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Review Article

Health Managements through Gut Microbiota

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Abstract

Gut microbiota is a diverse microbial community essential for maintaining human health and immune homeostasis. It regulates both innate and adaptive immune responses, influencing processes such as antigen presentation, T-cell differentiation, and Immunoglobulin A (IgA) production. By balancing immune tolerance and activation, the microbiota prevents autoimmunity while protecting against infections. Sequencing technology advancements have demonstrated the immune dysregulation, autoimmune and inflammatory disorders may result from dysbiosis, or changes in microbial makeup. Probiotics, prebiotics, and dietary changes that target the microbiome have encouraging medicinal promise. Human microbiota is full of microbial communities having trillions of microbes, more than 10 times of the human cells, that includes 1000 (approx.) bacterial species with dominance of *Firmicutes, Proteobacteria, Bacteroidetes*, Euryarchaeota, Actinobacteria, Verrucomicrobia, viruses and fungi. Human genome is estimated to consist of 61000 to 140000 genes while gut microbial genome may contain 1000,000+ genes and influence various functions of human body, help in health management and provides the signals to brain. Gut microbiome secretes vitamin K, B12, neurotransmitter metabolite like dopamine, short chain fatty acids like butyric acid, proteases, carbohydrate-active enzymes that include inhibitors of maltases and sucrases, manage 70% of total immunity, stimulate certain tissues of intestine, lympatic tissues, capillary density, production of cross-reactive antibodies that prevent infection and invasion by pathogens. For healthy, gut microbiota, avoid use of processed food and gluten containing grains. Social and environmental contacts also influence the gut microbiome. This review deals with role of gut microbiota in immune regulation and health management.

Introduction

The human body is closely related to a large number of architecturally and functionally varied microorganisms that live in various bodily sections. Examples of inhabited habitats include the skin, gastrointestinal tract, respiratory tract, oral cavity, and sexual organs [244,346]. According to estimates, the human microbiota has 1013-1014 microbial cells, which is around ten times more than the number of human cells and more than 100 times the quantity of genetic material compared to the human genome [278,300,329]. These figures are based on the total number of bacteria in the colon, which is 3.8 × 1013 bacteria, and the organ that has the highest density of microorganisms. The most densely populated areas are the mouth, the Gastrointestinal Tract (GIT), and the vagina. Microbiota is the term for this composition, which is acquired shortly after birth [183]. "Gut Microbiota" refers to the bacteria that are only present in the GIT. The majority of gut microbiota [184] is non-pathogenic, and it is essential for providing the host with health advantages [118]. The GI tract's many sections have different physiological traits, chemical compositions, and environmental features. As a result, microbiome kinds and quantities range [190-193] among regions. From the stomach to the small intestine to the large intestine, the number of bacteria generally increases. These microbes have been well studied and may be just as significant as bacteria since they probably regulate the host's and, most significantly, the gut microbes' activity. Consequently, the study of host-microorgan-

ism interactions gain a new perspective from the archaea, virome, phageome, and mycobiome. Phage populations, for instance, are not just ten times greater than bacterial populations, but they are also novel players in these intricate relationships [20,25,103]. The gut microbiota's makeup is rather simple and varies greatly across individuals throughout the first year of life [203]. The makeup of the adult's gut microbiota is thought to be significantly shaped by the early gut colonization. In support of this claim, revealed that the gut microbiota of the mice in their research was closely connected to that of their mothers, suggesting that kinship plays a role in determining the gut microbiota's makeup. They can range from 10 to 103 bacteria per gram of stomach and duodenal contents to 104 to 107 bacteria per gram in the small intestine and 1011 to 1012 bacteria per gram in the large intestine [275]. Furthermore, the microbial community's makeup differs between these locations, with the colon and small intestine having higher concentrations of particular bacterial phyla. The small intestine was shown to be enriched for members of the *Firmicutes* phylum, whereas the colon was found to be enriched for members of the phylum *Bacteroidetes* when biopsy samples from both areas of healthy people's guts were analyzed [93]. The human stomach supports a variety of dynamic microbial habitats. Numerous fundamental metabolic processes and the host's immune system development are influenced by the gut bacteria. Although over 95% of the gut microbiota may be categorized into four main phyla, each person's gut microbiota makeup is distinct following bacterial colonization in babies.

