

***E. coli* and normal microbiota; their interaction and role in health and disease**

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Abstract

Human microbiota is a complex of microorganisms, which are bacteria, fungi, archaea, viruses, and protozoans, located on and in the human body and are essential for physiological homeostasis. For instance, gut microbiota hosts a large population of microorganisms that are manyfold the human cells and genes, influence host metabolism, immune response, and regulatory functions. Biota is involved in various critical activities that include nutrient breakdown, synthesis of vitamins and acting as a shield against infections. However, imbalances in microbial populations or dysbiosis have been linked to diseases such as IBD, Obesity, Diabetes, and cardiovascular diseases. Technological improvements have expanded knowledge concerning microbiota construction and utilization, giving the possibility of curing these processes. Interventions like probiotics, prebiotics, fecal microbiota transplantation, and phage therapy are some of which are being sought to bring new balance to the microbial optimum. There is still some way to go, however, in getting these abilities to translate to clinical practice effectively, hence continued work has to be done on it. Microbiota holds a key for a fresh view on health and disease management and is being studied widely.

Introduction

The human body hosting the variety of microorganisms is referred to as microbiota constitutes the human body (Bhat et al., 2023). This microbiota consists of bacterial, fungal, archaeological, viral, and protozoan members that are distributed in diverse anatomic locations including skin, oral, gastrointestinal tract, and respiratory tract. These communities, also called microbiota, are essential for the host's physiological regulation and modulating its health by mediating nutrient acquisition, immune regulation, or pathogen defense mechanisms. Most prominently, gut

microbiota alone has over a hundred trillion microbial cells, ten times as many as human cells, and a significantly greater number of genes than the human genome. It was essential for me to grasp the differentiation between microbiota and microbiome as the base of the distinction (Dogan, 2024). Talking about microbiota as the sum of microbial cells residing in a given environment, microbiome is defined as microbial genomic, structural, and metabolic content, plus phyla or environment in which they exist (Burz et al., 2023).

The complexity of this complex ecosystem is gradually being unraveled by improved techniques, including metagenomic and high-throughput sequencing, which

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highlights the importance of this microbial interface (Nandy & Kapley, 2024). Microbial community composition also differs from site to site with respect to the local conditions which include pH, oxygen tension, and nutrient concentrations (Ning et al., 2024). For example, the communities of gut microbiota are mainly obligate anaerobic bacteria, mainly from the Firmicutes and Bacteroidetes divisions, and the skin microbiota is aerobic and facultative anaerobic bacteria such as *Staphylococcus*, *Propionibacterium*, etc. Indeed the existence, interactions, and sacrifices of these microorganisms and their host present significant impacts and consequences on systemic and localized health (Beharry et al., 2023). Other aspects of the microbiota's functional roles include the ability to ferment undigested polysaccharides and produce essential vitamins such as vitamin B12 and K and regulation of bile acid production. Inflammatory conditions including inflammatory bowel disease, obesity, cardiovascular disease, autoimmune disorders, and others, are linked to dysbiosis (Obayomi et al., 2024).

New data indicate that certain microbial taxa like *Escherichia coli* perform housekeeping functions and when in dysbiosis, can cause harm to the host organism (Davies, 2024; Lamaudière et al., 2023). Probiotics and prebiotics, Fecal microbiota transplantation, and phage therapy point of therapeutic approaches that are increasingly being applied (García-Cruz et al., 2023). These interventions targeting balancing microbial homeostasis provide prospects for the treatment of microbiota-associated diseases. Nevertheless, there remain issues in getting these therapies into clinics, meaning that more work is needed to decipher host-microbe interactions (Airola et al., 2023). The increasing interest in this research area shows that microbiota is a core determinant of neonatal health and disease, making it an emerging focus of biomedical science. Studying its specificity contributes not only to the knowledge of people's bodies and functions but also to the creation of extraordinary therapeutic possibilities.

Normal Microbiota

The microorganisms of a certain location, environment, or geological era are thus referred to as "microbiota" or "the microscopic living organisms of a region" (de LeBlanc & LeBlanc, 2014). The whole population of microorganisms that inhabit a certain area is referred to as the microbiota. This population comprises not only bacteria but also fungi, viruses, archaea, and protozoans (Jandhyala et al., 2015).

There are intricate colonies of microbes in the human body. It is believed that they number 10¹⁴ in total, which is ten times the amount of human cells in each person (Bik, 2009). Furthermore, the periods have a greater amount of genetic information than the human genome as a whole. The two terms, microbiota and microbiome, are radically used interchangeably, although they bear some dissimilarities. Microbiota can be defined as live microorganisms in a defined ecosystem including gut microbiota, oral microbiota etc. The term Microbiome is used to define the sum of microbial DNA in a habitats that includes the microorganisms themselves, their metabolites, any structural elements of the ecosystem as the conditions in the environment (Hou et al., 2022).

Composition and function

The digestion and synthesis of nutrients, energy metabolism, vitamin synthesis, epithelium growth, and immunological responses are all significantly influenced by our intestinal symbionts. In exchange, the gut microbes get a consistent supply of nutrients and favorable development circumstances (Bik, 2009). The two main polysaccharides that are resistant to the digestive enzymes of humans are cellulose and hemicelluloses. Nevertheless, 50–70% of ingested cellulose and hemicelluloses are broken down after going through the human digestive system because to microbial activity. Most gut microorganisms that can break down cellulose and hemicelluloses are members of the phylum Bacteroidetes (Rajilić-Stojanović, 2013).

Overview of the human microbiota across different sites (gut, skin, oral, etc.).

