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**Review Article**

# The Beneficial Role of Probiotics in the Maintenance of Immunologic Equilibrium for Functional Gastrointestinal Disorders in Infancy

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**Abstract:** In the human colon commensal bacteria and immune cells interact regularly in a stable environment to keep the immune system functioning normally. The balance between immunological tolerance and immunogenicity is maintained by a complex network of pathways that are dependent on immune system-microbiota cross-talk. To modify certain immune activities and immunological homeostasis, probiotic bacteria can interact with and stimulate intestinal immune cells as well as commensal microflora. Probiotic microorganisms have crucial immunomodulatory and health-promoting characteristics, according to growing research. Therefore, using probiotics might be a worthwhile strategy for enhancing immune system functions. Few research has been published so far on the probiotics' favorable immune-modulating effects. However, a great deal more has been published that are primarily concerned with their nutritional and metabolic characteristics. As a result, the processes underlying the interaction between probiotics and host immune cells have only been partially explained. In order to better understand how probiotic bacteria and immune cells interact to enhance immune functions, the current review attempts to compile and describe the most recent research findings and their implications. As a result, a description of the probiotic bacteria's currently understood immunomodulatory processes for enhancing the human immune system is given.

**Keywords:** Immune Cells, Probiotics, Human Health, Beneficial Microbes, Microbial Modulation Effects, Immune System, Immune Response, Functional Gastrointestinal Disorders

## 1. Introduction

Live microorganisms known as probiotics, which include bacteria and yeast, have been shown to improve human health. Probiotic microorganisms have recently received a lot of attention, and intriguing adjuvant therapies for a variety of intestinal illnesses are currently being examined [1]. Our

current understanding of the crucial functions probiotics plays in disorders linked to the human gut microbiota has been expanded by clinical trials and in vivo research. Numerous clinical studies have shown that probiotics may influence the intestinal microbiota, potentially influencing the management of a variety of bowel illnesses and promoting general health. The connection between probiotics and the human gut microbiota and its functions in disorders connected to the gut microbiome were the main topics of this review. Here, we also talk about future directions and areas of study that need to be clarified in order to comprehend the functions of probiotics in the management of intestinal disorders.

Probiotics have gained popularity in recent years as a means of enhancing human intestinal health, and the combination of prebiotics and probiotics, known as synbiotics, has also been suggested [2]. As a result, the worldwide probiotics business has expanded quickly, making probiotics both a food and a supplement. Probiotic use has been recommended to improve immunity and general health. The human gut microbiota may contribute to the onset of metabolic illnesses such obesity, diabetes, and inflammatory bowel disease, it is now well acknowledged [3]. It's interesting to note that probiotic supplementation has been found to enhance the management and prognosis of certain disorders. Additionally, although the genetic and microbiological traits of certain probiotic strains are significant, more research is required to fully comprehend how consumption of these probiotics affects the human gut microbiota. Probiotics' idea, purpose, and connection to disorders linked to the gut microbiota are briefly summarized in this overview.

### *1.1. Concept of Probiotics and Their Potential Benefits*

Probiotics are "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host," according to the Food and Agriculture Organization (FAO) of the United Nations and the World Health Organization (WHO) [4]. Probiotics are frequently utilized to preserve the intestinal health of people by enhancing the internal microbiota's balance. As a result, the quantity of bad bacteria that cannot live in an acidic environment is reduced, and the number of helpful bacteria that thrive in an acidic environment increase, bringing the gut microbiota into balance [5].

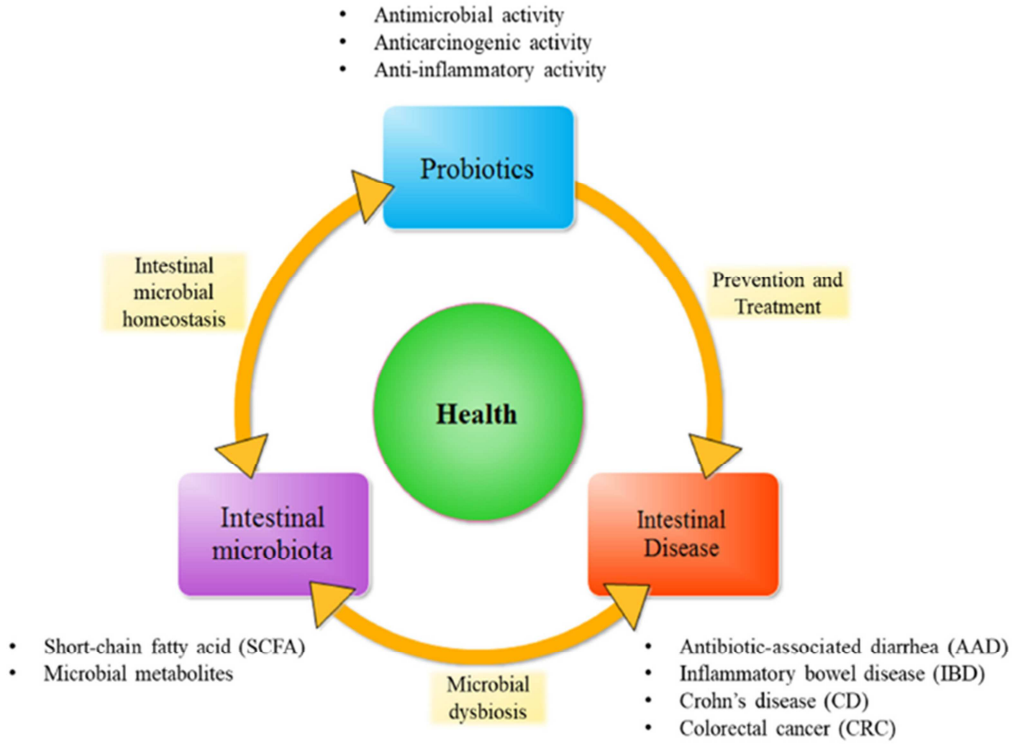


***Figure 1.*** *Role of probiotics relevant to intestinal diseases via recovery of dysbiosis in the intestinal microbiota [27].*