In the human stomach, microbial colonization starts from birth. At birth, the baby's gut is thought to be sterile and to have relatively few microorganisms, but during and after delivery, the GIT rapidly becomes colonized [101]. The technique of delivery is a key factor in determining the makeup of the newborn microbiota. Differences in newborns' gut microbiota have been connected to variations in delivery methods. According to [77] there was a clear correlation between the delivery technique and the gut microbiota's colonization pattern and diversity during the first three months of life, but the substantial differences vanished after six months. In the meanwhile, [38] shown that children born via c-section had considerably lower baseline evenness, richness, and phylogenetic diversity within the first month of life as compared to infants delivered vaginally. Children born by cesarean section subsequently had reduced richness and diversity until they were two years old, particularly after eight months. Probiotics like *Lactobacillus reuteri* and *Lactobacillus rhamnosus* are found in the birth canal. The mouth canal, nasal cavity, skin, and other areas of vaginally delivered newborns will be exposed to more beneficial bacteria than those of c-section babies. At birth, microbes colonize the baby's skin, stomach, and nasopharyngeal and oral membranes. Microbial communities that resemble the mother's vaginal flora and are dominated by *Lactobacillus*, *Prevotella*, and *Sneathia* species are acquired by a newborn when it goes through the birth canal [76]. The unique property of gut microbiota composition is generally basic and maintained over the first year of life, but there are significant inter-individual differences [298]. In addition to influencing the makeup of the adult GI microbiota, microbial diversity appears to be crucial for the harmonious interaction between the microbiota and host. Over the course of two to three years, the gut microbiota stabilises and completely reflects the bacterial makeup of the adult gut [18,38]. According to studies, kids delivered via caesarean section are more likely to have wheezing and allergy sensitisation throughout the first two years of life. Numerous internal and external host-related variables also have an impact on the GI microbiota. The kind of food consumed, the microbial load in the immediate surroundings, feeding practices, and the makeup of the mother's microbiota are examples of external influences [288]. Stresses connected to temperature and food have an impact on the microbial successions. Internal influences include ambient temperature, microbial interactions, intestinal pH, host secretions, bile acids, peristalsis, and immunological responses (bacterial mucosal receptors and medication therapy) [346]. Since Hippocrates stated in 400 B.C. that "Death sits in the bowls," there has long been recognition of the connection between intestinal health and human health. The substantial influence of gut microbiota on human health and illness has been the subject of several research conducted globally [1]. Around 100 trillion microorganisms are thought to reside on and within the human body, and they are crucial to many biological functions, including both health and illness [19]. Numerous bacteria, viruses, archaea, and unicellular eukaryotes inhabit the human body. Although bacteria are found on every surface of the human body, the gastrointestinal system and gut are home to a sizable population of them. The gut microbiota is a complex biological community made up of over a thousand different microbial species found in the human gut [173]. Since it interacts with almost every human cell, the gut microbiota is now regarded as a significant collaborator of human cells. Between 2013 and 2017, about 12900 articles were devoted to the study of the gut microbiota, with around 4000 papers focussing on this topic being published in 2017. This astounding figure accounts for almost 80% of all publications on the subject over the past 40 years (since 1977). This straightforward discovery thus demonstrates that this area of study is not only thriving but also strongly implies the need for further development [48].

Normal Flora

The population of microorganisms in a given environment is known as the "normal flora," while the collective genomes of these organisms are referred to as the "microbiome." With an estimated 100 trillion microorganisms (mainly bacteria, but also viruses, fungi, and protozoa) in the human gastrointestinal system, the microbiome is now best viewed as a virtual organ of the body. Huge numbers (10-100 trillion) of microorganisms colonize important parts of the human body, such as the skin, oral cavity, Gastrointestinal Tract (GIT), respiratory system, and urogenital tract [216]. Through evolution, several bacterial species have successfully adapted to the average human microbiome. It was not possible to cultivate most of these bacteria in vitro. Numerous infectious and non-contagious human diseases are caused by these bacteria, which also multiply inside the human body and participate in essential biological functions. It has also been well studied and widely accepted that germs may colonize body parts that are continuously exposed to outside

microorganisms, including the mouth, respiratory tract, GIT, skin, urethra, and vagina. Because of its impact on physiology, the microbiota-the body's natural bacterial flora-has drawn a lot of study. Although bacteria contribute far more genetic material, current estimates indicate a closer ratio of human to bacterial cells, which is contrary to the frequently cited statistic.

There is an indigenous microbiota in the upper respiratory tract, oral cavity, and some areas of the ears and eyes. Numerous diseases are shared by the resident flora of these locations due to the tight anatomical relationships between these structures. At various locations, the normal flora coexists in intricate ecosystems and has tight interactions with other bacterial species as well as the host epithelial layers. The makeup of this native microbiota is known to vary over time and is influenced by host age, uderlying illnesses, and chemotherapy [79,80,199,221,272]. The normal flora of the relevant structures must be understood in order to comprehend the microbial aetiology of head and neck illnesses. Understanding the baseline flora will assist direct antimicrobial therapy and identify the most likely cause of an illness. About half of the 300-500 bacterial species that are thought to reside in the oral cavity are currently uncultivable [130]. Eighty percent of the oral cavity's cultivable floras are *Veillonellae*, *diphtheroids*, and *streptococcal* species. According to quantitative research, obligatory anaerobes make up a significant portion of the oral flora found in homes. More than 80% of the entire cultivable oral flora is made up of species of *Streptococcus, Peptostreptococcus, Veillonella, Lactobacillus, Corynebacterium*, and *Actinomyces*. The most common elements of the typical oropharyngeal flora are viridans *Streptococci*, which include species from the S. salivarius, S. mutans, and S. anginosus families [258]. Five percent to ten percent of healthy, asymptomatic people have gram-negative diplococci, including N. meningitidis [50,115]. With ageing and the host's underlying circumstances, the oral microbiota is always changing. After being exposed to the mother's birth canal, the mouth cavity, which is sterile at birth, quickly gets colonized. Within a few hours, organisms can be found, including anaerobic species such *lactobacilli* and *Veillonella* species [49].