With a focus on the genera *Staphylococcus*, *Corynebacterium*, and *Propionibacterium*, which account for about 60% of the bacterial skin population in sebaceous regions, the bacterial phyla Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes are present on healthy human skin. Lipophilic *Propionibacterium* and *Staphylococci* species predominate in the areas with the lowest bacterial diversity, which include the forehead, retroarticular region, back, and lateral sides of the nostrils. Anelloviridae, Adenoviridae, Herpesviridae, Circoviridae, Polyomaviridae, and Papillomaviridae were all identified in a more recent investigation by Hannigan et al. But lately, a core phagosome including *Streptococcus*, *Staphylococcus*,

and *Propionibacterium* bacteriophages were discovered (Hrestak et al., 2022).

The combination of data from the Meta Hit and Human Microbiome Project has made the most thorough understanding of the human-associated microbial repertoire to date. These combined data showed 2172 species isolated from humans and placed in 12 phyla, with Proteobacteria, Firmicutes, Actinobacteria and Bacteroidetes comprising 93.5% of these species (Thursby & Juge, 2017). In the oral cavity, there are over 1,000 different kinds of bacteria, mostly belonging to the phylum Tenericutes, Firmicutes, Proteobacteria, Euryarchaeota, Fusobacteria, Actinobacteria, Bacteroidetes, and Chlamydia. The oral cavity is home to over 100 different types of fungus. Among the common genera include *Rhodotorula*, *Saccharomycetales*, *Aureobasidium*, *Aspergillus*, *Cladosporium*, *Candida*, *Fusarium*, *Cryptococcus*, *penicillium*, *Gibberella*, and *Schizophyllum*. Phage and eukaryotic viruses make up the oral virome. The Anelloviridae, Herpesviridae, and Papillomaviridae are the three primary families of these eukaryotic viruses (Li et al., 2022).

Role of microbiota in health

Sixty percent of the fecal bulk is made up of bacteria (Andoh, 2016). The scientists hypothesized that exposing pregnant women to microorganisms linked to farms may act as a natural immunotherapy, influencing the development of the child's immune system during pregnancy (Fujimura et al., 2010). Gut microbes specifically participate in metabolic processes like the fermentation of indigestible dietary fiber (resistant starch, certain oligosaccharides) with the retrieval of energy that has been consumed but not broken down by the host, the biotransformation of conjugated bile acids, and the breakdown of complexes based on oxalate, and the production of certain vitamins (like K and B12) (Montalto et al., 2009). According to recent studies, the human gut microbiota has a role in the breakdown of different polyphenols, which are phenolic chemicals found in food. The majority of polyphenols get to the colon after being poorly absorbed from the small intestine. Many plants, fruits, and foods of plant origin (tea, cocoa, wine) contain secondary polyphenolic compounds such as glycosides (conjugated with sugars like galactose, glucose, ribulose, rhamnose, arabinofuranose, and arabinopyrinose), including flavanones, flavonols, anthocyanidins, flavan-3-ols, flavones,

isoflavones, stilbenes, tannins, chlorogenic acids, and lignans. Once the gut flora has removed the sugar residue, the inactive polyphenols in the food are transformed into active molecules (Ilhan, 2018). In particular, studies in human obese subjects already confirmed changes in gut microbiota composition, including reduction of Bacteroidetes phylum and proportional increase of Firmicutes. In addition, overweight women had a decreased *Bifidobacterium* and *Bacteroides* and increased *Staphylococcus*, Enterobacteriaceae and *Escherichia coli* compared with normal weight pregnant women (Festi et al., 2014).

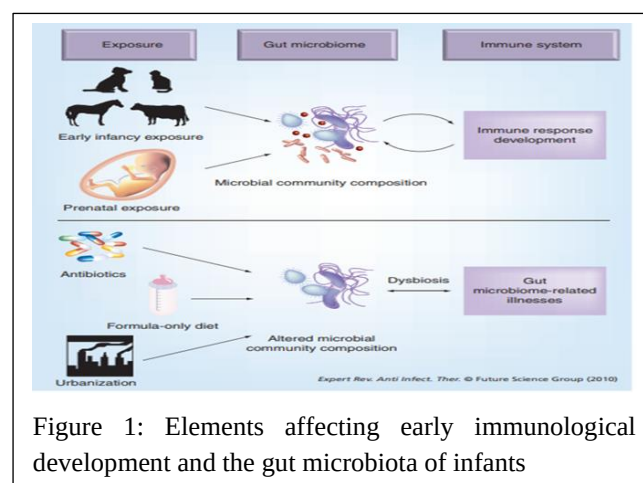
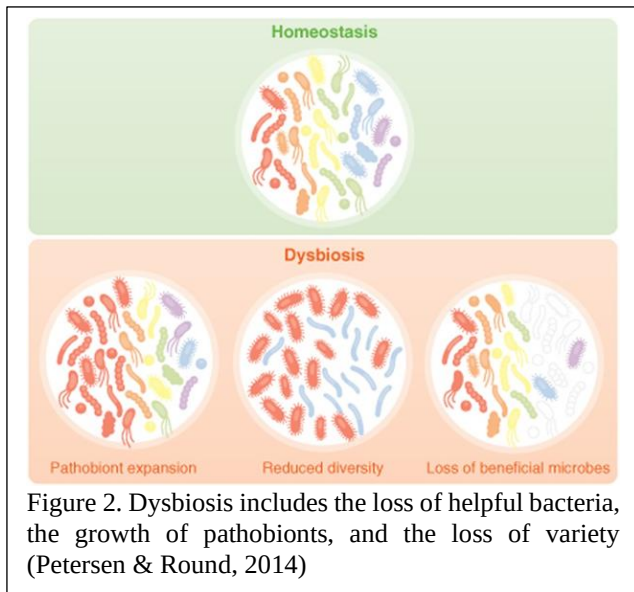


Figure 1: Elements affecting early immunological development and the gut microbiota of infants

Dysbiosis

Any alteration in the makeup of resident commensal communities in comparison to those observed in healthy people is referred to as dysbiosis. They start by classifying dysbiosis into three categories. These consist of (i) the decline of microbes that are helpful, (ii) the growth of pathobionts or possibly hazardous bacteria, and (iii) the reduction of microbial diversity in general (Petersen & Round, 2014).



