Chapter 6
Environmental Pollutants that Can Be Metabolized by the Host, but Would Be Harmful to Humans (e.g., Causing Cancers, etc.)

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6.1 Introduction

Environmental pollutants are gradually increased and the term xenobiotics are commonly used in context of environmental pollution because they are synthetic compounds produced from industries and agriculture [1]. Human body has number of microorganisms commonly called as human microbiota [2, 3]. The diversity and functioning of this community depend upon body size, shape, and different environmental conditions (e.g., pH, oxygen, substrate availability, humidity, and temperature) at different sites [3]. Site-specific microbiome which associate with skin, respiratory tract, and gut are the first to encounter xenobiotics and mediate a pass to internal organ system [4]. Besides, most interaction between human microbiota and xenobiotics occurs in human gut [4, 5]. The anaerobic environment of the gut is well-suited for a hydrolytic and reductive metabolism. And this will generate low molecular weight non-polar products that can easily absorbed by host cells. In comparison, the absorbed non-polar xenobiotics are metabolized and transported in liver by a rich collection of conjugative enzymes and these hepatic metabolisms may generate high molecular weight polar metabolites. The latter reach to the gut, secreted via bile and in gut they can be re-metabolized by hydrolytic and reductive enzymes [5, 6]. Hence, xenobiotics are metabolized by gut microbiota and can exert an intense influence on the bioavailability and toxicity of xenobiotics entering in gut from different routes.

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6.1.1 Probiotics and Gut Microbiota

Food and Agricultural Organization (FAO) of the United Nations and the World Health Organization (WHO) states that probiotics are supplements of feed and have so many benefits for human and affect the host by improving the microbial balance with immune system. Nobel laureate Elie Metchnikoff in 1907 introduced the concept of probiotics to the world of science. In his studies he reported that the longevity and viability of *Bulgarians* and *lactobacilli* with consumption of fermented milk products, which can be used as probiotics [7]. This study suggested that some microorganisms are beneficial for human health. From that onwards, probiotics had been widely consumed and marketed as functional food, Mechanisms of proboscis include stimulation of epithelial cells, immunomodulation, include manipulation of intestinal microbial communities, fortification of intestinal barriers, and differentiation [8]. Mostly probiotics are developed these days made from *Bifidobacteria*, *Lactobacilli*, and lactic acid bacteria, like *streptococci* and Lactococci. Other probiotic strains include microbial strains like *Bacillus*, *Escherichia*, and Propionibacterium and some yeast genera, mainly *Saccharomyces* [9].

From birth to adulthood there are many factors that may influence the gut microbiota which include diet during infancy that is the presence of antibiotics in food, exposure of antibiotics, from environmental conditions and mode of delivery [10]. The gut microbiota plays an essential role in shaping the intestinal mucus layer [11], which helps us to digest fibers and synthesize amino-acids and vitamins [12]. Such benifits help in immune system modulation, energy metabolism and storage, neurodevelopment and even regulate growth & behavior [13]. There are many diseases associated with the alteration of gut microbiota [14]. Gut microbiota dysbiosis is the major cause of obesity [15]. Although, gut microbiota is very sensitive toward the diet, drugs and environmental pollutants.

6.1.2 Classification of Probiotics

Most of the microorganisms can be used as probiotics [16]. Genus name (for example, *Lactobacillus*) is the first name given to the bacterial strains based on physical characteristics, metabolic needs, similarity of qualities and metabolic end products. Species is the second name of bacteria like *acidophilus*, based on the common characteristics and that will distinguish them from other species. Strain is the much more specific classification of bacterium which divide members of same species into subgroups and it is based on the properties that these bacteria have in common and distinct it from other species (e.g., strain LA5) [16, 17] (Table 6.1).

Table 6.1 Commonly used probiotic bacteria [16, 17].

Lactobacillus spp.	*Bifidobacterium* spp.	Others
L. casei (rhamnosus)	*B. longum*	*Escherichia coli*
L. bulgaricus	*B. breve*	*Saccharomyces cerevisiae*
L. plantarum	*B. infantis*	*Enterococcus faecalis*
L. reuteri	*B. bifidum*	*Bacillus cereus*
L. acidophilus	*B. adolescentis*	*Streptococcus thermophilus*

6.1.2.1 *Lactobacillus*

It involves various Gram-positive facultative anoxic or microaerophilic bacteria. These are the essential part of the lactic acid bacteria group (including *Enterococcus*, *Pediococcus*, *Lactobacillus*, *Lactococcus*, *Gonococcus*, *Streptococcus,* and *Leuconostoc* species) that can convert hexose sugars to lactic acid and produce an acid in the environment which can inhibit the growth of harmful species [18]. In humans, *Lactobacilli* are present in the GIT and vagina with *Bifidobacterium* which is one of the first bacteria colonized the infant gut after delivery [19].

6.1.2.2 *Bifidobacterium*

Bifidobacterium includes Gram-positive non-motile anoxic bacteria. They are endo-symbiotic inhabitants of the vagina and gastrointestinal tract of humans [20]. Strains of the genus *Bifidobacterium* are also used as probiotics because they have resistance mechanism to bile salt and many beneficial effects on other probiotic bacteria, which are generated in the presence of biological fluid [21].

6.1.2.3 *Saccharomyces*

Saccharomyces contains several yeasts including: *Saccharomyces cerevisiae* used for making bread plus beer, *Saccharomyces bayanus* which is used for making wine, and *Saccharomyces boulardii* used in medicine as a probiotic [22].

6.1.2.4 *Bacillus*

Bacillus sp. are Gram positive, aerobes or facultative aerobes capable of spore formation. Various species of *Bacillus* have been reported to have potential such as *B. subtilis*, *B. cereus*, and *B. coagulans* [23]. The use of *B. coagulans* as a therapeutic like other probiotics strains such as *lactobacillus* and *Bifidobacterium* sp. has been reported, whereas presence of *B. coagulans* in the composition of normal gut microbes has not been reported [24].

6.1.2.5 *Escherichia*

Escherichia sp. comprises of Gram-negative bacteria belonging to *Enterobacteriaceae* family, mostly reported with virulent serotypes (*E. coli* O157: H7). *Escherichia coli* is commonly found in lower intestine as a normal microbe of gut microflora with a known probiotic strain: *Escherichia coli* Nissle 1917 (EcN). A study revealed the effect of *Escherichia coli* Nissle 1917 amalgamated with other probiotics strains on the treatment of constipation [25]. The effects of this strain on gastrointestinal disorder, Crohn's disease [26], ulcerative colitis, IBD, and colon cancer have been studied [27].