The nasopharynx's typical colonising flora is a reflection of the nearby adjacent structures. The predominant *Streptococci* are Viridans. In a healthy state, the middle and inner ears are likewise regarded as sterile habitats. Microorganisms primarily related to the skin flora are found when the typical flora in the external ear canal is examined. In healthy adults and children, the most common isolates are S aureus, coagulase-negative *Staphylococci*, and *Corynebacterium* species [75]. The skin, the largest organ in the human body, is home to a wide range of microorganisms, the majority of which are harmless or even beneficial to their host. One factor that affects how effectively skin works is a healthy skin microbiome. Colonization is driven by the ecology of the skin surface, which varies significantly depending on topographical location, endogenous host traits, and external environmental conditions [116]. Species from the genera *Cutibacterium*, *Staphylococcus*, and *Corynebacterium* have been found in almost every area of the skin, and may make up 45-80% of the total skin microbiome. Additionally, it has been demonstrated that Thaumarchaeota and other microbes from the Archaea domain are present in human skin. Approximately 4% of the genes in the microbiome are found in this taxon, according to research employing 16S rRNA sequencing. Furthermore, fungi, mostly of the *Ascomycota* and *Basidiomycota* types, are a part of the skin microbiome. The most common genus is Malassezia. The host's age, sex, and health, as well as their cleanliness habits, way of life, and surroundings, all have a substantial impact on the makeup of their skin microbiome. Skin flora comes in two varieties: transitory and resident. The organisms that are consistently found on the entire skin's surface, including those found in the deeper layers like the sweat gland follicles and sebaceous ducts, are referred to as the resident flora. This flora consists predominantly of *Staphylococcus* epidermidis, micrococci, and diphtheriods (Figure 1). Small numbers of anaerobic cocci and propionibacteria also may be present.When the transient flora which includes a greater variety of organisms than the resident flora come into contact with the skin's outermost layers, it can be from the environment, another person, or the individual's own digestive system, including the kidney, ureter, bladder, and urethra. This condition is called a urinary tract infection.

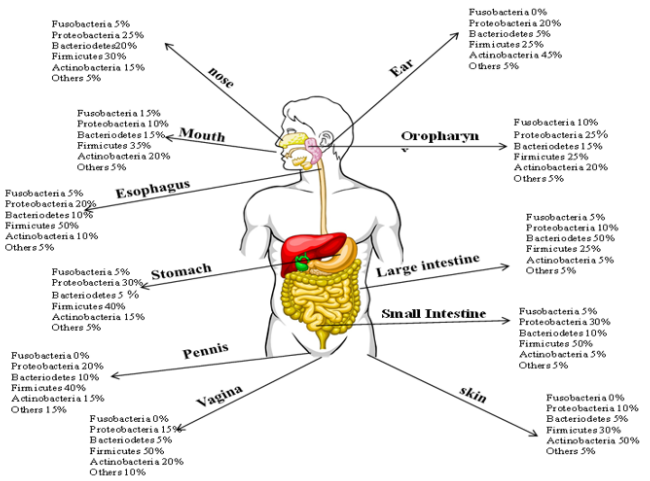

Figure 1: Sites of human body showing percentage of normal flora.

Benefits of Normal Flora

Ocular Flora

The human eye hosts a variety of bacteria, primarily in the cornea and conjunctiva. These bacteria form a protective microbiota that helps prevent pathogenic microorganisms from colonizing the ocular surface. Key genera in the ocular microbiota include *Pseudomonas, Propionibacterium, Acinetobacter,* and *Corynebacterium* [241]. Environmental factors, infections (like blepharitis or conjunctivitis), and behaviors such as improper contact lens use can disrupt this microbiota, potentially leading to ocular diseases. In children, common bacteria in the conjunctival sac include *Staphylococcus epidermidis*, *Staphylococcus aureus, Streptococcus mitis, and Streptococcus pneumoniae*, with higher bacterial diversity found in those with positive flora in both eyes [153,154].