The pathophysiology of intestinal and extra-intestinal illnesses is increasingly linked to dysbiosis of gut microbiota. While extra-intestinal problems include metabolic syndrome, obesity, asthma, allergies, and cardiovascular disease, intestinal disorders include inflammatory bowel disease, irritable bowel syndrome (IBS), and celiac disease (Carding et al., 2015). The investigation of mechanistic causal links between host immunity and commensal microbiota is significantly impacted by the use of germ free (GF) animal models. Early research on GF mice shows that significant intestine abnormalities in lymphoid tissue architecture and immunological activities are linked to the lack of commensal microorganisms. GF mice have much less $\alpha\beta$ and $\gamma\delta$ intra-epithelial lymphocytes (IELs), and de novo colonization may significantly increase their numbers. A key component of protective mucosal immunity is the induction of IgA antibodies, which are decreased in infants and GF animals before returning to almost normal levels with microbial (Zheng et al., 2020). The relationship between gut microbiota and CKD has been known for a long time. With CKD progression, the kidney loses the ability to eliminate catabolites produced by human metabolism⁸⁻¹⁰ and by its symbiote (gut microbiota)¹¹. Some of these substances are included in the “uremic toxins” category. Among those of intestinal derivation, the main and most studied are p-cresyl sulfate (p-CS), indoxyl sulphate (IS), indole 3 acetic acid (IAA) and trimethylamine N-oxide (TMAO). The latter is a

derivative of the catabolism of products of animal origin containing choline, phosphatidylcholine, carnitine, and betaine^{13,14}. With the progressive loss of kidney function, toxic compounds accumulate in the bloodstream causing the uremic state. Therefore, it is speculative that CKD not only induces a reduction in the elimination of uremic toxins, but it also favors their production¹⁵, involving in this process the gut microbiota. In fact, an alteration in the gut microbiota composition might be influenced by many factors including smoking, drugs, food patterns and some pathological conditions. Among these, the gut microbial composition in CKD patients is ultimately different from healthy subjects because several studies have shown that (Noce et al., 2022).

E. coli characteristics

Theodor Escherich, a Bavarian physician, isolated and identified *Escherichia coli* for the first time in 1885 (Martinson & Walk, 2020). *Escherichia coli*, which belongs to the Enterobacteriaceae family of bacteria, is one of the most common commensal occupant of the gastrointestinal tract of warm-blooded animals and humans and is also one of the major pathogens. Since hosts carry it in a mutually beneficial relationship, illness is seldom caused (Allocati et al., 2013).

Although it is less frequent, *Escherichia coli* may also be discovered in the gut microbiomes of fish, birds, reptiles, plants, soil, and food. In nature, it is primarily a component of the mammalian gut microbiome. The most prevalent aerobe in animals' lower intestines is usually *E. coli*. But since the gut is essentially an anoxic environment, obligatory anaerobes like those belonging to the Bacteroides and Firmicutes groups, together account for at least 90% of the whole gut microbial population—dominate the very vast and varied (500+ species) gut microbial community. In contrast, *E. coli* usually makes up just 0.1 to 5% of the population, which is partially due to the fact that it occupies a niche in the gut's relatively thin mucus layer. One of the sources of *E. coli*'s diverse diet is the complex, multi-species biofilm it forms in the mucus layer, where it competes for a variety of nutrients. Despite inevitable and frequent bulk losses, this abundant food source allows *E. coli* to sustain population densities of 10^6 – 10^9 cells per gram of fecal matter (Blount, 2015).

Role of *E. coli* in homeostasis

The word "homeostasis" comes from "same" and "steady," as any mechanism by which organisms are actively preserving the relatively constant environment necessary for existence. The word was first used by the doctor Walter Cannon in 1930. The human body is explained by his book, *The Wisdom of the Body*, how it stabilizes its temperature as well as blood oxygen, calcium, protein, fat, salt, sugar, and water content. Similar mechanisms dynamically preserve environmental steady-state conditions on Earth (Cannon & Rosenberg, 1932).

Interactions Between *E. coli* and Other Members of the Microbiota

Nearly all of the bacteria in the *Escherichia coli* species are nonpathogenic. More than 90% of adults in cross-sectional studies have *Escherichia coli* in their gut microbiota. One of the earliest bacteria to infiltrate newborns, *Escherichia coli* is a pioneer of the human stomach. Even though most of the literature refers to the species as "commensal," human-associated *Escherichia coli* may by definition be regarded as a mutualist due to its function in neonatal guts, its ability to make vitamin K, and its propensity to impart colonization resistance (protection against infections) (Horrocks et al., 2023).

Competition and cooperation in nutrient acquisition

One of the earliest bacteria to infiltrate newborns, *Escherichia coli* is a pioneer of the human stomach (Martinson & Walk, 2020). Many other investigations have shown that commensal *Escherichia coli* may compete with *E. coli* O157 H7 for nutrients. First, Maltby and co-workers demonstrated intestinal colonization competition between two commensal *Escherichia coli* (*E. coli* HS, *E. coli* Nissle 1917) strains and *E. coli* O157 H7 (Horrocks et al., 2023). *E. coli* O157 H7 could use the mucus associated monosaccharides including mannose, galactose, N-acetylglucosamine, ribose and arabinose to promote their development. *E. coli* HS and *E. coli* Nissle 1917 both did use arabinose, galactose, N-acetylglucosamine and mannose (but not ribose). But neither strain was able to fully occupy the nutrient niche of *E. coli* O157 H7, limiting the growth of *E. coli* O157 H7 in isolation. These lactose positive bacteria were, however, unable to ferment all sugars that *E. coli* O157 H7 was able to, until when *E. coli* O157 H7, *E. coli* HS, and *E. coli* Nissle 1917 were cultivated together they were able to consume all five sugars *E. coli* O157 H7 was able to. This

allowed these two commensal strains to completely occupy the nutritional niche and limit *E. coli* O157 H7 development. Another investigation demonstrated by Momose et al showed that commensal *Escherichia coli* and *E. coli* O157 H7 compete over proline (Fujimura et al., 2010).