6.1.2.6 *Streptococcus* and *Enterococcus*

Streptococcus and *Enterococcus* genera belong to the category of lactic acid producing bacteria and are reported to have various species that can cause heath implications such as *Streptococcus pneumoniae*, *Streptococcus pyogenes*, and vancomycin-resistant *Enterococcus faecium* [28]. Some species of *Enterococcus* like *Enterococcus faecium* PC4.1 show commensal relationship with skin, mouth, and intestine [29]. The potential probiotic strains are *Streptococcus thermophilus*, *Enterococcus durans,* and *Lactobacillus delbrueckii* subsp. *bulgaricus* [30, 31]. The use of *Enterococcus faecium* as probiotics has a long history, and proved its effectivness against antibiotic-associated diarrhea [32], the opportunistic strains of the genus serve as a reservoir of virulence and antibiotic resistance in animal study models (animal study). The use of opportunistic strains of these genera is not categorized under (GRAS) for humans consumption, but can be used as probiotics for animals [33, 34].

6.1.2.7 *Lactococcus*

Lactococcus genus consists of Gram-positive, lactic acid producing bacteria used to produce fermented products in the dairy industry. The acidification property of these bacteria is helpful in preventing the spoilage of milk by inhibiting the growth of spoilage microorganisms. The other properties of some species like *Lactococcus lactis* subsp. *lactis* as a probiotic of niacin production and adhesion to vaginal epithelial cells have been studied. A study on the use of *Lactococcus lactis* subsp. *lactis* CV56 in combination with other probiotics to treat antibiotic-associated diarrhea has been given [35–37].

6.2 Function Mechanism of Probiotics

6.2.1 Gut Barrier Function

The gut barrier defense system consists of the secretory IgA, antimicrobial peptides, mucous layer, and the epithelial junctional adhesion complex [38]. The location of epithelial cells in the center stage of the barrier effect has been reported, these cells receive molecular signals from the lumen of gut and exchange them with the underlying cells of immune system. These cells can communicate with the whole organism by the circulation of signaling molecules. Gut barrier defense plays an eminent function in the pathogenesis of various diseases associated with the GI tract like irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), infectious enterocolitis plus coeliac disease [39].

Studies conducted on the use of *L. rhamnosus* GG (LGG) and probiotic mix VSL#3 on mice and Caco-2 intestinal cells have shown the influence of the strain on epithelial cells of intestine to maintain the coherence of the epithelial barrier. The persistence of LGG in the GI tract was connected with its in vivo expression of pili containing a mucus-binding domain [40]. An in vitro study on LGG and its soluble factors (p75 and p40) has revealed the prevention of apoptosis in epithelial cells by activating anti-apoptotic Akt and suppressing NF-kB. In addition, an increase in the secretion of mucin by epithelial cells was observed [41].

The effect of *L. plantarum*, *L. casei*, *L. rhamnosus,* and *L. acidophilus*, on the stimulation of distinct pathways of gene-regulatory networks in the human mucosa has been reported. These regulations involve upregulation of an activator of NF-kB signaling cascade known as IL-1b, involved in the transcription of genes responsible for the maturation of B-cell and lymphogenesis, thus supporting the barrier function [42].

The effect of *Lactobacillus, Bifidobacterium*, and *Streptococcus* as probiotics on post-infectious irritable bowel syndrome (PI-IBS) caused by *Trichinella spiralis* showed positive results in a mouse model. *Bifidobacterium* or *Lactobacillus* treatment on PI-IBS mice showed reduction in the abdominal contractile response and withdrawal reflex score, D-lactate level, and reduced plasma diamine oxidase (DAO) concentration. The suppression of proinflammatory cytokine IL-17 and IL-6 has been reported after probiotic administration and enhancement in the expression of occludin and claudin proteins of tight junction of cells [43].

6.2.2 Production of Inhibitory Compounds by Probiotics

The antibacterial property of probiotics against Gram-negative and Gram-positive bacterial pathogens involves the production of various antibacterial substances. These substances include production of organic acids, bacteriocins, diacetyl, ethanol, hydrogen peroxide, and carbon dioxide [44, 45]. The mechanisms of action of

bacteriocins to inhibit the growth of pathogens include the pore formation in the cell walls of targeted cells and inhibition of synthesis of cell wall. Nisin an antimicrobial compound associated with the formation of a complexes with the precursors of cell wall and lipid II, to inhibit the synthesis of cell walls, and also prevent pore formation in the membranes by removing complex aggregates and incorporates peptides. Bacteriocin production potential offers various advantages to the strains in complex microbial environments as they have antimicrobial properties and can inhibit the pathogens of GI tract [46, 47].

Lactobacillus acidophilus can produce various antimicrobial compounds such as acidolin. acidophillin, and lactocidin and *Lactobacillus planatarum* can produce another antimicrobial compound "lactolin" [48]. The effect of bacteriocin producing *Lactobacillus salivarius* UCC118 strain on *Listeria monocytogenes* infected mice have shown protective results. The effect of bacteriocin Abp118 on stimulating antimicrobial response was confirmed by this study, where *Lb. salivarius* showed antagonistic relationship with the pathogen [49]. The inhibition of *Helicobacter pylori*, *E. coli*, *Listeria monocytogenes*, Rotavirus, and *Salmonella* by *Lactobacilli* and *bifidobacteria* have been reported [50].

Several strains of *Bifidobacterium* (*B. bifidum* NCFB 1454) have shown the production of a unique bacteriocin (bifidocin B), effective against Gram-positive bacteria. A high inhibition rate of *E. coli* C1845 and *Salmonella enterica ser. Typhimurium* SL1344 by two *Bifidobacterium* strains has been studied [50]. Inhibition of *Yersinia enterocolitica* an entero pathogen by twenty strains of *Lactobacillus* has been reported in addition with the inhibition of *Listeria monocytogenes* by *Lactobacillus plantarum* C4 and *Salmonella enterica serovar Typhimurium* by *Lactobacillus casei*. The main mechanism of inhibition involves the elevation of pH mainly from dextrose fermentation by *Lactobacillus* [51] (Table 6.2).

6.2.3 Adhesion Mechanism of Probiotics

Attachment to intestinal mucosa, an important characteristic for probiotics, is required for its colonization in intestine along with antagonism towards pathogens and variation of immune system. Various Lactobacillus proteins accompanied by saccharide moieties and lipoteichoic acids can improve the adhesion to mucous and bacterial surface adhesions that facilitate adhesion to the mucous layer [50, 65]. Bacterial adhesins, mucus-binding protein (MUB), from *Lactobacillus reuteri* are reported [66]. Probiotics, such as *L. plantarum*, can prevent the attachment of enteropathogenic *E. coli* by induction of MUC2 and MUC3 mucins. Therefore, protection against pathogens is provided by glycocalyx overlying and increased mucous layers. Moreover, due to the attachment of probiotic organisms gut epithelial surfaces, the adhesion sites are blocked for pathogen colonization [67]. Upon the ingestion of *lactobacilli*, it competes for the binding sites due to which few sites are available for pathogenic bacteria. Attachment is facilitated by Mannose specific adhesion proteins, that also attaches to cell surface and are important for pathogens

Table 6.2 Example of different inhibitory compounds produced by probiotic strains [51].