Nasal and Oral Flora

The microbiota in the nasal cavity and oral cavity includes various bacterial species, predominantly *Actinobacteria* and *Firmicutes*. These bacteria help protect against infections and maintain the health of the respiratory and digestive systems. For instance, *Corynebacteriaceae* and *Propionibacteriaceae* are abundant in the nasal cavity, and their balance is crucial for preventing infections. Imbalances, particularly the presence of *Staphylococcus* aureus, can lead to infections in the nasal or other parts of the body.

Gastrointestinal Flora

The human gut microbiota is an intricate ecosystem composed of bacteria, fungi, archaea, and viruses. These microbes interact to support various physiological processes, including digestion, immune system regulation, and disease prevention. The microbiota's genetic content far exceeds that of the human genome, emphasizing its critical role. The balance of gut bacteria, such as *Firmicutes*, *Bacteroides*, and *Proteus*, is vital for maintaining homeostasis. An imbalance, particularly the *Firmicutes*/*Bacteroidetes* ratio, can indicate gastrointestinal disorders. The gut flora also influences mental health, with altered microbiota linked to depression and anxiety [229]. Notably, gut bacteria have shown promise in cancer therapies, where they can either target tumor cells or deliver anticancer agents.

Immune system development by early colonization of mucosal surfaces by microbes is essential for developing a healthy immune system. In the first few years of life, the microbiota undergoes significant changes that influence immune responses. The "window of opportunity" for establishing a strong immune defense is especially critical in newborns. Breastfeeding plays a vital role in transferring maternal antibodies to the infant, providing passive protection. Research suggests that the commensal microbiota of pregnant women contributes to the infant's immunity, highlighting the importance of microbial exposure early in life for immune system development.

Urinary and Reproductive System Flora

In the urinary and reproductive systems, the normal flora is essential for preventing infections such as Urinary Tract Infections (UTIs) and vaginal yeast infections. For example, *Lactobacillus* species are important in the vaginal flora, where they help maintain an acidic pH, protecting against pathogens [107]. Disruptions, such as the use of antibiotics, can disturb this balance, leading to infections caused by opportunistic pathogens like *Candida albicans*. In the urinary tract, the flora helps protect against infections that may result from pathogens that enter the system from the skin or perineum (Figure 2).

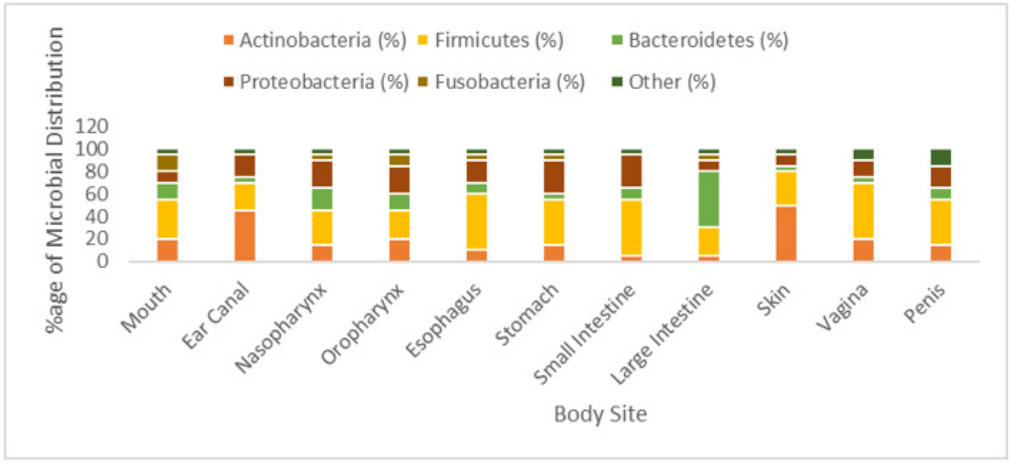

Figure 2: Per cent microflora present at different body site.

Microbial Succession

The human gut microbiota is first assembled at birth when environmental microorganisms colonize the body. The mother's faecal and vaginal microbiomes are often the most significant source of inoculum during the first few hours of life [120,307]. Bacteria like *Bifidobacterium*, which are well-suited to break down milk oligosaccharides, can proliferate during the first few months of a milk diet [277]. A transition towards the bacterial consortia that charac-