Mucins, which are proteins rich in galactose, fucose, mannose, N-acetylglucosamine, N-acetylgalactosamine, and sialic acid, form the mucus layer that protects the gut epithelium. Saccharolytic microbiota members, such as Bacteroidales in the gut, extract these sugars, making them accessible to microbiota species that are not able to do so. However, the availability of these carbohydrates may also be used by harmful bacteria in the stomach to further their own growth (Bäumler & Sperandio, 2016).

Role of *E. coli* and the Microbiota in Health

The gut microbiota's makeup varies from person to person and may change significantly within a single person. In addition to variations in host genomes, environmental variables including antibiotic usage, lifestyle, nutrition, and cleanliness also contribute to interindividual variance in bacterial diversity. Dysbiosis, or a changed gut microbial makeup, may be detrimental and put a person at risk for illness (Janssen & Kersten, 2015).

Protective roles of *E. coli* in microbial balance.

Human health benefits from the composition of *Escherichia coli* strains; for instance, alterations in the makeup of *Escherichia coli* strains have been linked to intestinal inflammatory illnesses in humans. Although it is well acknowledged that the makeup of the *Escherichia coli* strains in the human gut flora is related to health, the precise molecular mechanism is yet unknown. Using in silico modeling, we identified the prevalent strains of *Escherichia coli* found in the human gut and compared their functions in a methodical manner (Gao et al., 2014). Some Gram-negative bacteria are also employed as probiotics; for example, *E. coli* Nissle 1917 has been used in veterinary medicine and in humans to treat colitis, constipation, and diarrhea. Additionally, reports suggested that a special LPS found in the probiotic *E. coli* Nissle 1917 had immunomodulatory effects without exhibiting immunotoxicity (Nakkarach et al., 2020).

Contribution to immune system development and modulation

Research is ongoing to better understand how the microbiota that reside in the gastrointestinal tract interacts with the human immune system. Under normal conditions, the gut microbiota generates compounds that interact indirectly and directly with host immune cells, play important roles in inflammatory signaling, and communicate with the immune system to modify immunological responses. *Roseburia intestinalis*, *Anaerostipes butyraticus*, and *Faecalibacterium prausnitzii* are among the bacteria that ferment complex carbohydrates to produce short-chain fatty acids (SCFAs), which control host immune cells and provide colonocytes a fuel source. SCFAs are metabolites generated by the microbiota that are abundant in the gut lumen. They are mostly composed of propionate, butyrate, and acetate. SCFAs are crucial for lowering local inflammation, preventing pathogen infiltration, and preserving the integrity of the intestinal barrier because they bind G-protein coupled receptors (GPCRs) and change gene expression by decreasing the activity of histone deacetylases (Yoo et al., 2020). The lamina propria is a crucial immunological compartment in the colon, home to many macrophages, DCs, T cells, and B cells that secrete IgA. MLNs and Peyer's patches (PPs) are the main imprints of acquired immune response in GALT. In fact, regulatory cells are also found in the lamina propria, where they preserve resistance to self-antigens and diets. While some CD8 lymphocytes move to the tip of the villous, where they form IELs, B cells in the lamina propria become activated and become IgA-producing plasma cells. The lamina propria also contains resident CD4, CD8, and B cells. In response to gut antigens, DCs pick up antigens collected in the lamina propria and transport them via draining lymphatic arteries to the MLNs and, subsequently, to the gut lymphoid tissue (PPs). IgA is then transferred across the epithelial barrier and released in the gut lumen. The existence of specialized ECs known as micro folds, or M cells, is a crucial characteristic. On their basolateral surface, the M-cells carry bacteria to professional antigen-presenting cells, including DCs, after sampling the antigens in the gut lumen (Purchiaroni et al., 2013).

Interplay with dietary factors and gut health.

Circadian rhythms, which are linked to the daily cycles of eating and fasting, are experienced by the body and by each individual cell. Immersed in these waves, the microbiota serves as a response element as well as a signal trigger. Furthermore, since the immune system and the microbiota are

closely related, the immune system also plays a role in synchronizing circadian clocks; both systems transmit information that is obtained from outside stimuli. By combining signals from hormones, nutrition, and innate immunological sensing, the gut microbiome coordinates host diurnal rhythms in the gut and other digestive glands and organs. The gut microbiota's composition and function change during the day in both humans and animals and this is linked to eating habits such as how often you eat and how long you fast overnight (Nova et al., 2022).

It has taken more than 50 years, but the Mediterranean diet has been established as the 'gold standard' in preventative medicine and health promotion. Myriad unprocessed olive oil, whole plant foods, dairy, moderate amounts of poultry and seafood, and little red meat are the emphasis of the Mediterranean diet. Diet can have very positive or very negative implications on the taxonomic and functional makeup of the gut microbiome. Dietary fiber is beneficial for human health for reducing long-term weight gain. Eating low fiber increases type 2 diabetes, and colon cancer risk (Ross et al., 2024). Research on protein intake has identified the ways in which the composition and functional capacity of human gut bacterial populations are influenced by the consumption of a Western diet heavy in meat, which is generally high in animal-based protein. Numerous chronic illnesses that are impacted by the kind and quantity of dietary fat consumed are closely linked to the gut microbiota. As an example, obesity has been linked to taxonomically significant alterations in the gut microbiota, although these alterations may more accurately be the result of variations in dietary fat content or lipid composition (Danneskiold-Samsøe et al., 2019).