Compound	Example	Strain	Spectrum	References
Bacteriocins	Pediocin PA-1	*Ped. acidilactici*	Broad spectrum: Gram-positive bacteria	[52]
	Nisin	*Lc. lactis subsp. lactis*	Broad spectrum: Gram-positive bacteria without nisinase	[53]
	Enterocin AS48	*Ent. Faecalis*	Gram-positive bacteria, *Salmonella enterica, Bacillus subtilis, E. coli, B. cereus, B. circulans, Enterococcus faecalis, C. bovis, Micrococcus lysodeikticus, S. aureus, Ent. faecium, Enterobacter cloacae, Klebsiella pneumoniae, Salmonella typhimurium, Pseudomonas fluorescens, P. aeruginosa, Corynebacterium glutamicum, Nocardia corallina, Mycobacterium phlei, Micrococcus luteus, Proteus incontans, shigella sonnei.*	[54, 55]
	Enterolysin A	*Ent. Faecalis*	*Lb. sakei, Lb. brevis, Lb. curvatus, Lc. cremoris, Lb. lactis, Ped. pentosaceus, Ped. acidilactici, Ent. faecium, Ent. faecalis, L. innocua, L. ivanovii, Bacillus subtilis, B. cereus, S. carnosus, Propionibacterium jensenii*	[56]
Bacteriocin-like inhibitory substance (BLIS)		*Lc. lactis* subsp. *lactis* CECT-4434	*Staphylococcus aureus*	[57]
		Ped. acidilactici Kp10	*L. monocytogenes*	[58]
		Leuc. mesenteroides 406	*L. monocytogenes*	[59]
Antibiotic	Reuterin	*Lb. reuteri* DSM 20016	*Gram-positive (Clostridium and Staphylococcus) and Gram-negative (Escherichia, Salmonella, Shigella) bacteria, against the yeast, Saccharomyces cerevisiae, and against the*	[60]

(continued)

Table 6.2 (continued)

Compound	Example	Strain	Spectrum	References
			protozoan, Trypanosoma cruzi	
	Reutericyclin	*Lb. reuteri*	*Gram-positive bacteria (Lactobacillus, Bacillus, Enterococcus, Staphylococcus, and Listeria)*	[61, 62]
Organic acids	Lactic acid, Acetic acid	LAB	Broad spectrum: Bacteria affected by pH	[63]
Hydrogen peroxide		*Ped. acidilacti, Leuc. mesenteroides, Lb. brevis, Lb. plantarum, Lb. casei*	Broad spectrum: Catalase negative bacteria	[63]
Others	Ethanol	*Bifidobacterium longum*	Broad spectrum: Bacteria affected by membrane	[64]
		Ent. Faecalis, Lb. acidophilus, Lb. fermentum, Lb. plantarum, Weissella confuse	Dissociations	
	Diacetyl	*Lb. plantarum, Lb. helveticus, Lb. bulgaricus, Ent. Faecalis, Leuc. mesenteroides*	*E. coli, Listeria, Yersinia, Salmonella, Aeromanas*	[62]
	CO_2	*Heterofermentative* LAB	Broad spectrum: Aerobic bacteria	[62]

binding in gut, facilitates the attachment of *L. plantarum* Lp6 onto rat mucus preventing pathogen colonization [68]. Acid resistant strains from *Bifidobacterium longum* and *B. catenulatum* are reported to have effective attachment properties to human intestinal mucus in comparison to acid-sensitive [69]. In *Bifidobacteria*, acid resistance improves functionality through enhancing stability plus improving surface properties.

Combination of probiotics with VSL#3 improves the mucins synthesis and facilitate expression of mucin gene, therefore, enhancing the bacterial attachment to the epithelium of intestine [70]. Keratinocyte cell death, due to *Staphylococcus aureus*, in undifferentiated and differentiated keratinocytes is reduced by potential probiotics, *Lactobacillus reuteri* ATCC 55730 and *Lactobacillus rhamnosus* AC413. Probiotic efficiency was higher for Keratinocyte survival when they were applied before or simultaneously with *S. aureus* infection. *S. aureus* needs α5β1 integrin for attachment to keratinocytes, protective effect like probiotic was observed by blocking of α5β1 integrin. The competition for the binding site between pathogens and *L. reuteri* might be the protection mechanism for keratinocytes. Therefore,

inhibition of *S. aureus* colonization and infection prevention can be achieved by application of topical probiotic prophylactically [71].

6.3 Probiotics and Nutrients Competition

One of the mechanisms for inhibiting pathogens form colonization in human gut might be the nutrient competition. There are two different ways for such competition; firstly, preventing the nutrient and energy source uptake by pathogen which is required for growth and proliferation in human gut. Secondly, production of metabolites like short chain fatty acids (SCFAs) and organic acids through fermentation and metabolism which lowers the gut pH making it unfavorable for most of the pathogens, e.g. *E. coli* and *Salmonella* [50]. *Bifidobacterium adolescentis* S2-1 prevents the growth of *Porphyromonas gingivalis* by outcompeting it for vitamin K and other growth factors [72]. After the exposure to probiotic (*Lactobacillus paracasei* or *Lactobacillus rhamnosus*), changes in pathways such as short chain fatty acids (SCFA), amino acid, and methylamines metabolism were observed in mice (germ free) colonized with microbiota of human baby [73].

Probiotics, for example, *L. delbrueckii* and *L. acidophilus*, prevent the availability of ferric hydroxide to pathogens by binding them to its cell surface [74]. Probiotic strains and exert inhibitory effects on Biofilm formation of pathogenic *Listeria monocytogenes* and *Salmonella typhimurium* are inhibited by *L. rhamnosus* and *L. paracasei* probiotic through different mechanisms including competition, displacement, and exclusion. A decrease of more than three log cycles biofilm cells was observed for *L. monocytogenes* [75].

6.4 Probiotics and Immune System

Immune system is affected by various reported pathways due to potential application of probiotics [76, 77]. Stimulating specific and nonspecific immunity is one of the possible mechanisms through which probiotics helps to prevent the intestinal disease in host. LAB products have immunomodulatory action through Toll like Receptors (TLRs) expression regulation, inflammatory responses inhibition, Dendritic cells (DCs) activation, and Natural Killer (NK) cells, among innate immunity; lymphocytes propagation, balancing the response of T-helper (Th1/Th2) cells, specific IgA secretion, in further ways [78]. *Bacillus subtilis* B10 and *Saccharomyces boulardii* targets specific TLRs and associated factors, hence, having a major role in controlling immunological functions of chicken bone marrow DCs. Probiotics get attached to surface of DCs. Upregulation in expression level of MHC-II, CD40, CD80, and CD86 genes was observed. Additionally, the expression of TLR1, TLR2, TLR4, and TLR15 (chicken specific) was enhanced and increased in levels of downstream related factors TRAF6, MyD88, NFκ- B mRNA, and TAB1was observed [79].