Numerous gastrointestinal conditions, including AAD, IBD, CD, and CRC, are known to be strongly correlated with intestinal dysbiosis between host-beneficial and host-harmful bacteria. When the delicate balance of the intestinal microbiota is thrown off, it can result in inflammation, diarrhea, and even colon cancer [7]. Probiotic administration has been proposed as a treatment strategy to stop certain intestinal disorders. Probiotics may help restore the imbalanced gut microbiota since they are known to have antibacterial, anti-inflammatory, and even anti-carcinogenic properties. The symptoms of certain intestinal illnesses may also be lessened or reduced by this recovery. Based on this knowledge, it is now commonly accepted that probiotics, the intestinal microbiota, and both health and illness of the intestines are strongly related [5].

Probiotics may have beneficial effects leading to therapeutic improvements, according to a prior study on the anti-inflammatory effects of probiotics in patients with IBD

[7]. Probiotics provide a variety of positive health effects, including as preventing constipation, antibiotic-associated diarrhea (ADD), and boosting the immune system. Probiotics may be used to treat and prevent a range of intestinal illnesses since gut microbial populations are not permanent and can be altered by numerous variables such as lifestyle, food, and antibiotics. Numerous research has proven the positive benefits of probiotics and their connection to digestive illnesses [1].

### *1.2. The Homeostasis of Human Gut Microbiota and Its Potential Roles in Human Gastrointestinal Tract*

Live organisms known as "probiotics" work in symbiosis with the body, most frequently in the gastrointestinal (GI) tract. Bifidobacteria, lactobacilli, and the yeast Saccharomyces boulardii are the most often used probiotics in different formulations [8]. There are many different probiotic supplements, formulas, and strains to choose from. GI conditions like antibiotic-associated diarrhea, chronic pouchitis linked to ulcerative colitis, constipation, diarrhea in adults and children, Helicobacter pylori in conjunction with standard therapies, irritable bowel syndrome (IBS), and lowering the risk of C. difficile infection may benefit from the use of certain probiotics, according to the available evidence. A "possibly effective" grade in the natural medicines database is typically defined as having "some clinical evidence supporting its use for a specific indication." However, the evidence is constrained by inconsistent or low-quality findings. Product rankings [9].

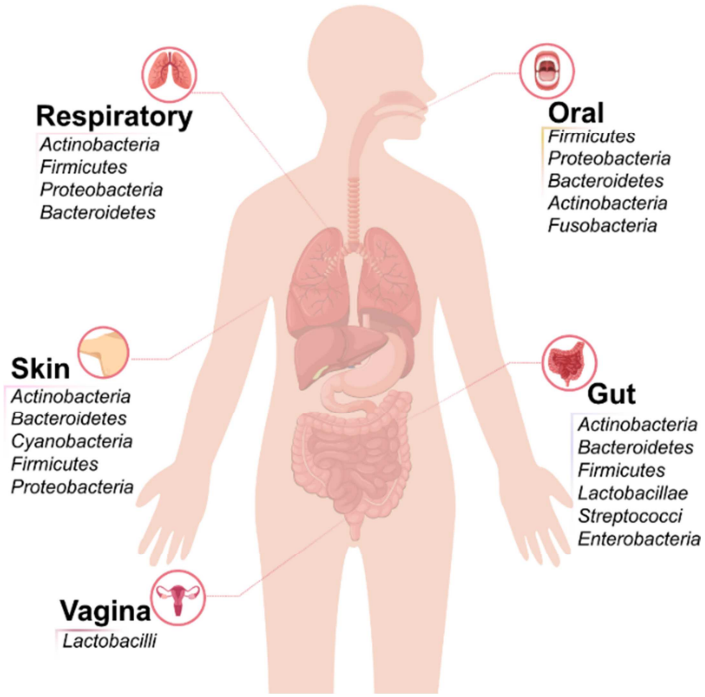


***Figure 2.*** *Microbiota Composition in Different Region. [28]*

Clinical practice recommendations on the use of probiotics for gastrointestinal illnesses were released by the American Gastroenterological Association (AGA) in 2020. The AGA came to the conclusion that certain probiotics could help keep C. difficile inpatients from using antibiotics, but the quality of the evidence was low and called for more research. Similar conclusions were reached by the AGA on the use of probiotics in patients with IBS and inflammatory bowel disease (IBD). In individuals with IBD-related pouchitis, an 8-strain combination probiotic containing different lactobacillus and bifidobacteria species was beneficial. There was evidence to support the use of specific probiotics comprising lactobacilli and bifidobacteria in preterm newborns to avoid necrotizing enterocolitis. When used properly, probiotics are safe and well tolerated in persons who are typically healthy. Some reports of minor GI side effects, such bloating [10].

### *1.3. How Probiotics Play Key Role in Gut Microbiota*

The majority of the microorganisms included in probiotics are bacteria that are similar to the good bacteria found in the human gut naturally. They come in a number of forms, such as capsules, packets, or dietary supplements, and can be purchased without a prescription or over-the-counter (OTC). Although the majority of probiotics may be purchased without a prescription, people with prescription medication coverage may benefit from the possibility that probiotics are a covered benefit. One in five Americans use probiotics for gastrointestinal (GI) disorders, and probiotics have been extensively researched in a wide range of GI ailments. The Lactobacillus, Bifidobacterium, or Saccharomyces species are responsible for the majority of human use probiotics that have been researched [11]. This article eliminates probiotics for

non-GI ailments in favor of focusing on probiotic usage in newborns, kids, and adults with GI issues.