***E. coli* and microbiota in disease**

Human digestive tracts are home to a diverse collection of bacteria known as the gut microbiota, which coexists harmoniously with the host. A number of gastrointestinal conditions, including irritable bowel syndrome, inflammatory bowel disease, which is represented by Crohn's disease and ulcerative *E. colitis*, and colorectal cancer, are linked to dysbiosis, which is defined by an imbalance between the advantageous and opportunistic gut microbiota. The mucosal barrier may be compromised by dysbiosis, which might prolong inflammation and carcinogenesis. In IBD patients, it is known to follow the inflammation-dysplasia-cancer sequence, and has been associated with the rise of particular groups of harmful bacteria, including

Escherichia coli, enterotoxigenic *Bacteroides fragilis*, and the release of pro-inflammatory and carcinogenic mediators, to increase the risk of colorectal cancer (CRC) (Quaglio et al., 2022).

There is mounting evidence that gut microbiota has a role in the emergence and/or persistence of lesions in inflammatory bowel disease. Patients with IBD have been shown to have altered intestinal microbiota composition, with a decrease in some stringent anaerobes and microaerophiles and an increase in certain bacterial groups, often facultative aerobes. *Escherichia coli* has been a natural target of research in the quest for an infectious element in the pathogenesis of IBD since it is a major facultative aerobe of the colon (Thomazini et al., 2011). According to some research, people with IBD have a quantitatively higher population of *E. coli* in their intestinal mucosa and feces.

Dysbiosis and pathogenic transformation of *E. coli*

The host's health is improved by the gut commensals, which are often symbiotic or benign bacteria that reside in the gastrointestinal system. Certain conditions, which are greatly influenced by the tissue microenvironment and the dynamic host-microbe interaction, determine whether gut bacteria are classified as pathogens or non-pathogens. In the presence of favorable conditions, commensals might undergo overgrowth and become opportunistic pathobionts. These circumstances include alterations in the physiology of the host, concurrent infection with other pathogens, efficient nutrient utilization, interactions between bacterial species, the development of protective biofilms, genetic mutations that increase pathogenicity, the acquisition of virulence-related genes, and the capacity to evade the host's immune response. As the importance of the gut microbiota to human health has come to light, it has become clearer that certain tissue-specific favorable conditions that dictate viability and efficiency in a given microenvironment are necessary for obligate pathogens to cause diseases or for beneficial microorganisms to change into opportunistic pathogens (Tewari & Dey, 2024). The three primary categories of these mechanisms are hosting immune evasion, pathoadaptive mutation, and colonization fitness. The relative abundances and individual components of the microbiome, which fluctuate according to their composition and relative abundances throughout health state, may change significantly and negatively in dysbiosis (Sudhakara et al., 2018). Inflammatory bowel illnesses (IBD), including Crohn's disease and ulcerative *E. colitis*, as

well as metabolic, autoimmune, and neurological conditions, are characterized by dysbiosis. Necrotizing enterocolitis is one example of how dysbiosis may cause illness in the first few weeks of birth. Necrotizing enterocolitis is one example of how dysbiosis may cause illness in the first few weeks of birth. The most common method of absorption of medication is oral delivery. This path's ease of use makes it possible to regularly take medications without the need for medical assistance, which increases the gut microbiota's exposure to medications and fosters dysbiosis (Weiss & Hennet, 2017).

Disease linked to *E. coli* overgrowth or infections (e.g., UTIs, Inflammatory bowel disease)

Urinary Tract Infections

Up to 150 million instances of urinary tract infections are reported annually globally, making it one of the most common bacterial illnesses in people. UTIs result in a variety of health issues and financial strains on nations due to the need of treating or hospitalizing those who are afflicted (Zalewska-Piątek & Piątek, 2019). Women are more likely than males to have UTIs. According to estimates, 50% of women will get a UTI at some point in their lives, and more than 30% will receive antibiotic treatment for a UTI before turning 24. Within months of their first UTI episode, 20–40% of the affected women also encounter one or more recurrent infections. Consequently, recurrent antibiotic treatment is necessary for frequent infection recurrences. Drug resistance in uropathogens is encouraged by such UTI therapy (Zalewska-Piątek & Piątek, 2019).

Although a variety of bacteria may cause UTIs, uropathogenic *Escherichia coli* strains (UPECs) account for over 80% of cases of both complex and simple UTIs. Numerous virulence factors, such as adherence and colonization, invasion and persistence, biofilm formation, the formation of intracellular bacterial communities (IBCs) and quiescent intracellular reservoirs (QIRs), kidney colonization, and epithelial damage, are encoded by UPEC and are necessary at different stages of UTI pathogenesis. However, bacterial adhesion and colonization of the host cells and tissues is the most crucial step in the pathophysiology of UTIs (Wang et al., 2002).

Recent developments in our knowledge of the gut microbiota indicate that host variables alter the makeup of the gut's UPEC reservoir, which in turn affects host vulnerability to both acute and rUTIs. These host factors have a direct

effect on susceptibility to bladder colonization by UPEC. *Escherichia coli* is the main facultative anaerobe in the GIT microbial community and makes up around 0.8% of the total microbiota in healthy humans. Although most individuals have asymptomatic *E. coli* in their guts, *E. coli* blooms are linked to a variety of intestinal illnesses, such as colorectal cancer, inflammatory bowel disorders (IBD), including Crohn's disease, and diarrheal diseases. Inflammation, which may be brought on by a variety of factors such as a pathogen infection, an imbalance in the preexisting microbiota, or exposure to drugs during therapeutic intervention, is a significant host factor that probably affects the *E. coli* population in the gut (Schreiber IV et al., 2017).

Inflammatory Bowel Disease

The term commensal gut microbiota refers to the diverse bacteria that colonize the human gastrointestinal (GI) tract. Because of the profound effects that various microbiota have on their hosts, some scientists have proposed that humans may be considered "superorganisms" containing both bacterial and human DNA. The particular metabolic profiles of the human body are determined by these genes. In individuals with a variety of gastrointestinal ailments, such as inflammatory bowel diseases (IBDs), functional dyspepsia, and irritable bowel syndrome, dysbiosis in the intestinal microbiota has been seen. The pathophysiology of IBD has been linked to dysregulation in host-commensal interactions. Gut microbial population imbalance or dysbiosis has significant functional ramifications and is linked to a number of digestive disorders, such as IBD and colorectal cancer (Khan et al., 2019).