Accumulation and growth of healthy microorganisms in gut result in maturation of the several immune mechanisms, especially, for the IgA and IgM secreting cells circulation. After preparing, Memory B besides T cells move towards the effector sites, actively proliferate, then local stimulation of various cytokines and secretory IgA generation. Probiotic stimulates the IgA production upon entering the gut. Studies in mice (kept germ free) evidenced the IgA production in immune system [80]. Several studies suggested that improvement of innate and adaptive immunity along with alleviate allergies, prevention of gastric mucosal lesion development, and put up defense against intestinal pathogen infection was observed due to lactic acid bacteria (LAB) such as *Bifidobacterium* and *Lactobacillus* and also due to their fermented products [78].

Feeding to 1.4 years old rats resulted in enhanced immunosenescence associated Th1/Th2 imbalance, higher resistance to *E. coli* infection of aged mice, and increased antioxidant capacity were observed as a result of feeding *Lactobacillus rhamnosus* to mice (16 months old). Increase in levels of IFN-γ and decrease in levels of IL-4 and IL-10 production, increase in phagocytosis and neutrophil respiratory burst enzymes with no aggravation in plasma levels of MCP-1 and TNF-α was observed in the mice feed with probiotic. IgE levels and IgG1/IgG2a ratio decreased along with increase in activities of antioxidant enzymes were found in the probiotic fed mice, *E. coli* translocation to the organs of the mice were also reduced significantly [81].

6.4.1 Degradation of Toxins Receptors through Probiotics

Enzymatic modification of toxin receptor is done by probiotics; host is protected from intestinal disease of *Clostridium difficile* due to modification in toxin receptor in intestinal mucosa by *Saccharomyces boulardii*. Various other reported mechanisms are decreasing toxin production, lowering gut pH and decrease of virulence [50]. Probiotics could change receptors for toxins as well as prevent against pathology caused by toxins. *Saccharomyces boulardii* have the ability to degrade toxin receptors for *Clostridium difficile* in ileum of rabbit and by polyamines production, it can prevent cholera-prompted secretion in jejunum of rat. Impact of a multi-strain probiotic plus synbiotic formulation (*Lactobacillus paracasei F8*, L. *plantarum* F44, *Bifidobacterium lactis* 8:8, *B. breve* 46, resistant starch, isomaltooligosaccharides, and galacto-oligosaccharides) was studied in *Clostridium difficile NAP1/027 infected* C57BL/6 mice. Upon the formulation feeding, *lactobacilli* and *bifidobacteria* counts increased without detecting any caecal toxins. *C. difficile* DNA copies were found in significantly decreased after the qPCR of caecal [82].

6.4.2 *Probiotics Roles in Anti-Proliferative*

Due to the reduction in putrefactive bacteria including *Bacteroides, Clostridium*, and *coliforms* species and increase in *lactobacilli* and *bifidobacteria* that facilitate in reducing risk for colorectal cancer, probiotics are supposed to have anti-cancer activity. Probiotic, *Lactobacillus salivarius* ssp. *Salivarius*, reduced prevalence of adenocarcinoma in colon of IL-10 knockout rats [83]. Probiotic, *Streptococcus thermophilus* strain TH-4 have an anti-inflammatory activity along with the ability of high folate production which is important in epithelial cells for DNA repair [84, 85].

6.5 Gut Microbiota Modulation

Human gut microbes always have been immersed in the regulation of various biological functions, varying from cognitive processes and energy regulation to improving host immunity against harmful microorganisms and also neutralization of toxins. The potential application of probiotics and prebiotics always involves in the maintaining of host ideal gut health, treating/preventing host recurring inflammatory, and immune system linked diseases [86]. Probiotics have a wide range of application in prevention and treatment of several diseases which are induced or associated with the dysbiosis of gut microbiota such as acute infectious diarrhea and antibiotic-associated diarrhea, and also other GI tract diseases like colic's or irritable bowel syndrome. At the time of treatment the gut microbial community makeup stays more steady and that it positively relates with recovery of disease symptoms [87].

6.6 Probiotics and Health

Probiotics enhance the nutritive and microbial balance of host gastrointestinal tract. Probiotics work as a carrier that transport their beneficial functional components to different target locations in the gastrointestinal tract. Ingestion of live probiotic strains has more effective results which varies from strain to strain [88]. Whereas, it is not always essential to accomplish profits [89].

6.6.1 Probiotics Role in the Treatment of Gastrointestinal Disorders

6.6.1.1 Antibiotic-Associated Diarrhea (AAD)

A systemic review study on treating of antibiotic-associated diarrhea (AAD) by usage of probiotics in aged patients (more than 65 years) and in adults (18 to 64 years) evaluated 30 random managed tests that fit in the previously developed inclusion measures. The clinical studies proposed that probiotic act as an adjuvant for antibodies which lower down the chances of antibiotic-associated diarrhea (AAD) in adults, but not in aged persons [90]. PROSPERO study proved that a number of probiotic strains such as *S.boulardii* and *lactobacillus rhamnosus* GG have involved in the prevention of antibiotic-associated diarrhea but other strains such as Lactobacillus bulgaricus, L. delbrueckii, and S.salivarius are not capable of preventing ADD [91–93].

6.6.1.2 Irritable Bowel Syndrome (IBS)

Several physiological, epidemiological, and clinical studied data have indicated that gut microbiota involves in the pathogenesis of irritable bowel syndrome, however, IBS pathophysiology still undiscovered [94, 95].

A functional study showed that altering the host gut microbes in conjugation with probiotics can influence some host intestinal functions, like sensitivity and motility, which seems to be related to the irritable bowel syndrome pathogenesis I [96]. A clinical experiment showed that the group of patients (35,624) that have intake of *B. infantis* significantly improved their disease symptoms in comparison to placebo. Moreover, the serum IL-10/IL12 ratio normalized, indicating that probiotic can helps in remission of proinflammatory state associated with irritable bowel syndrome [97, 98]. In addition, *L. plantarum* is better than placebo in remission of few symptoms in IBS patients. Specifically, the DSM 9843 strain radically decreased flatulence, and the 299 V and LPO1 strains appreciably lowered the intestinal pain [99–101].

6.6.1.3 Ulcerative Colitis

A clinical experiment showed that the mesalamine treatment with strain *Lactobacillus GG* might be more efficient than standard treatment for preventing the relapsing time of disease [102]. *E. coli* strain Nissle 1917 showed similar effective results as of 5-aminosalicyclates in averting the relapsing of ulcerative colitis in adults [103].