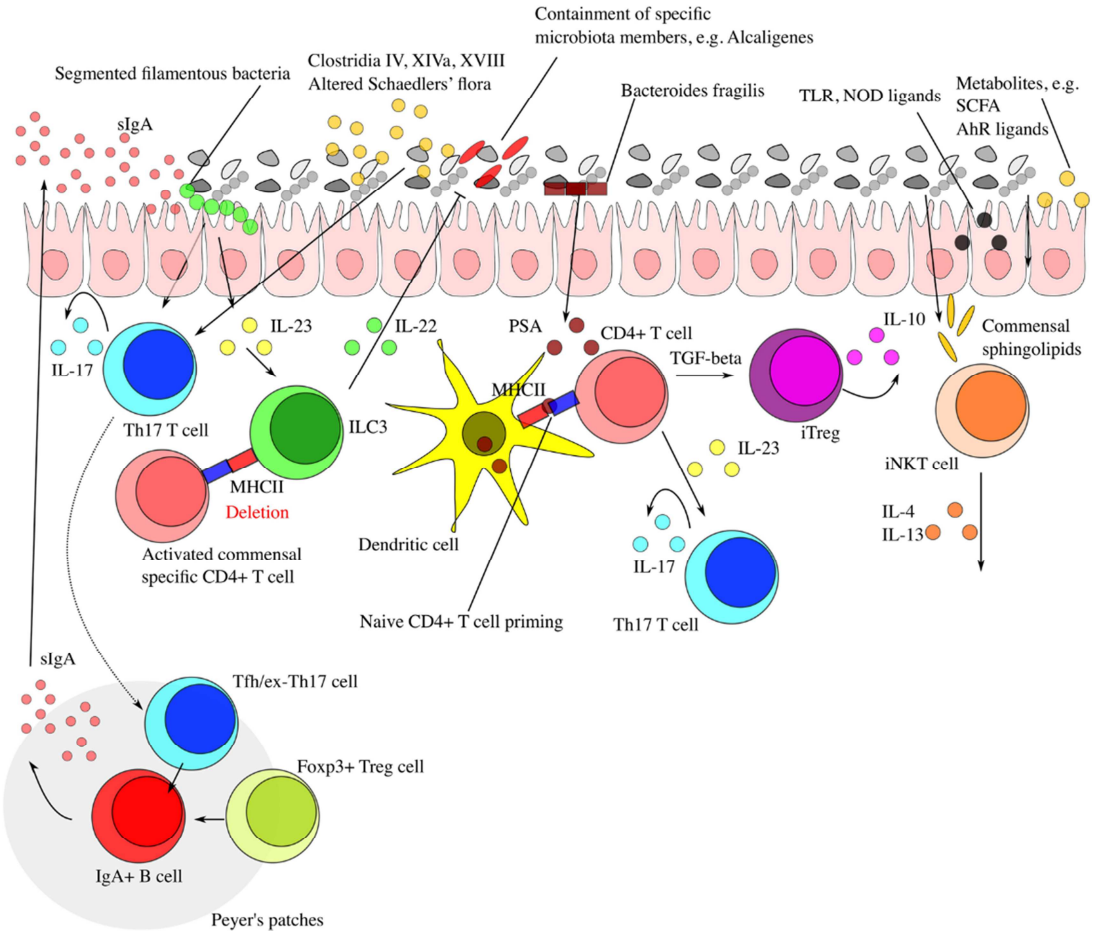


***Figure 3.*** *Intestinal Microbiota-immunity interplay in hemostasis. [29]*

The microorganisms that live in the gut and make up the intestinal microbiome can be influenced by a person's food, lifestyle, exposure to toxins, and usage of antibiotics. Disease, health, the immune system, and alterations in the microbiota are all related [12]. Through their direct interactions with immune cells, probiotics play a significant part in the preservation of immunologic balance in the GI tract. Broad-spectrum probiotics may improve treatment efficiency, and the diversity of the microbiome is probably crucial for maintaining good health. Probiotics' intricate methods of action probably vary depending on the species [12].