Escherichia coli and IBD

The pathophysiology of CD and UC, the two primary idiopathic IBDs, may be influenced by changes in the gut flora (Martinez-Medina & Garcia-Gil, 2014). According to a research, the pathophysiology of IBD is functionally linked to a number of elements, including immunological responses, genetic vulnerability, diverse bacterial populations (including *E. coli*), and external environmental circumstances. Mucosa-associated *E. coli* is very prevalent in IBD patients, and it is particularly noticeable in the ileum of CD, as well as in the sigmoid colon and rectum of both UC and CD (Khan et al., 2019).

The *E. coli* strains that were recovered from individuals with IBD are clonally heterogeneous and fall into several

sequencing types and serotypes. The idea that there is a specific clone linked to IBD has been substantially disproved, despite the discovery of a tight genetic association in a study of juvenile IBD patients. Conversely, as compared to healthy controls, *E. coli* strains recovered from IBD patients mostly fall into the B2 and D phylogroups when colonized by B2+D phylogroups; nevertheless, in other investigations, the distribution of phylogroups between IBD and healthy participants is comparable (Martinez-Medina & Garcia-Gil, 2014).

Role of microbial imbalance in systemic disease:

Diabetes

The mode of birth initiates the development of the gut microbiome, which is impacted by environmental factors, food, and certain drugs, such as antibiotics. The gut microorganisms of persons with diabetes and those without the disease vary from one another. Many disorders, including diabetes mellitus, are influenced by gut dysbiosis. The development of DM may be influenced by endocrine disruptors as well as changed GM. The development of diabetes mellitus is influenced by the kind of gut microorganisms and the alterations seen with them (Alagiakrishnan & Halverson, 2021).

Dysbiosis is the persistence of pathogens in the oral microbiome, not only transient changes and pathogen overexpression. Chronic inflammation in diabetics is mostly linked to oral dysbiosis brought on by the ongoing growth of commensal bacteria as a consequence of the host immunological response. Phagocyte-platelet interactions are dysregulated in type 2 diabetes in particular, which jeopardizes the healing of inflamed tissue (Georges et al., 2022).

Obesity

The microbiota, which makes up this "microbial organ," influences immune response, insulin sensitivity, and energy metabolism in addition to promoting homeostasis. The number of microorganisms rises from the proximal small intestine (approximately 10⁵) to the colon (about 10¹²), where there is a high density of anaerobes because of the low O₂ tension, after an initial fall from the mouth (10⁹) to the stomach (10³) maybe as a result of increasing acidity. The colon is the most extensively researched gastrointestinal region in connection to microbiota composition and obesity

risk because it has the largest density of bacteria and is simple to sample using feces as a stand-in for colonic microbiota. Numerous disorders, including obesity, are linked to changes in the microbiota's composition on or inside the body via a number of ways. A positive energy imbalance, or more energy being ingested than expended, is the primary cause of obesity (Amabebe et al., 2020). A rising amount of research indicates that the pathophysiology of obesity and its related consequences may be influenced by interactions between the gut microbiota, host genetics, nutrition, and other environmental variables. Type 2 diabetes mellitus (T2DM) and obesity have been linked to gut microbial dysbiosis, according to extensive metagenome-wide investigations conducted in China and Europe. These investigations all found that opportunistic infections increased whereas butyrate-producing microorganisms decreased (Vallianou et al., 2019).

Significant research on the connection between intestinal microbial flora and obesity has shown significant alterations in the metabolic activity and composition of the gut microbiota in obese people, which seem to allow the "obese microbiota" to get more energy from the food. Furthermore, recent investigations have shown that the gut microbiota indirectly regulates energy storage and expenditure via interactions with host epithelial cells (Tilg & Kaser, 2011).

Therapeutic interventions:

Probiotics:

Originating from the Latin *pro*, which means "for," and the Greek *bios*, which means "life," the term "probiotic" was first used in 1954 to refer to elements that were necessary for a healthy existence. Among many definitions, the one put out by a joint FAO/WHO panel (FAO/WHO, 2001) is the most popular and recognized: "Live microorganisms that benefit the host's health when given in sufficient quantities" (Binns, 2013).

Selection of probiotic candidate:

The main factor influencing the choice of probiotic strain is its ability to improve human health, not only safety. It is generally accepted that probiotics used in meals must endure until they reach the area of the GI system where they have the desired impact. Probiotics must, for instance, be resistant to stomach acid, salivary enzymes, tiny intestine bile and enzyme secretions, pH fluctuations, and the chemical

environment of other foods and drinks they will come into contact with while traveling through the GI tract in order to be effective in the colon. They also have to contend with the local microbiota. Lastly, a chosen strain must meet certain technical criteria, including large-scale culturability, genetic stability, and sustaining viability in a food product or supplement. Therefore, finding appropriate probiotic strains deserving of further investigation is a difficult and intricate procedure that may need a significant investment of time and energy. Although yeasts like *Saccharomyces* spp. have also been utilized, organisms from the genera *Bifidobacterium* and *Lactobacillus* are the most often seen probiotics in food (Binns, 2013).

Prebiotics:

A dietary prebiotic is defined as a selectively fermented substance that alters the gastrointestinal microbiota's composition and/or activity in a way that benefits the host's health.