6.6.1.4 Crohn's Disease

Clinical experiments performed with *E-coli* strain *Nissle* 1917 and with distinct strains of *Lactobacillus* had not shown any higher effect than placebo in averting the occurrence of Crohn's disease [104, 105]. A studied proved that daily intake of 3 g mesalamine alone was less effective than 2 g daily intake of mesalamine along with *S. boulardii* in lowering the relapsing of Crohn's disease in patients. But later on a clinical study did not verify these results [106, 107].

6.6.1.5 Pouchitis

Pouchitis is an inflammatory condition of the ileal reservoir in patients with acute and chronic refractory ulcerative colitis experienced restorative proctocolectomy with ileal pouchanal anastomosis (IPAA) [108]. Several clinical trials with probiotics have been conducted that have shown their safety and effectiveness in sustaining the reduction of pouch inflammation, also antibiotic treatment attained subsequent, like 5-aminosalicyclic acid also helps in relapsing of chronic pouchitis and prevention of acute pouchitis [109, 110]. A systematic review from the Cochrane Collaboration showed that VSL#3 was very efficient in sustaining the reduction of chronic pouchitis and also in averting the onset of pouchitis than placebo [111].

6.6.2 Probiotics for Depression and Anxiety

Depression and anxiety are two most common human mental health conditions, with lifetime prevalence rates worldwide. Gut and brain interact with each other through a particular pathway called gut-brain axis pathway that includes immune, endocrine, and neural systems. Administration of probiotic mixture containing *Bifidobacterium longum* BL04, *L. plantrum* LP, *Lactobacillus fermentum* LF16, and *L. rhamnosus* LR06 was given to examine the effect of probiotics on depression and anxiety was reported. The study did not provide any positive effect on sleep quality and depressive mood state [112]. Thus more significant clinical trials are needed to explore the effect of probiotics on depression and anxiety.

6.6.3 Human Gut Microbial Community

Human gut microbiota is the microorganisms that live in the human gut. It is complex community of microbes—estimated to contain 200 trillion cells and containing greater than 1000 diverse microbial species Fig. 6.1. Human gut

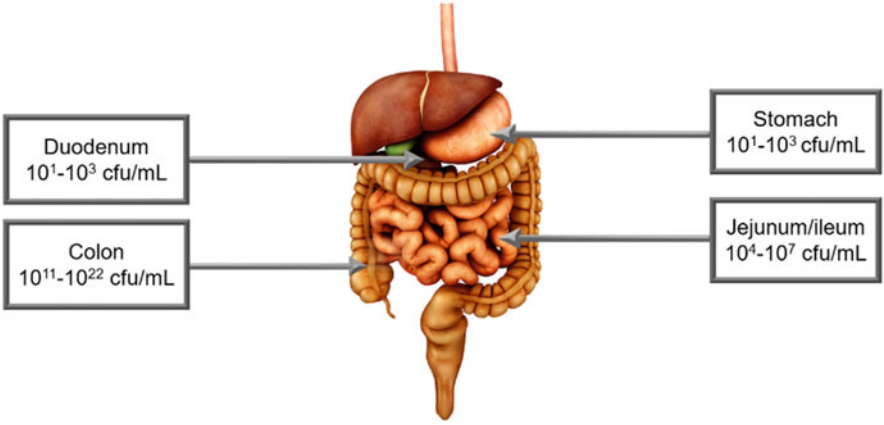

Fig. 6.1 Microbial density in the gut [114]

microbiota is composed of a wide range of bacteria, fungi, archaea, and viruses [113]. Gut microbiota—biome of microorganisms that live in the digestive tract of human beings whether on the intestinal mucosal surface or within the gut lumen.

Individual has their own stable fecal microbiota for lifetime and harbors different characteristic pattern of gut microbial flora. Around 90% of human gut microbiota are made up of *Bacteroidetes* and *Firmicutes*.

6.6.3.1 Function of Gut Microbiota

Intact microbiome is essential for the development of the GIT in many ways including—immune tolerance, the mucosa associated immune system, motility and vascularity, epithelial and barrier function. The microbiota which exhibiting commensalism in host provide homeostatic functions like immunomodulation, pathogen exclusion, upregulation of cytoprotective genes, regulation prevention of apoptosis, and maintenance of barrier function.

6.6.3.2 Metabolic Functions

N-digestible dietary residue fermentation e.g. cellulose, starch by aerobic bacteria, and short chain fatty acids (SCFAs), are the source for energy of both host and resident bacteria Gut Bacteroides involves in the breakdown of complex N-glycan with the help of enzymatic apparatus which is encoded by multiple co-regulated genetic loci [115]. Putrefaction of exogenous and endogenous protein (like sloughed epithelium and lysed bacteria) has been done by anaerobic bacteria, SCFAs as well as toxic substances like ammonia and amines [116].

6.6.3.3 Trophic Functions

Short chain fatty acids induce the differentiation and proliferation of epithelial cell. Moreover, butyrate promotes cells reversion from neoplastic to non-neoplastic phenotype (Fig. 6.2).

6.7 Development and Homeostasis of Immune System

Specialized epithelial cells (M cells), sample luminal antigens as well as the microflora transport them to the lymphoid follicles to develop tolerating anti-inflammatory response (Th2 response) through the production of IL 10 and TGFB. Due to the pertinacious interactions between the host and its bacteria the immunity of host constantly changed. Host microorganisms try to change the immune response by changing its surface antigenicity, so that organism can avoid detection by immunosurveillance and maintain predominance of ecological niche in intestinal tract. Bacteria commensalism have play an essential role in sustaining the intestinal epithelial homeostasis and these gut bacteria are recognized under normal steady-state conditions by TLRs. TLRs activation through commensal microflora is important for protection from gut injury and associated mortality [118].

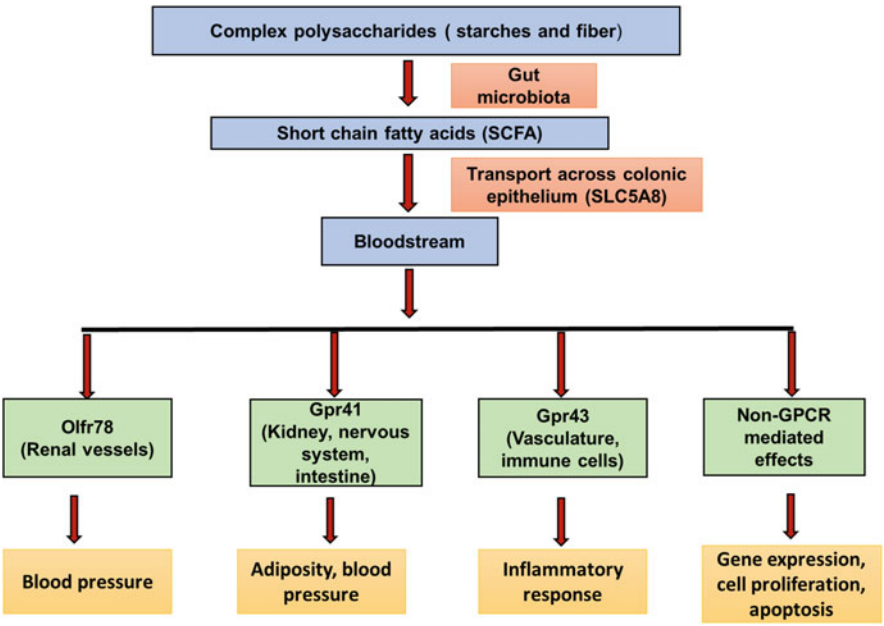

Fig. 6.2 Microbiota derived SCFAs and atherosclerosis [117]