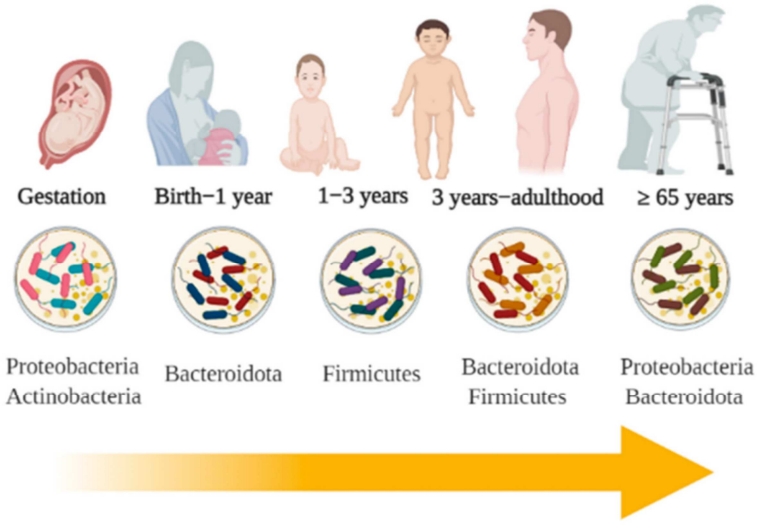


***Figure 4.*** *Dominant gut microbiota phyla in different life stages. [30]*

## 2. Human Gut Microbiome-Associated Diseases and Probiotics Applications

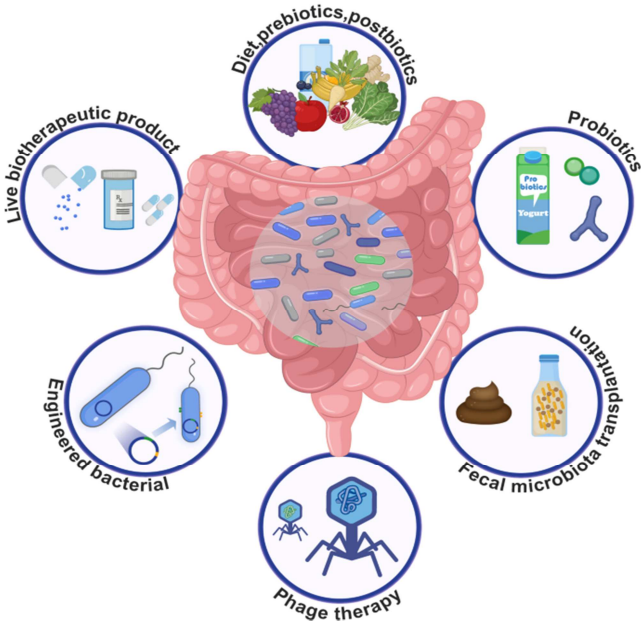


***Figure 5.*** *Microbiota in Disease Treatment. [28]*

Human Gut Microbiota Dysbiosis The imbalance of the structure and operation of the gut intestinal microbiota is known as microbial dysbiosis. It is a widespread issue in the modern period and is brought on by bacterial infections, dietary changes, and antibiotics. Recent studies have shown that intestinal illnesses including IBD, irritable bowel syndrome (IBS), and celiac disease are related to dysbiosis of the gut microbiota [13]. Because they compete with pathogenic bacteria for resources and space, beneficial bacteria in the digestive system prevent their invasion and expansion. Intriguingly, probiotics are one of the most important treatments for reestablishing the gut's microbial balance and preventing infections in patients after antibiotic therapy, which results in dysbiosis of the gut microbiota. Antibiotic-Associated Diarrhea (AAD) AAD is a common adverse effect of antibiotic treatment, Diarrhea Associated with Antibiotics (AAD) The alteration of the gut flora causes AAD, a frequent side effect of antibiotic therapy. A disease-causing bacteria called Clostridioides (previously Clostridium) difficile, which has decreased antibiotic resistance, can infect the large intestine, is one of the causes of AAD [14]. A number of randomized controlled studies (RCT) have interestingly revealed that probiotics may be helpful and safe in the prevention of AAD. For instance, probiotics have been shown to be helpful in preventing diarrhea caused by C. difficile in both adults and children by Goldenberg et al. The preventive benefits of probiotics as adjunct therapy may be employed to prevent AAD in outpatients of all ages, according to a prior study and meta-analysis. According to this study, probiotic treatment may cut the risk of AAD by 51% while appearing to have no negative side effects. Additionally, aggregated data from several trials revealed that Saccharomyces boulardii and Lactobacillus rhamnosus provided the greatest protection against AAD [14]. To clarify the underlying processes of AAD as caused by bacterial infection, additional research is required as the precise etiology of the disease has not yet been identified.

IBD, or inflammatory bowel disease IBD is a chronic inflammatory condition that affects the digestive system. IBD includes Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC), which can be distinguished based on where the gastrointestinal (GI) tract inflammation is located. IBD is assumed to be caused by an aberrant immune system response, while the exact etiology is still unclear. Stress and an unbalanced diet are thought to be possible causes of IBD.

IBD pathogenesis may be influenced by gut microbiota, according to some studies. Furthermore, several studies have demonstrated that the microbiome of IBD patients differs from that of healthy persons [15].

Gut microbial imbalance, known as dysbiosis, can include an increase in the proportion of small bowel bacteria, alteration in the relative proportion of benevolent microbes to pathogenic ones, as well as the translocation of colonic bacteria [16].

Additionally, it has been proposed that preserving the equilibrium of the gut microbiota may be crucial for avoiding IBD. Probiotics have drawn a lot of interest recently as a potential treatment to alter the microbiota's positive effects on IBD [17]. Probiotics have been used, for instance, to treat ulcerative colitis and induce remission. Probiotic supplementation in patients with inflammatory bowel disease, however, appears to be a viable adjuvant therapy for UC but not CD, according to new research. As a result, there is still not enough information about the effectiveness of probiotics to provide broad recommendations for usage in CD patients. The whole GIT is affected by Crohn's Disease (CD), an inflammatory bowel condition that causes weight loss, diarrhea, fever, lethargy, and abdominal discomfort. Despite the fact that the exact etiology of CD is still unclear, it has been theorized that a number of variables, including microbiological, genetic, and environmental ones, may contribute to its onset [18]. There are several treatments to treat CD's symptoms, but there is still no known cure. For instance, immunosuppressants can be used to lower immune system activity and steroids can be used to treat intestinal inflammation. Probiotics may provide an alternate strategy in addition to traditional therapy in a similar manner. For instance, Fedorak et al. showed that probiotic supplementation in CD patients was advantageous following surgery compared to late treatment. Another recent study, however, found that intestinal inflammation in CD patients did not significantly alter after receiving multi-strain probiotic adjuvant therapy. Consequently, as a result of discrepancies in the findings of clinical research using probiotic supplementation as a therapy.