terised the adult microbiota is signalled by the introduction of solid meals [235]. Sterility is lost when the amniotic sac ruptures. The newborn receives their first round of microbial inoculation through the vaginal flora when they pass through the birth canal [99]. These microorganisms deoxygenate the gut and create the conditions necessary for healthy development and growth. The manner of distribution has a significant impact on microbial colonization, as we describe below. Caesarean Section (CS)-delivered babies have a different, less advantageous microbial inoculation [226]. In the end, this shift in delivery method could help to explain why CS is linked to certain chronic health issues. Important skin microorganisms are transferred to the infant through skin-to-skin contact during infancy and the postnatal period [10] (Figure 4). Many of these organisms have antimicrobial qualities that help them fight off infections. Although human skin serves as a useful inoculator for newborns, breast milk is the most potent and pervasive source of microorganisms [268,37]. One of the main effects of regular and exclusive breastfeeding is the formation of commensal and symbiotic gut microorganisms, which also aids in a child's healthy growth and development. Primate milk contains complex milk oligosaccharides that serve as prebiotics, giving symbioses a selective growth edge against pathogens and as well as [37,3,4,208]. Anti-adhesive antimicrobial compounds (which bind microorganisms selectively) [57], and antibiofilm substances (which are bacteriostatic against certain infections), [2,3,62,293]. Due to the many short- and long-term advantages of breastfeeding, the World Health Organization advises exclusive nursing during the first six months of a child's life, followed by supplementary breastfeeding for up to two years when solid meals are introduced (*Band Ravel* and *Smith* ,2017). Breast milk is essential for preventing infections and promoting the immune system's growth in babies. Immunoglobulins (IgA, IgM) found in breast milk, especially in the colostrum, aid in protecting the baby's digestive tract against infections. IL-6, IL-8, and IL-10 are examples of cytokines that contribute to the development of an infant's immune system. Bioactive substances including growth factors, which are vital for an infant's development, are found in human milk. These include Neural Growth Factors (NGFs), which are crucial for brain development, and Epidermal Growth Factor (EGF), which promotes the intestinal epithelium's maturation. Human milk contains Erythropoietin (Epo), which promotes intestine growth and red blood cell synthesis, lowering the risk of anaemia [22,92].

The composition of breast milk is dynamic and changes to meet the nutritional needs of the infant. Initially, colostrum is produced, rich in immunologic and growth factors but low in nutritional value [108]. Over the first few weeks postpartum, the milk transitions to mature milk, with less variation in its composition after about four weeks. Breast milk contains proteins, lipids, and carbohydrates, with fats contributing to brain and gastrointestinal development [217,222,237]. Human Milk Oligosaccharides (HMOs) are important prebiotics that shape the gut microbiota by promoting beneficial bacteria like *Bifidobacterium* while preventing harmful pathogen colonization.

Breast milk has probiotic qualities in addition to prebiotic ones, bringing good bacteria like *Lactobacillus* and *Staphylococcus* into the baby's digestive system [201,209,211]. Particularly during the first six months when breast milk serves as the main source of sustenance, this microbial exposure promotes a healthy gut flora. Formula-fed infants experience different gut microbiota development, with their microbiome resembling that of an adult more quickly [243,274,73]. Formula supplementation, due to the lack of bioactive components found in breast milk, may lead to a gut microbiota dominated by bacteria like *Staphylococcus*, *Enterococcus*, and *Clostridium* (Figure 3). However, formula manufacturers often add prebiotics and probiotics to promote the growth of beneficial bacteria [155].

Numerous internal and external host-related variables also affect the GI microbiota [245,206]. The kind of food consumed, the microbial load in the immediate surroundings, feeding practices, and the makeup of the mother's microbiome are examples of external variables [348]. Stresses connected to nutrition and temperature have an impact on the microbial successions. Internal influences include temperature, microbial interactions, intestinal pH, and physiological elements such as bile acids, host secretions, immunological responses, and peristalsis (Medication and receptors on bacterial mucosa) [251,283]. The complexity of gut microbiota may be influenced by a variety of factors, including host genetics, age, lifestyle, hygiene issues, interaction with allergens, diets, use of probiotics or prebiotics, infections, and other factors outside delivery method, baby food, and antibiotics [14,103,290].

When solid foods are added to the diet, the microbiome starts to change from a simple environment with a lot of *Bifidobacterium* (microbes that break down human milk oligosaccharides) to a diverse flora with a lot of species like *Bacteroides* that break down the starches in a more structured diet. The gradual cessation of nursing has the most significant impact, even while the introduction of solid meals starts alterations in the microbial ecology. when a result, a toddler's gut starts to mature when weaning begins, resulting in a varied adult flora. Advancements in gut microbiota research have transformed our understanding of these vital organisms. Historically, the knowledge of adult human gut microbiota came from labor-intensive culture-based methods. With the advent of culture-independent approaches, our understanding has significantly broadened. DNA sequencing technology, combined with bioinformatics, has revolutionized microbiomics [26,27,64]. These methods involve amplifying and sequencing targeted microbial DNA regions and then using statistical analysis to identify and assess the diversity of microbes based on sequence similarity to genomic databases [166]. The 16S ribosomal gene (16S rDNA) is a popular approach for targeting bacteria and archaea because it contains nine hypervariable sequences (V1-V9) that differ between species. Recently, researchers have shifted focus from 16S rRNA sequencing to shorter sub-regions of the gene, examined in greater depth. Whole-genome shotgun metagenomics is now considered a more reliable method for estimating microbiota composition and diversity due to its higher resolution and sensitivity. Despite these devel-

opments, direct comparisons across various sequencing studies are made more difficult by variations in sample processing strategies, sequencing technology, and statistical approaches [252,339]. Approximately 93.5% of the 2172 species that have been isolated from humans and categorised into 12 distinct phyla are *Proteobacteria*, *Firmicutes*, *Actinobacteria*, and *Bacteroidetes*. Interestingly, just one species from each of these phyla like *Akkermansia muciniphila* from *Verrucomicrobia* has been isolated from humans. Furthermore, 386 of these species are exclusively anaerobic and inhabit mucosal areas such as the gastrointestinal system and oral cavity (Figures 3,4).