Animal's colonization with major gut microbes, Bacteroides fragilis, physical and cellular maturation during immune system development is directed by a bacterial polysaccharide (PSA). During the colonization of B. fragilis, main activities of PSA are directing lymphoid organogenesis, correcting systemic T cell deficiencies and T (H)1/T(H)2 imbalances [119]. Communication between the host immune system and symbiotic microbiota facilitate by the bacterial metabolites and also affecting the balance between pro- and anti-inflammatory mechanisms [120]. Short chain fatty acids (SCFA), microbial metabolites regulate colonic Treg cell homeostasis [121].

6.7.1 Protective Function (Barrier Effect)

In barrier protective function microorganisms compete and attach to the brush border of host intestinal epithelial layer. Beneficial microorganisms compete for accessible nutrients and secrete antimicrobial (bacteriocins) [122].

6.7.2 Colonization Mechanism

Inflammation host responses change in microbiota composition and growth suppression induced by *Salmonella enterica* subspecies 1 *serovar Typhimurium* (S. Tm). Avirulent invGsseD mutant failed to trigger the colitis which was surpass by the gut microbiota in compare to wild type S. Tm. Inflammation can cause colonization resistance. Host immune defense system can alter the equilibrium between the pathogen and defensive microbiota in favor of the harmful microorganism [123].

6.7.3 Function of Uncultured Bacteria

The human gut microbial composition is associated with diseases and health of the host environment, but the awareness of different host microbial community is still needed for identifying the vast biological roles of the gut microbiota. The whole composition of human gut microbiota remains unknown. A study reported the identification of 1952 uncultured candidate bacterial species from 11,850 human gut microbiomes via reconstructing 92,143 metagenome-assembled genomes (Fig. 6.3). The identification of these species can help in understanding the interaction between probiotics and their beneficial effects [124].

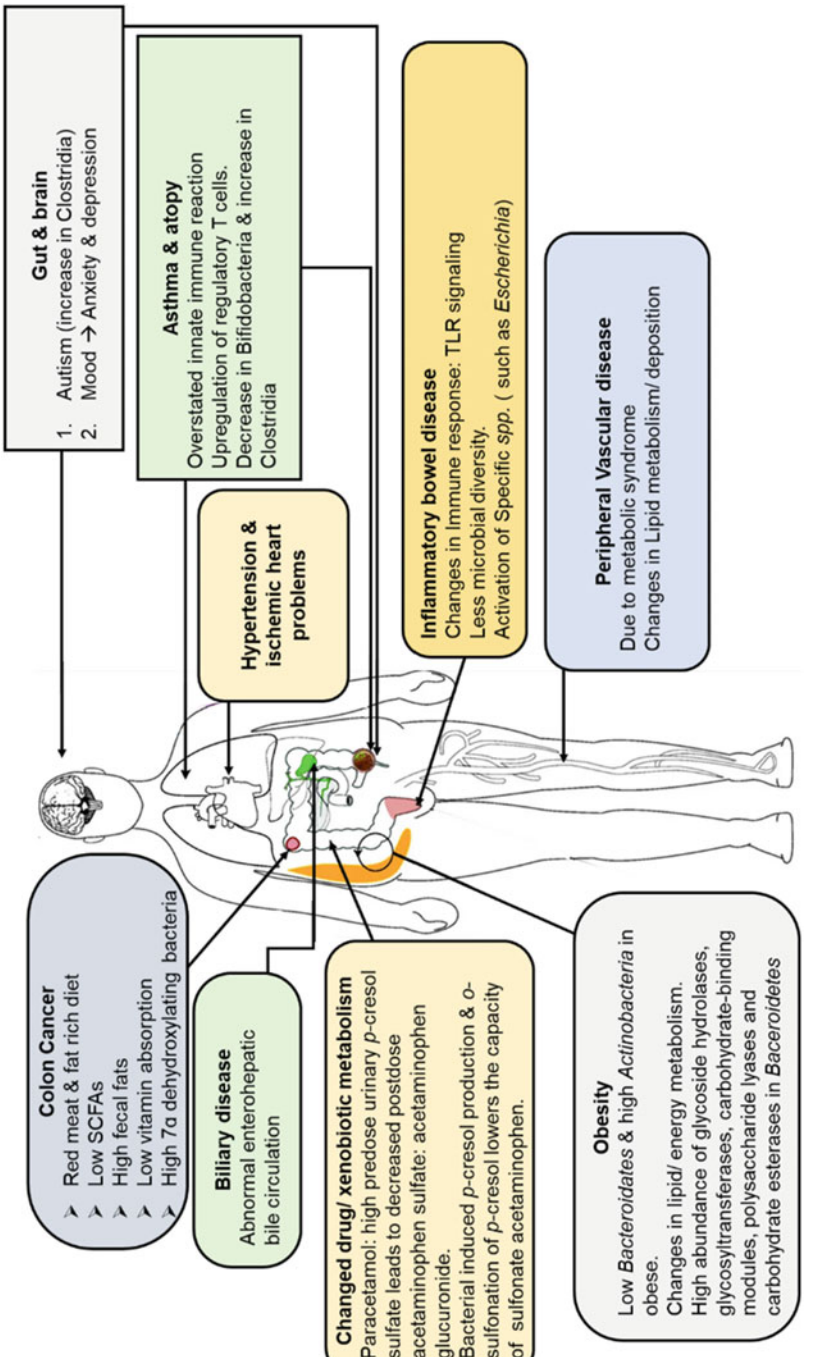

Fig. 6.3 Influence of gut microbial metabolism on human health [125]

6.8 The Gut Microbiota and Cancers

Colorectal cancer increases in human beings having age less than 50 years and it is related with human diet factors and daily eating habits which eventually affect the gut microbiota and CRC is the third most widespread cancer worldwide. In vitro experiments proliferation of CRC cells promoted by *F. nucleatum*. in mice, it is derived from the patient cells by CRC xenografts. Enterotoxigenic *Bacteroides fragilis* is the most long-studied human bacterial pathogen which causes diarrhea and inflammation in gastrointestinal tract of human beings. Enterotoxigenic *Bacteroides fragilis* (ETBF) increases colorectal cancer formation in mice. Currently, it was found in precancerous colonic lesions and biofilms coating human CRCs called adenomas (Fig. 6.4). Escherichia coli improve tumorigenesis in preclinical CRC experimental models by expressing the genomic island polyketide synthase (pks+) and are enriched in human colorectal cancer (CRC) tissues. Pks + *E. coli* secrete the genotoxin colibactin which caused alkylation in DNA, resulting in DNA adducts in colonic epithelial cells [126].