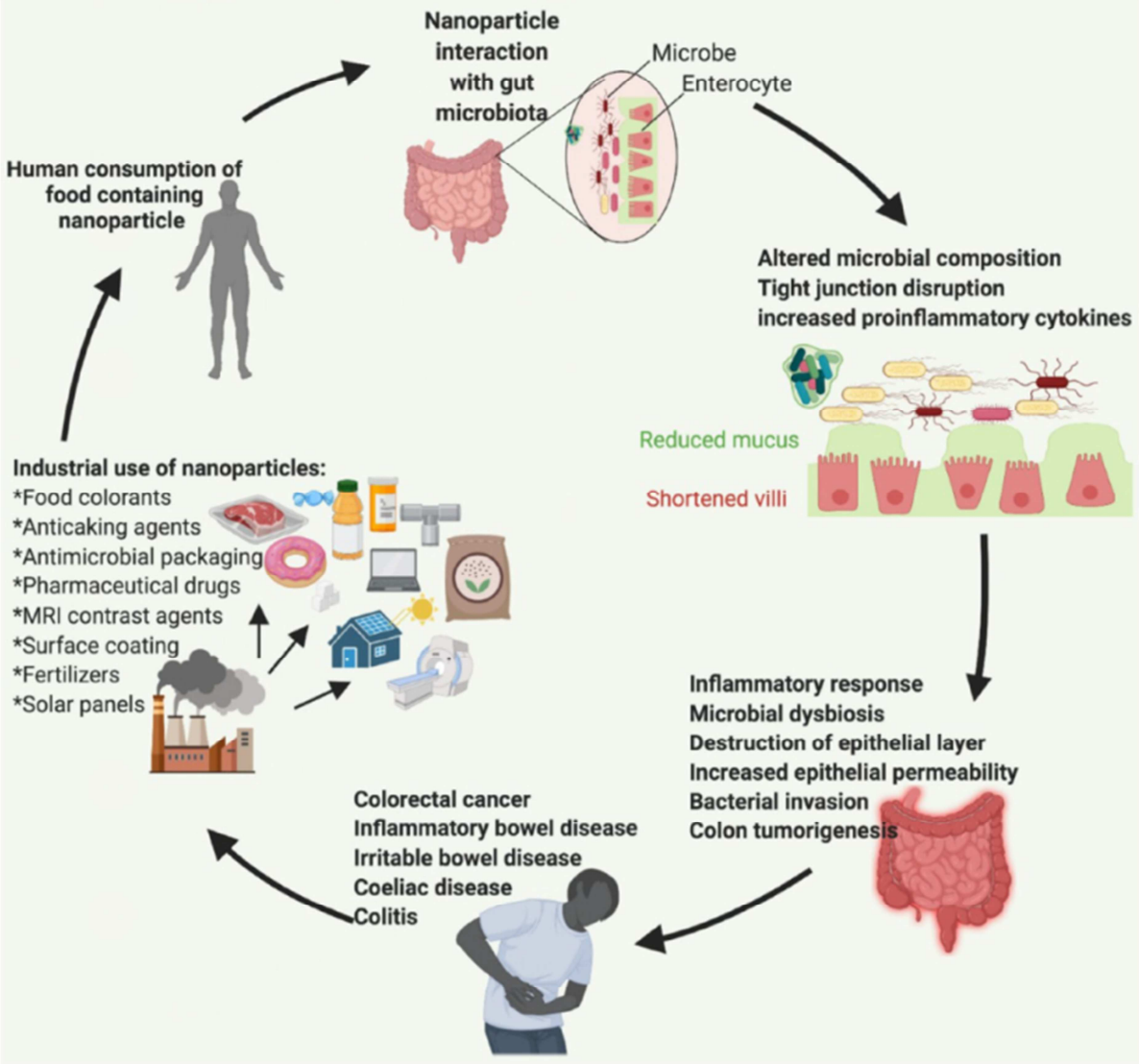


***Figure 6.*** *Contamination due to industrial use of nanoparticles in food processing and other industries and their potential impact on human health and diseases through the gut microbiota. [31]*

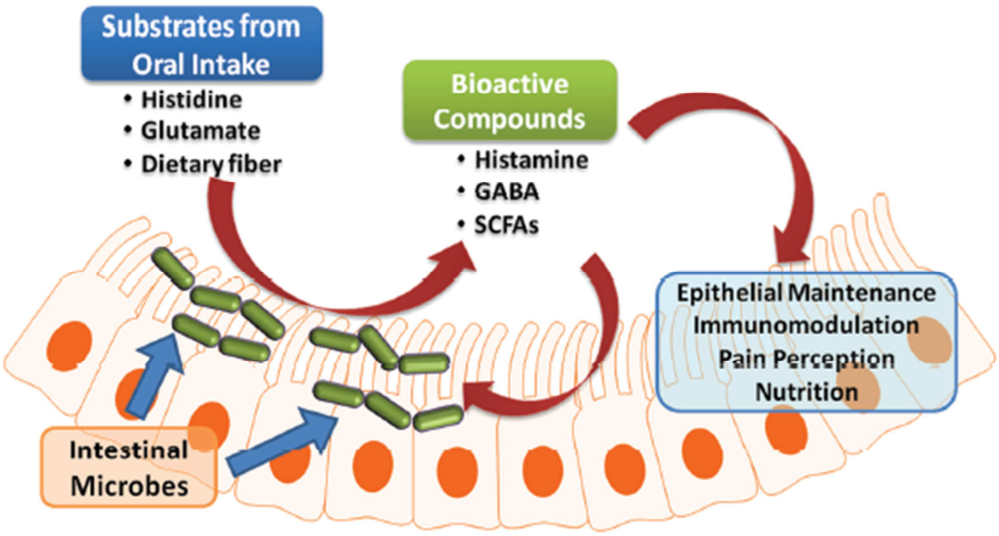


***Figure 7.*** *Luminal conversion by intestinal microbes may play an important role in host–microbiota interactions. Orally consumed nutrients may be converted by intestinal microbes into bioactive compounds that could affect the health of the host and the intestinal microbiota. GABA, gamma-aminobutyric acid; SCFAs, short-chain fatty acids. [5].*

## 3. Dysbiosis of the Human Gut Microbiota

The imbalance of the gut intestinal microbiota's structure and function is known as microbial dysbiosis. It is a widespread issue in the modern period and is brought on by bacterial infections, dietary changes, and antibiotics. Recent studies have shown that intestinal illnesses including IBD, irritable bowel syndrome (IBS), and celiac disease are related to dysbiosis of the gut microbiota [19].

By competing with pathogenic bacteria for resources and space in the digestive tract, beneficial bacteria prevent harmful bacteria from colonizing and spreading. Interestingly, probiotics are one of the most effective ways to cure patients whose gut flora have become dysbiotic as a result of antibiotic therapy and to avoid infections [1].