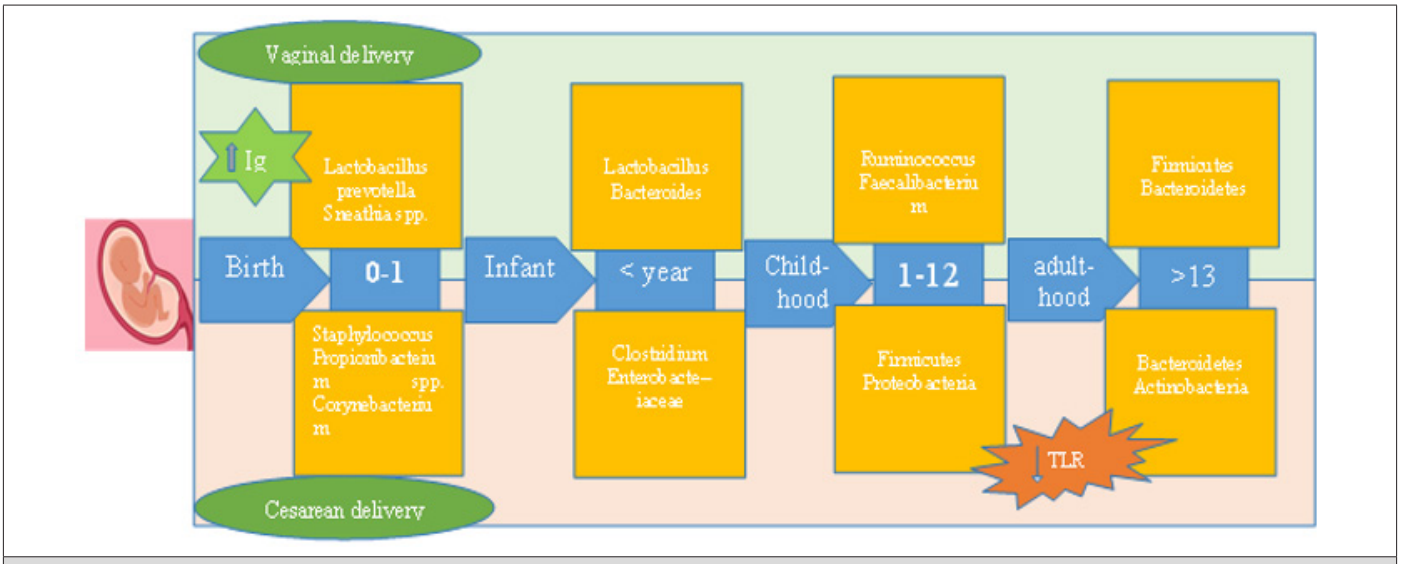

Figure 3: Microbial succession from birth to adult.