6.9 Gut Microbiota and Malabsorption Syndrome

Malabsorption syndrome is not exceptional, and it refers to the number of intestinal disorders which mimic the functional GI tract disorders. It is mainly due to the poor absorption of dietary carbohydrates, like fructose, lactose, etc. Occurrence and degree of malabsorption due to dietary lactose are widely diverse in the world with distinct population but most common in Asia than in America and Europe [127]. Number of host factors involves in the development of malabsorption such as degree of visceral hypersensitivity, host functional issues, cognitive dysfunction, colonic transit, host gut microbiota and also on the subtypes of microorganisms; bacteria such as *Methanobrevibacter smithii* effects on the intestinal transit due constipation and excess production of methane, however, hydrogen sulfide (H_2S) consider as a diarrhea biomarker [128].

6.10 Gut Microbiota and IBD

Irritable bowel disease related with the metabolic and compositional changes in the host intestinal microbiota. A study showed the effect on different microbial species of IBD suffering host, comprising decrease in *Dialister invisus*, *Bifidobacterium adolescentis, Faecalibacterium prausnitzii* and an increase in *Ruminococcus gnavus* and an unidentified member of Clostridium cluster XIVa [129]. A study revealed the wide range of data report about the host and microbial responses in 132 IBD patients,

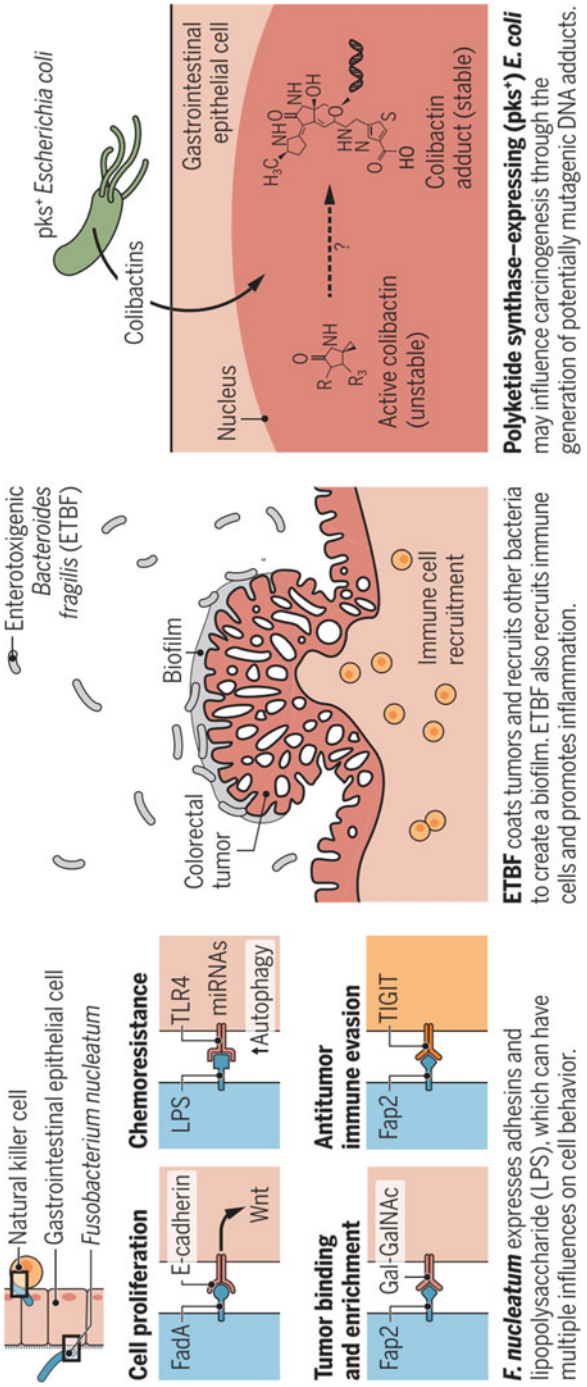

Fig. 6.4 Microorganisms may derive colorectal cancer [126]

showing the host immune factors, molecular functional profile, and gut microbiome in relation of metabolome [130].

6.11 Gut Microbiota and FBD

Functional bowel disorders are known as "irritable bowel syndrome" and they are very similar to the number of GI tract diseases without any clear pathogenesis. A profound sequencing of the microbiome (150-times fold as related to the human genome and bacterial genes regulating functions) has supported that the irritable bowel syndrome gut microbes are aberrant in count and has diverse number of bacterial families [113, 131]. This report presented that the *Firmicutes* and *Bacteroides* ratio might act as an indicator of microbial imbalance in irritable bowel syndrome [132].

6.12 Gut Microbiota and CDI

Clostridium difficile is a potential pathogen associated mostly with diarrhea caused by the frequent intake of antibiotics. The infections caused by *C. difficile* possess major health issues and are known as *Clostridium difficile* infections (CDI). The role of gut microbes in pathogenesis of CDI grabs the attention of researchers [133]. The patients suffering from reoccurring CDI have shown alterations in gut microbial composition, also associated with frequent intake of antibiotics. A study conducted on CDI patients who have undergone fecal microbiota transplantation (FMT), reduction in Firmicutes and Bacteroidetes population, and increment in Proteobacteria was observed in pre-FMT fecal samples [134]. Another study on CDI patients showed decrease in lactate producing phylotypes and opportunistic pathogens associated with endotoxin production (Fig. 6.5). An increment in the butyrate-producing anaerobic bacteria was also reported when compared to healthy control groups [135].

6.13 Gut Microbiota and Health

The microbes of human gut can affect the physiology of host in various dimensions and their interaction built a beneficial relationship for both host and gut microbes. Mutually beneficial bacteria help in providing vital nutrients, metabolize the complex compounds, produce inhibitory compounds against pathogens, and help in the formation of intestinal architecture [137] (Table 6.3).

