significant role in individual health and in the overall organism function. Recent research indicates that microbiota can communicate with distant organs, such as the liver, kidneys, brain, testis, bones, and eyes, through various intricate mechanisms, leading to a range of alterations[51] (Fig. 3).

Advancements in technology have facilitated the discovery of a gut-eye connection, where an imbalance in the intestinal microbiota could be a key factor in the origin and evolution of eye diseases like uveitis, dry eye, or glaucoma, a phenomenon known as the gut-eye axis. Today, doctors utilize prebiotics and probiotics to help restore normal microbiota in patients experiencing eye-related issues[52].

Similarly, the gut-kidney axis suggests that dysbiosis is directly linked to chronic kidney diseases. The underlying mechanisms of dysbiosis could involve immunological, metabolic, or systemic disturbances that directly impact kidney function. Additionally, dysbiosis may also be associated with arthritis, as the inflammatory processes driving these microbiota changes can exacerbate the condition. However, these relationships are still not fully understood[51].

Another key organ influenced is the liver, via the gut-liver axis. Toxins produced by harmful bacteria can enter the bloodstream and spread throughout the body, potentially leading to cell death. Hepatic cells are particularly vulnerable to these infections, and their death can result in serious health complications, from inflammation to multiorgan failure. These liver diseases, known as acute-on-chronic liver failure (ACLF), are marked by acute organ failure, which can ultimately lead to death. The composition of the microbiota significantly impacts this decompensation process, and strategies to prevent or treat ACLF symptoms could prove highly beneficial[53].

Hormones, such as androgens, can also reshape the gut microbiota through the intestine-hormone axis, a field now known as "microgenderoma". Studies performed in recent years have reported that intestinal microbiota can regulate androgen production and even influence spermatogenesis[54].

Bone health is also connected to dysbiosis through the intestine-bone axis. Osteoporosis (OP), a degenerative disease marked by bone loss and deterioration, is a topic of growing interest due to its widespread impact. This area of research is particularly important because modulating the microbiota could prevent or slowdown the evolution of this disease[55,56].

Advances in microbiology and a deeper understanding of the gut microbiota have led to stablish the connection between gut and brain. Bipolar disorder (BD), a mental health condition shaped by both genetic and environmental influences, is closely associated with the gut-brain axis. Recent research has shown that individuals with BD exhibit a different gut microbiota in relation to healthy people. This distinction could be induced by the microbiota′s role in in the modulation of inflammatory mediators (IL-6, TNFα, and IFN1 signaling). These changes can induce inflammation in the peripheral and central nervous systems, contributing to BD development. Additionally, IFN1 has been linked to the expression of TRANK1, a factor that increases blood-brain barrier permeability, potentially worsening BD symptoms[57].

Conclusion

Although much progress has been made in understanding microbial communities thanks to methods based on the study of bacterial DNA, these methods provide only potentially limited information. The metabolic functions performed by microorganisms within the host still cannot be identified. However, advances in other technologies such as metabolomics, transcriptomics, and proteomics, could discover important information on active components and metabolic products synthesized in microbial communities. In addition, the development of computer science and big data allows the integration of clinical data of both the host and the microbiota, in the generation and evaluation of mechanisms associated with microbiota diversity and health[58].

Advances in the field of genomic sequencing have made it possible the study of the composition and role played by the gut microbiota in the health of the host. The microbiota has been proposed as an independent organ, capable of performing physiological, metabolic and immune functions. However, the main mechanisms that the microbiota uses in the regulation of these processes remain unknown. Furthermore, and like any other organ, it is susceptible to being colonized by pathogenic microorganisms. Generally, the interaction with the microorganisms is beneficial, however, and in the worst case, can cause disease like cancer, obesity, diabetes or intestinal bowel disease. Recently, a direct relationship between microbiota and exposure to radiation in cancer patients, SARS-CoV-2 infection or different distal diseases induced via several corporal axes have been described.

Getting to understand how the intestinal microbiota works will allow great medical advances, such as the possibility of modifying its diversity and abundance through diets, prebiotics, probiotics, postbiotics, synbiotics, specific antibiotics to prevent or treat diseases and fecal microbiota transplantation. In addition, technological advances will allow us to know the different metabolic routes of the microorganisms present in the intestinal tract, what are the main synthesized compounds and what impact it has on the host.

Conflict of interest

The authors declare no competing interests.

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