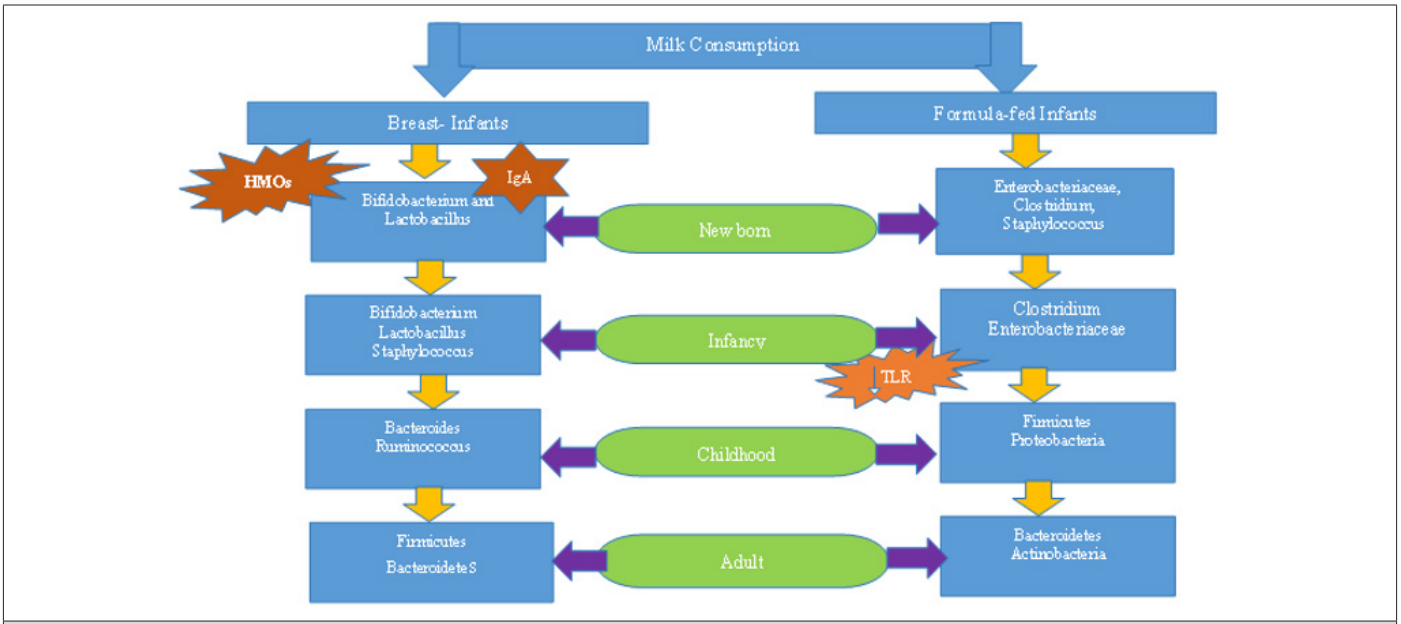

Figure 4: Difference in microbial succession on the basis of milk consumption.

Why gut is Crucial for Health?

Gut microorganisms have a crucial role in immunological, metabolic, and neurobehavioral characteristics, among other facets of human health [123,124,187]. The function of gut microbiota in human health is supported by varying degrees of evidence, including research on humans and animal models [28,86,87,257,291]. The fermentation of indigestible substrates, such as food fibres and endogenous intestinal mucus, depends on the gut microbiota. This fermentation promotes the development of specialized microorganisms that generate gases and Short-Chain Fatty Acids (SCFAs) [262,329]. Butyrate, propionate, and acetate are the main SCFAs that are generated [264]. Butyrate is necessary for epithelial cells to use β oxidation to absorb significant amounts of oxygen, creating a hypoxic environment that keeps the gut's oxygen balance stable and avoids dysbiosis of the gut microbiota [125]. In addition to being the primary energy source for human colonocytes, butyrate

has positive effects on glucose and energy balance by activating intestinal gluconeogenesis and inducing death in colon cancer cells. Obesity development and progression appear to be influenced by the gut microbiome. The majority of research on overweight and obese individuals reveals a dysbiosis marked by reduced variety [175,231,306]. Numerous mechanisms, such as immune dysregulation, altered energy regulation, altered gut hormone regulation, and pro-inflammatory mechanisms (like lipopolysaccharide endotoxins crossing the gut barrier and entering the portal circulation), likely contribute to gut microbiota dysbiosis, which in turn causes diet-induced obesity and metabolic complications [98]. This microbe and others such as Akkermansia correlate with lower visceral fat deposits. The microbiota in various organs has unique compositions and traits. Consequently, the microbiota engages in interactions with several host biological processes. the relationships between immune system development and the human microbiota in the stomach, oral cavities, lungs, skin, and vagina. Numerous immune cells are found in the GI tract, and they are in continual communication with the gut flora. The growth of commensal microorganisms is necessary for the immune system to mature. One way that the gut microbiota influences the immune system is by influencing neutrophil migration, which in turn influences the differentiation of T cells into diverse kinds, including regulatory T cells and helper T cells (Th1, Th2, and Th17) [234]. During the immune system's maturity, abnormalities in microbiota formation may result in autoimmune disorders and a decline in immunological tolerance [279]. Furthermore, the many compounds that the microbiota produces have the potential to trigger an immunological reaction, promote inflammation, or cause long-term tissue damage [265,266,273]. Trillions of microorganisms make up the intricate systems known as microbiota. The majority of microbiota-related research, thanks to advancements in sequencing tools and analytics, is on the connection between changes in microbiota composition and different disease states [181]. External alterations can alter the microbiota community's equilibrium, which can result in illnesses and dysregulation of body processesas of right now, there is growing evidence linking microbiota to the onset of Cardiovascular Illnesses, Cancer, Diabetes, IBD, Mental Disorders, Chronic Kidney Disease, and Liver Disease.