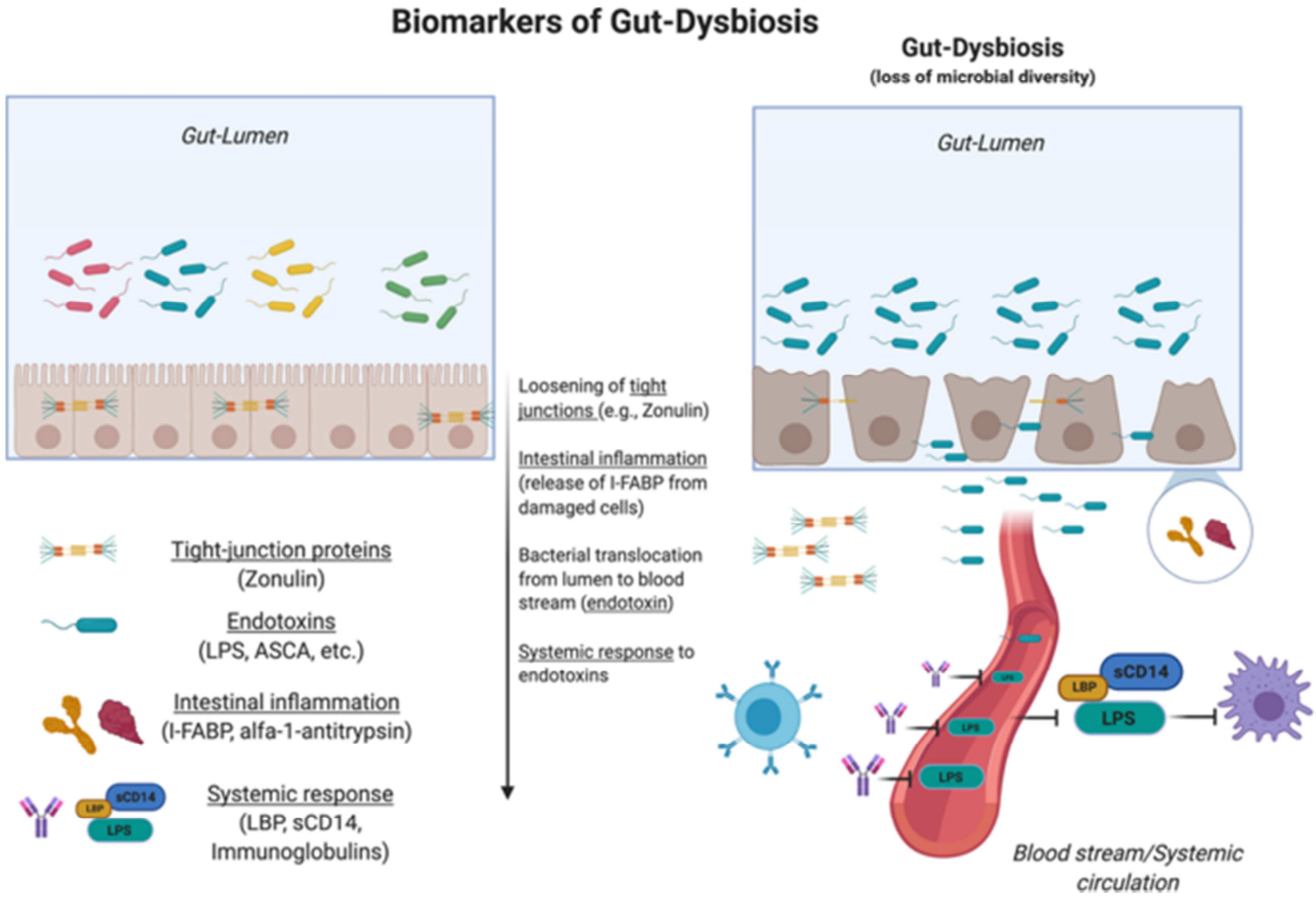


***Figure 8.*** *Gut dysbiosis (i.e., reduced gut-microbial diversity. [36]*

### *3.1. Antibiotic-Associated Diarrhea (AAD)*

The alteration of the gut flora causes AAD, a frequent side effect of antibiotic therapy. A disease-causing bacteria called Clostridioides (previously Clostridium) difficile, which has decreased antibiotic resistance, can infect the large intestine, is one of the causes of AAD. It's interesting to note that probiotics have been touted as potentially helpful and secure in AAD prevention [20].

Probiotics, for instance, have been shown to be useful in preventing diarrhea caused by C. difficile in both adults and children, according to Goldenberg et al. The preventive benefits of probiotics as adjunct therapy may be employed to prevent AAD in outpatients of all ages, according to a prior study and meta-analysis. According to this study, probiotic treatment may cut the risk of AAD by 51% while appearing to have no negative side effects. Additionally, aggregated data from several trials revealed that Saccharomyces boulardii and Lactobacillus rhamnosus provided the greatest protection against AAD. There is a summary of other ADD clinical studies [21].