Criteria for prebiotic selection:

Prebiotics work in a way that is different from but complimentary to that of probiotics. Exogenous microorganisms known as probiotics are consumed to support a certain health outcome. The prebiotic concept, on the other hand, is predicated on the selective stimulation of the host's own beneficial microbiota. The prebiotic is the substrate that is fermented (selectively), creating the desired health effect by promoting the growth and activity of the specific microorganism or group of microorganisms of interest. The colon is where prebiotics mostly work. For a prebiotic to reach the colon undamaged, it must be able to withstand the impacts of digestive enzymes and stomach acid. Once there, prebiotics stimulate the development and/or metabolic processes of the bacteria that ferment them, hence providing their alleged advantages. *Bifidobacteria* and *lactobacilli* are the most common target genera for prebiotic activity, however this might alter as our understanding of microbial variety and function grows. However, it is possible that prebiotics have a direct influence on health, such as via the immune system or by influencing how bacteria connect to receptors (Binns, 2013).

Probiotics and prebiotics targeting *E. coli* and the microbiota:

Probiotics' primary mechanisms of action on human health are numerous and include immunomodulation, enhancing the intestinal barrier, producing neurotransmitters, producing bacteriocin, vitamins, and short-chain fatty acids (SCFA), and competing with pathogens for nutrients and adhesion sites (Ballan et al., 2020).

Probiotics interactions with host gut microbiota:

Probiotics may compete with pathogens for resources and epithelial attachment, produce antimicrobial compounds to antagonize them, cross-feed other commensal bacteria, and prevent the development of bacterial toxins, among other methods, to interact with the host microbiota. Antibacterial peptides such as bacteriocins, particularly class II and III bacteriocins, which may be active in various mucosa and prevent pathogen proliferation, may be produced by *Lactobacillus* species. A saccharolytic feature that produces organic acids helps create an acidic environment that prevents pathogen development. As previously stated, *F. prausnitzii* may utilize the fermentation end product acetate from *Bifidobacterium* as a substrate, describing the cross-feeding process and potentially enhancing the balance of the microbiota (Ballan et al., 2020).

Microbiota modulation by prebiotics:

Because the gut is a complex ecosystem and prebiotics promote the selective development of native gut bacteria, consuming various prebiotics may increase the number of a given species based on the individual metatype (i.e., the metabolic reactions of a group of people). Similar to probiotics, prebiotics may influence the gut microbiota in a variety of ways. Their primary impacts include immunological response, pathogen-defense mechanisms, bowel function and stool consistency, satiety-related hormone synthesis, and subsequent metabolic consequences. The gut microbiota may be shaped by bioactive substances found in plants, despite the fact that prebiotics are typically thought of as carbohydrate based. Two essential ones are phenolic chemicals and polyunsaturated fatty acids (Ballan et al., 2020).

Prebiotics and human metabolism:

Prebiotics have been proposed to alter cholesterol and blood triglyceride levels. However, since human lipid metabolism is so complicated, thorough research is difficult to conduct and sometimes yields contradictory findings.

Higher molecular weight inulins have demonstrated greater efficacy in lowering triglyceride levels, indicating that these prebiotics have no negative effects on people with mild hypercholesterolemia or hypertriglyceridemia. Data for the consumption of FOS indicate either no effect or a slight decrease in circulating triacylglycerols and plasma cholesterol concentrations (Tuohy et al., 2003).

Probiotics targeting Enterohemorrhagic *E. coli*: (EHEC)

A model for a multipurpose bacterial species, *Escherichia coli* includes both pathogenic and benign commensals that may cause intestinal or extra-intestinal illnesses in humans. Among the pathogenic groups that cause human enteric infections, enterohemorrhagic *Escherichia coli* (EHEC) are a major public health issue due to their link to widespread outbreaks and potentially fatal consequences. Mild watery diarrhea, hemorrhagic colitis, and in extreme situations, hemolytic-uremic syndrome (HUS), which may be fatal, particularly in children under five, are all included in the spectrum of diseases linked to EHEC (Cordonnier et al., 2017).

Probiotics' antagonistic effects on enteric pathogens have been thoroughly investigated, and three broad categories of anti-pathogenic mechanisms have been put forth: Immunomodulation, competitive exclusion, and direct hostility.

Direct antagonism

Direct antagonism occurs when probiotics suppress the production of virulence factors like toxins or adhesins or kill or stop the development of pathogens to stop the infection from spreading. By co-culturing probiotics and pathogens, it has been shown that strains of *Lactobacilli*, *Escherichia coli* Nissle, and *Clostridium butyricum* may limit the development of EHECs in a straightforward in vitro method.

Immunomodulation:

Both innate and/or adaptive immunity may be impacted by probiotic interactions with the host immune system. The methods by which *Lactobacillus casei*, *Lactobacillus rhamnosus*, and *Bifidobacterium thermoacidophile* boosted the cellular immune response and/or the local immunological response against EHEC and Stx in mouse or rabbit models are yet unclear.

Exclusion:

Probiotics may modify the microenvironment via an exclusion mechanism to reduce the attachment, entrance, or translocation of pathogens like EHEC, to enhance intestinal barrier function, or to prevent pathogens from reaching their proper receptors (Cordonnier et al., 2017).

Prebiotics targeting *E. coli*:

Escherichia coli that produces Shiga toxin (STEC) is a serious health risk because it may cause the crippling hemolytic uremic syndrome when consumed via contaminated food. It may be possible to use pectic oligosaccharides (POS) as dietary components to manage STEC infections (Di et al., 2017).

Antibiotic stewardship and its impact on *E. coli* dynamics:

Aims of antibiotic stewardship:

The two main objectives of antibiotic stewardship are: To guarantee that patients suffering from bacterial infections get proper treatment (Bassetti et al., 2022) and to limit collateral harm and cut down on needless antibiotic usage (Salah et al., 2021).