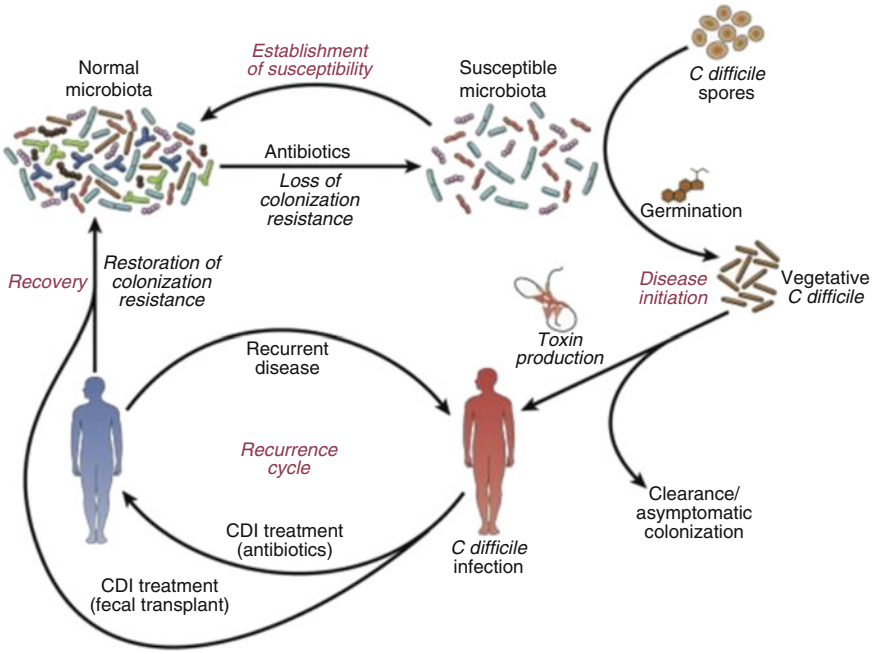

Fig. 6.5 Human gut microbiota and diseases [136]

6.13.1 Immune Regulation

Gut microbes can stimulate the normal development of host humoral and cellular mucosal immunity. Hematopoietic and non-hematopoietic cells of innate immunity can recognized the metabolites and signals of microbes and converted into physiological functions [151]. Clinical studies reported that the GF mice have showed defects in the formation of antibodies and gut-associated lymphoid tissues as comparison to normal mice [152]. A study has showed that the tolerogenic responses produced by gut microbes affect the gut dendritic cells and ceased the anti-inflammatory pathway of Th17 helper cells [153].

6.13.2 Drug Metabolism by Gut Microbiota

Microbiome-encoded enzymes elucidate the drug-metabolizing activities of host gut microbes and different communities on the basis of their genomic structural content and significantly affect the intestinal and systemic drug metabolism of mice [154].

Table 6.3 Gut microbiota, their metabolites and function [137].

Bacteria	Metabolites	Functions	References
Lactobacilli, Bifidobacterium	Vitamins: vit. B, K, biotin, riboflavin, folate, thiamine	Cofactor: Enzymatic reactions, regulate cell proliferation, enhance immune function.	[138, 139]
Clostridium, Bifidobacterium, Lactobacillus, Enterobacter, Roseburia	Acylglycerols, conjugated fatty acids, cholesterol, sphingomyelin, phosphatidylcholine, triglycerides	Improve intestinal permeability, decrease host fat mass and body weight, bile acid and production.	[140]
Clostridium, Bifidobacterium, Lactobacillus, Enterobacter, Bacteroids	Bile acids: glycocholate, cholate, etc.	Maintenance of intestinal barrier functions enhance lipid absorption, bile acid accumulation by some *Bifidobacteria.*	[141–143]
Clostridium, Bifidobacterium sp, coprococcus, roseburia	SCFAs: acetate, hexanoate, butyrate, propionate, isobutyrate	Lower the colonic pH, lower the level of cholesterol, pathogen inhibition, stimulate Na and H_2O absorption	[143, 144]
Lactobacillus, Bifidobacterium, Clostridium difficile, F. prausnitzii	Phenyl derivatives, benzoyl, phenol	Chronic diabetes and hepatities, asthma indication (urinary 3-Nitrotyrosine and 3-Nitro-4-hydroxyphenylacetic acid), obesity and hypertension biomarkers in humans.	[145]
Firmicutes, Actinobacteria, Proteobacteria, Bifidobacterium, Faecalibacterium prausnitzii	Choline metabolites: betaine, dimethylglycine, methylene, dimethyline, trimethyline	Neurotransmission, methyl transfer, cell membrane functioning	[146]
Clostridium sporogenes, E-coli	Indole derivatives	Protection against stress-induced GI epithelial damage	[147]
Lactobacillus acidophilus, Bacteroids fragilis	Polysaccharide A and B, Exopolysaccharides	Ceases cytokines levels, decreased neutrophil infiltration, host immune modulation.	[148]
Clostridium saccharolyticum, Campylobacter jejuni	Polyamines: cadaverine, spermine, spermidine, putrescine	Cell growth, apoptosis, increased calcium ion accumulation in mitochondria	[149]
Lactobacillus paracasei, Lactobacillus brevis	Gamma aminobutyric acid (GABA)	Inhibits CNS functions, decreases weight loss, promotes diuresis and hypotension	[150]

6.13.3 Bacterial Metabolite Enhances Athletic Performance

Veillonella strain enhance the mice treadmill run time and also increases the specific run time of marathon athletes. *V. atypica* improves the athlete's performance during physical activities (running) by metabolic conversion of lactate into propionate, hence consider as a natural microbiome-encoded enzymatic process [155].

6.13.4 Alleviation of Food Allergy (FA)

In food allergic infants dysbiotic fecal microbiota developed with in time but unsuccessful in mice. Therapy with *Clostridiales* strains, either as a monotherapy with Subdoligranulum variable or consortium, suppressed food allergy in mice. However, immunomodulatory *bacteroidales* consortium bacteriotherapy induced expression by regulator T (Treg) cells of the transcription factor ROR γt in a My D88-dependent manner, which was less in food allergic mice plus infants and futilely persuaded by their microbiota [156].

6.14 Conclusions

Industrial, agricultural, and domestic use of synthetic compounds produce large amount of environmental pollutants. From past several decades' environmental pollutants cause various health hazards and these pollutants can alter the functioning of gut microbiota. Use of probiotics will protect against the toxicity caused by these pollutants. There are number of bacterial, yeast, and fungal species which are used as probiotics. Various types of inhibitory compounds produced by probiotics shows antagonistic effect against pathogenic strains. It has been stated that probiotics produce extensive range of different *bacteriocins* such as *nicin* which constitute the major mechanism of antimicrobial act. *Lactobacilli* and *bifidobacteria* genera have been informed to produce *bacteriosins*, *lactolin*, *acidophillin acidolin*, and *lactocidin*, protection against infection with the foodborne pathogens. The identification of these species may help in understanding the interaction between probiotics and benefits with probiotics. Probiotics may increase the microbiological and nutritional balance of the gastrointestinal tract and used for the treatment of various gastrointestinal disorders like irritable bowel syndrome, Crohn's disease, pouchitis, antibiotic-associated diarrhea. Probiotics also used for enhancing the immune system by improving gut microbiota. It is concluded that the probiotics are essential for immune regulation, improve gut microbiota and for the treatment of gastrointestinal disorders.

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