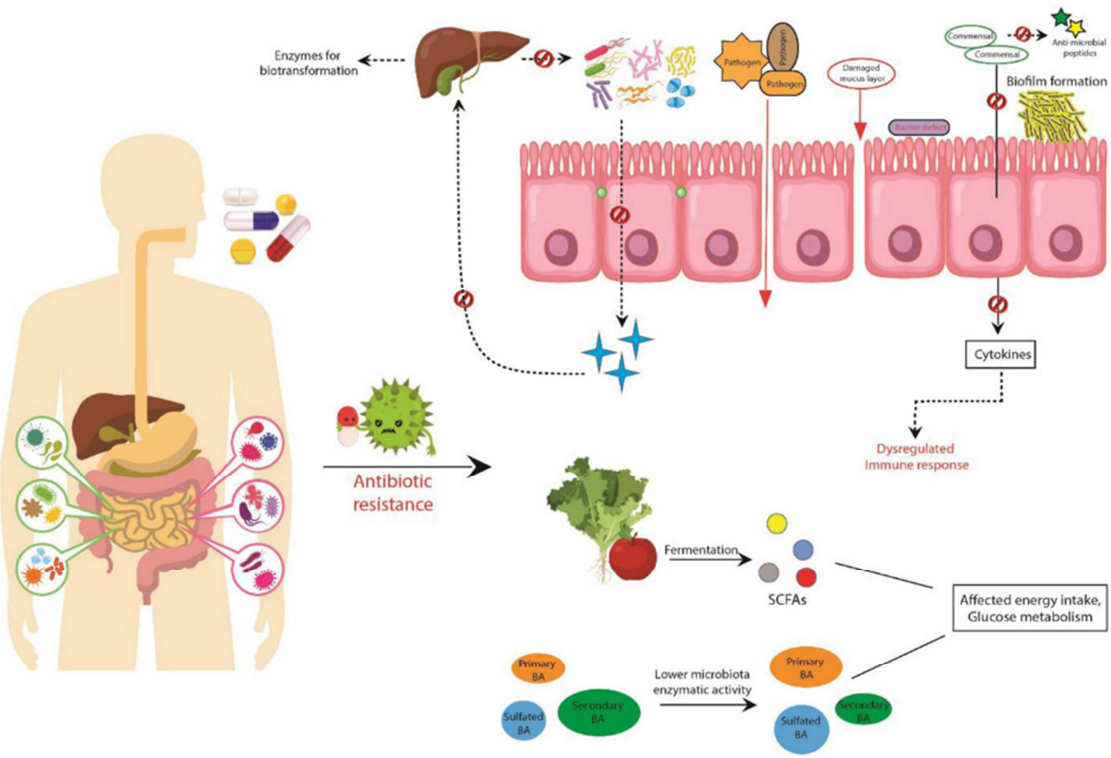


***Figure 9.*** *Impact of antibiotics on the human microbiome and consequences for host health. [32].*

### *3.2. Inflammatory Bowel Disease (IBD)*

IBD is a chronic inflammatory condition that affects the digestive system. IBD includes Crohn's disease (CD), ulcerative colitis (UC), and indeterminate colitis (IC), which can be distinguished based on where the gastrointestinal (GI) tract inflammation is located. IBD is assumed to be caused by an aberrant immune system response, while the exact etiology is still unclear. Stress and an unbalanced diet are thought to be possible causes of IBD. IBD pathogenesis may be influenced by gut microbiota, according to some studies. Furthermore, several studies have demonstrated that the microbiome of IBD patients differs from that of healthy persons.

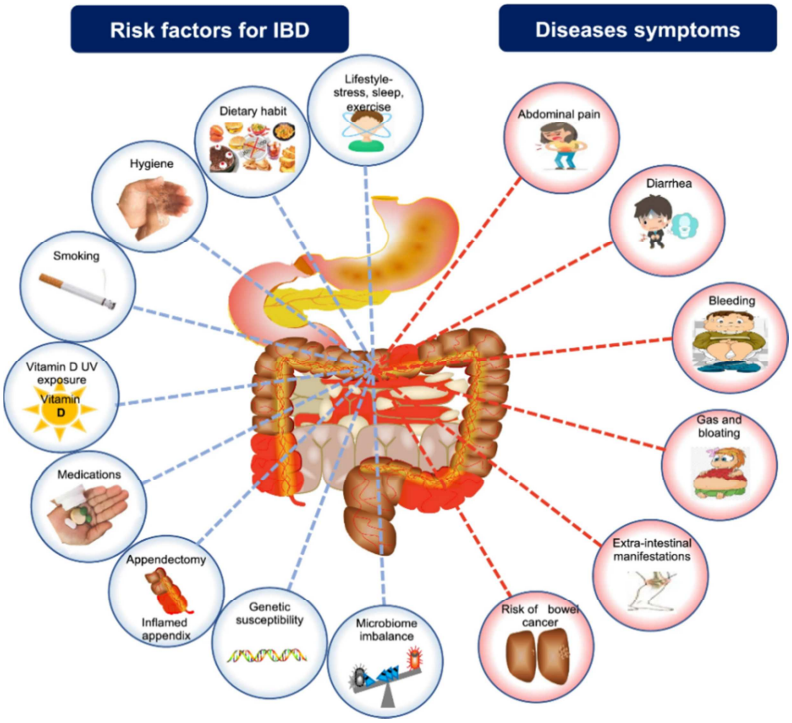


***Figure 10.*** *Risk Factors of IBD. [33].*

Additionally, it has been proposed that preserving the equilibrium of the gut microbiota may be crucial for avoiding IBD. Probiotics have drawn a lot of interest recently as a potential treatment to alter the microbiota's positive effects on IBD. Probiotics have been used, for instance, to treat ulcerative colitis and induce remission. Probiotic supplementation in patients with inflammatory bowel disease, however, appears to be a viable adjuvant therapy for UC but not CD, according to new research. As a result, there is still not enough information about the effectiveness of probiotics to provide broad recommendations for usage in CD patients [22].

### *3.3. Crohn's Disease (CD)*

Abdominal discomfort, diarrhea, fever, exhaustion, and weight loss are some of the symptoms of CD, an inflammatory bowel disease that affects the entire GIT. Despite the fact that the exact etiology of CD is still unclear, it has been speculated that a number of variables, including microbiological, genetic, and environmental ones, may contribute to its development. There are several treatments to treat CD's symptoms, but there is still no known cure.

For instance, immunosuppressants can be used to lower immune system activity and steroids can be used to treat intestinal inflammation. Probiotics may provide an alternate strategy in addition to traditional therapy in a similar manner. For instance, Fedorak et al. showed that probiotic supplementation in CD patients was advantageous following surgery compared to late treatment [23]. Another recent study, however, found that intestinal inflammation in CD patients did not significantly alter after receiving multi-strain probiotic adjuvant therapy. Therefore, further study is required to determine the functions of probiotics due to discrepancies in the findings of clinical trials utilizing probiotic supplementation in the treatment of CD [24].