Stewardship at the patient level is defined as the optimal selection, dosage, and duration of antimicrobial treatment that leads to the best clinical outcome of infection or infection prevention with the least toxicity to the patient and the least impact on subsequent resistance. Stewardship at the organizational level refers to evidence-based initiatives and programs that track and guide the use of antibiotics. Preventing the careless use of broad-spectrum antibiotics is a major goal of hospital stewardship initiatives (Hand, 2013). Reducing the prevalence of resistant illnesses and lowering treatment costs without sacrificing treatment quality are the two major objectives of ASPs. Peragine et al. found a 13% (0.87–1.04, $p = 0.13$) reduction in hospital-acquired MDR organisms and a 9% (0.91–1.09, $p = 0.03$) reduction in hospital-acquired antibiotic resistant organisms. However, an educational community-based intervention ASP resulted in a decrease in the ESBL-producing *E. coli* in urine cultures for Penalva et al. Since *E. coli* resistance is one of the most prevalent pathogens that cause infections that are clinically significant, we decided to focus on it as the intervention's focus. Additionally, as *E. coli* resistance is usually plasmid-mediated, it is subject to quick changes. As a consequence, it would serve as a marker for the early effects of shifts in

antibiotic pressure that lead to modifications in resistance patterns. The long-term impacts on antibiotic usage demonstrate that, although being examined by annual quarters, the ASP intervention is a process. Our findings are consistent with those of Penalva et al., who demonstrated that a lower incidence of antibiotic-resistant bacteria was linked to antibiotic dosage limitation and dose reductions in a community environment (Ziv-On et al., 2021).

Emerging therapies (e.g., Fecal microbiota transplantation and phage therapy)

Fecal microbiota transplantation:

Currently, many illnesses are being treated by fecal microbiota transplantation (FMT), which is the process of transferring gut microbiota from a healthy donor to repopulate or reconstitute the stable microbial population of the gut. However, a speed blender is often used to create a feces slurry out of a preliminary homogenization of donor stools (~100–150g) with a sterile saline solution (NaCl, 0.9%). The freshly secreted homogenous liquid fresh fecal sample can be put in sterile syringes and ready for the FMT in less than six hours after the emission, filtering out bigger particles, fibres and undigested food using a metal sieve. The preparation may also undergo several filtering steps, with filter diameters decreasing from 2 to 0.1 mm. To assist shipping, it can then be cry protected in 10% glycerol, placed in liquid nitrogen and frozen, and stored in -80 °C for subsequent FMTs. Once frozen slurry is thawed overnight at 4 °C and reconstituted with regular saline, it is before FMT. The preparation containing freeze-drying protectant glycerol is carried out in 20% then centrifuged at 400 x g supernatant is discarded and centrifuged again at 10,000 x g to obtain products as FMT capsules. Then the sediment is put in enteric soluble capsules and stored at -80 °C (Borody & Khoruts, 2012).

FMT in inflammatory bowel disease:

Only a small number of patients with the two primary types of IBD had clinical remissions linked to a high donor gut microbiota richness in the first clinical studies. The subsequent clinical studies only looked at one kind of IBD. Moayyedi and colleagues (2015) conducted the first placebo-controlled randomized study, which included giving 50 mL by retention enema once a week for six weeks to individuals with active ulcerative *E. coli* tis (but not infectious diarrhea). The experiment found that FMT is safe, with no side effects,

and 24% of patients had ulcerative *E. coli* tis remission. In a second randomized, double-blind, placebo-controlled study, individuals with active ulcerative *E. coli* tis received FMT colonoscopic infusion and enemas five days a week for eight weeks. The patients had 78% adverse effects and 27% remission (Biazzo & Deidda, 2022).

One of the authors of the 1989 article on FMT for IBD had very active ulcerative *E. coli* tis that was resistant to corticosteroids and aminosalicylates. He used a retention enema to transfer healthy donor feces. After FMT, symptoms subsided for six months, and a follow-up colon biopsy sample revealed no active inflammation. Significant clinical improvements were seen in a number of gastrointestinal disorders, including Crohn's disease (CD), IBS, UC, and constipation, according to another early case report using FMT enema. Anecdotal reports and short case series in patients with IBD and concomitant CDI followed these investigations, demonstrating the positive impact of FMT (Choi & Cho, 2016).

Phage Therapy:

Since there aren't many treatment alternatives for individuals who don't respond to traditional antimicrobials, phage (bacteriophage) therapy has attracted renewed attention in recent years. The efficiency of antibiotics has declined due to a combination of factors such as antimicrobial resistance and the growing use of implanted devices, which are vulnerable to infections caused by biofilm. Phage therapy is an experimental anti-infective treatment for infections caused by biofilms, refractory infections, and/or multidrug-resistant (MDR) infections. These conditions include recurring and chronic infections, including MDR respiratory infections, skin and soft-tissue infections, rhinosinusitis, and urinary tract infections (UTIs), as explained below. Infections linked to biofilms include lung infections in the context of cystic fibrosis (CF), PJI, hardware-associated osteomyelitis, and infections of cardiac devices. Phages have the ability to reduce uropathogen colonization of urinary catheters as well as the gut reservoir of uropathogens. According to in vitro research, phage-treated catheters may be shielded against typical uropathogen colonization. Another example of a successful phage-based UTI therapy is a liver transplant patient who had recurring *Escherichia coli* UTIs that produced extended-spectrum beta-lactamases (ESBLs) (Suh et al., 2022).

Conclusion

The immunomodulatory and metabolic host functions are modulated by the microbiota productive and protective physiological roles. The organization of these microbial communities is critical in maintaining health and disease because imbalances are associated with disease states. Modern knowledge of the interactions between microbial communities and hosts has increased the understanding of the work of individual taxa for both health and disease, leading to the development of such strategies as the use of probiotics and prebiotics, as well as the constant development of new approaches based on microbiomes, including phage therapy and fecal microbiota transplantation. As these interventions hold the prospect for rehabilitation, questions regarding their applicability and sustained effectiveness remain host-microbe interactions and intervention need further investigation. So, in the context of the present and further research, it is comprehensible to achieve actuality that the program of the microbiota's deep exploration and its potential will create foundations for receiving unprecedented approaches to disease prophylaxis and therapy.

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Conflict of Interest

The authors declare no conflict of interest.

Authors' Contribution

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