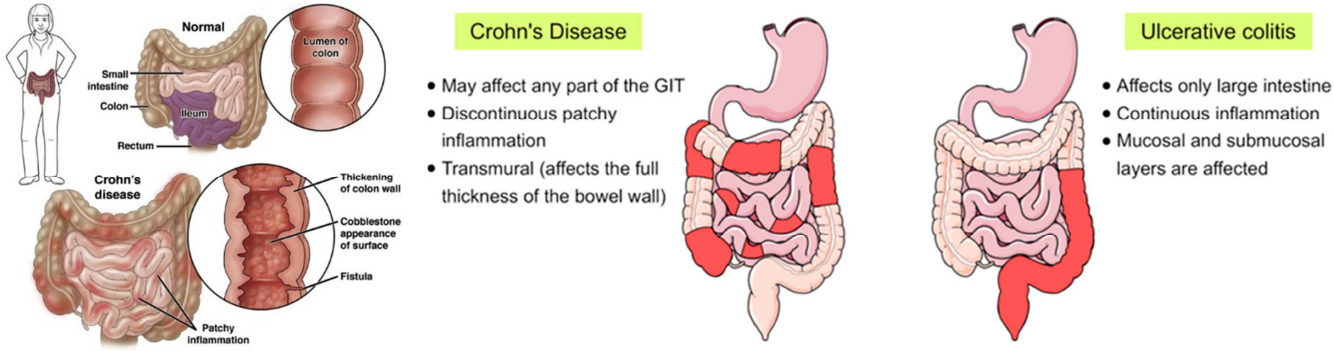


***Figure 11.*** *Crohn's disease is a chronic inflammatory condition of the gastrointestinal tract. [34]*

### *3.4. Colorectal Cancer (CRC)*

CRC, commonly referred to as bowel cancer or colon cancer, is a cancer that can develop in the colon or rectum as well as any other region of the large intestine. In affluent nations like Europe, the United States, and Australia, colon cancer incidence rates have been rising. Bloody feces and weight loss are two signs of the illness. However, hereditary instances are rare and are mostly brought on by aging and lifestyle. The prevalence of colon cancer in young individuals is high in poor nations, where routine health monitoring is not feasible. Additionally, those who have inflammatory bowel diseases like UC or CD are more likely to acquire colorectal cancer. It's interesting to note that current research has examined the potential benefits of probiotics in the prevention of colorectal cancer [25].

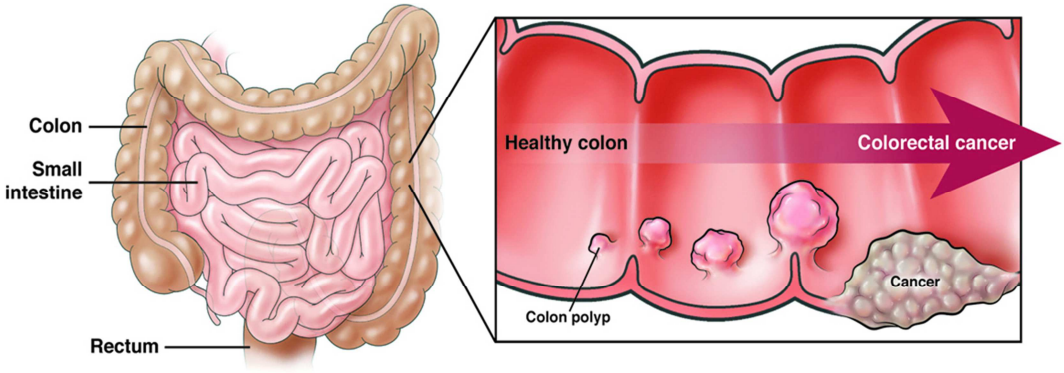


***Figure 12.*** *Colorectal Cancer with Polyps.[35]*

Although several clinical trials and animal tests have demonstrated the benefits of probiotics, there is still more to learn. According to the analysis of clinical studies, using synbiotics significantly altered the intestinal microbiota of

people with colorectal cancer, with an increase in Lactobacillus [26]. Improvement of mucosal structure in the form of enhanced epithelial barrier function was confirmed in some individuals who had colonic resection. As a result, consuming synbiotics may potentially change how the intestines process food. These results imply that probiotics are useful for treating and preventing intestinal problems like colorectal cancer in humans as well as in animals.

# 4. Conclusion

Through their direct contact with immune cells, probiotics are essential for maintaining the immunologic balance in the digestive system. Probiotics are beneficial for treating acute infectious diarrhea, antibiotic-associated diarrhea, Clostridium difficile-associated diarrhea, functional constipation pylori eradication, and IBS, according to high-quality research. Probiotics may benefit human nutrition, health, and the control of typical GI problems. Recent studies on the structure and operation of the microbiome have suggested that diet may directly affect the intestinal microbiota and the health of humans and animals. Disruptions in the relationships between microbes and humans may lead to various disease states, such as chronic inflammation, autoimmune diseases, and neurological disorders. Probiotics have been suggested as both therapeutic and preventative approaches to help the gut microbiome return to its normal state of composition and function. However, information from research on the human microbiome may help identify new native microbial species and develop techniques to favorably influence changes in the microbial populations in the gut. An understanding of the biology and possible manipulation of the human host's microbiome may be obtained via carefully planned investigations carried out in suitable experimental models (in vitro or in vivo). Global studies of the interactions between probiotics, intestinal bacteria, and the mammalian gastrointestinal system can be conducted using metagenomic, meta transcriptomic, and metabonomic technologies. Future methods for promoting health, preventing illness, and treating various ailments may involve new varieties of probiotics or pharmaceutical substances produced from the microbiome.

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