Microbiome

The gut microbiome is a complex community of bacteria that colonize the colon from birth [220]. The bacteria that settle their ultimately grow into a vibrant, mature community that changes throughout a person's lifespan in tandem with the host. They are essential for immunological homeostasis, gut barrier integrity, and the activation of neurological and endocrine pathways [5,253,259]. Furthermore, the gut microbiota ferments indigestible food ingredients and releases bioactive metabolites that can either enter the bloodstream and act as effectors on organs at distant locations or be used by the colon's mammalian cells [104,216]. The growth of human life is known to depend on the microbiome, which is also intimately linked to the incidence of several illnesses in addition to playing a significant role in many vital physiological functions including immunological responses and metabolic processes [292,275,322,342]. Some microbiomes arise from mothers through vertical transmission during the perinatal period, while microbiomes across body locations evolve from an extremely young age. All bodily areas are colonized, but the gut, which has been the subject of much research, has the greatest microbial counts [198]. Millions of bacteria are present in the oral and saliva microbiomes of healthy individuals, and they are swallowed with our food every day. However, a number of factors, such as the stomach's acidity, the duodenum's and other organs' production of Bile Acids (BAs), digestive enzymes, and antimicrobial proteins, hinder the bacteria's ability to persist in the gut. Further downstream microbial colonization is influenced by numerous other significant factors, including physical characteristics like gut architecture, peristalsis, and transit times, as well as chemical parameters like pH, oxygen concentrations, and redox potential, as well as the biological production of mucus, bile, and antibodies. Despite having fairly identical microbial taxa, the microbial abundance in duodenal aspirates was found to be 1000 times lower than that of oral samples, indicating the presence of a concentration gradient of microorganisms along the small intestine [24]. As a result, the small intestine has a growing number of cells per gramme of substance, ranging from hundreds to several hundred million. The two main phyla are *Proteobacteria* and *Firmicutes*, which are somewhat oxygen-tolerant [185,275]. Since transit in the colon is more than a dozen times longer than that in the small intestine, all of this culminates in the lower gut, where climax communities of up to 100 billion cells per gramme stay for a few days. Therefore, anaerobic bacteria, comprising thousands of species and millions of genes, dominate the colonic microbiome. These bacteria are found in the major phyla of [280,289,290]. *Firmicutes* (mainly *Ruminococcaceae* and *Lachnospiraceae*), *Bacteroidetes*, *Actinobacteria, Proteobacteria*, and *Verrucomicrobia (Akkermansia)* [346,247,249,296]. A study of small intestine effluent after ileostomies revealed that it contained up to 100 million microorganisms per gram of wet weight, forming individualized communities with day-and-night cycles that reflected food processing and intake [39]. The colonizing *Streptococcus* and *Lactobacillus* species were found to express a large reservoir of highly effective transport systems that compete with the host for sugar uptake and use, producing lactate and acetate that are substrates for [299,301,303]. *Veillonella* species and are subsequently converted into propionate, according to functional (transcriptomics and targeted metabolomics) and metagenomic analysis of such samples [347]. Recent research employing specially designed catheters validated these communities and showed that, in contrast to the jejunum, the intestinal compartment with the largest surface area and the site of the majority of digestion and absorption of sugar, protein, and fat, the duodenal microbiota showed higher compositional dynamics correlated with pH [186]. Numerous metabolic and perhaps immunological disorders have been linked to the duodenum and its microorganisms [310-312]. Furthermore, it has been discovered that duodenal perfusions of either living or dead *Lactobacillus* species alter the host immune response, offering a human discovery experimental system. [308,305,313,314]. The colon has been the subject of the

greatest research on the horizontal gradient, despite the gut's obvious vertical gradient. The colon has been the subject of the greatest research on the [317-321,323,324] horizontal gradient, despite the gut's obvious vertical gradient. Crucially, the architecture of the microbial communities is influenced by oxygen, redox, and mucus gradients that extend from the mucosal surface to the lumen [298].

Numerous intestinal and extra intestinal conditions have been linked to the gut microbiota. Numerous extensive studies have examined the gut microbiome and its significance in relation to particular Gastrointestinal (Gi) Disorders, including Colorectal Cancer (CRC), Coeliac Disease, Irritable Bowel Syndrome (IBS), Intestinal Bowel Diseases (IBDs), Chronic Liver Diseases, or Pancreatic Disorders [8,254]. The gut microbiome composition of IBDs, the prototypical inflammatory disorders of the intestine, is known to deviate, and facultative anaerobes have been observed to outgrow, particularly when there is active inflammation and metabolite disturbances, such as those involving BAs, Short Chain Fatty Acids (SCFAs), and acylcarnitine pathways[327,331]. Over the past several years, a lot of research has been done on the gut microbiota in relation to obesity and conditions including type 2 diabetes (T2D) and non-alcoholic fatty liver disease (NAFLD). In fact, interventional trials using specific bacterial strains, including *Akkerman Sia muciniphila,* have demonstrated impacts on obesity-related parameters. Numerous research has attempted to connect an altered gut microbiota to obesity [74]. In both Asian and European cultures, T2D has also been associated with a compromised gut microbiota [161,162,164]. A number of research suggested that the gut microbiota influences glucose control, and microbial differences were highly associated with insulin resistance in T2D [332-337]. The control of several facets of metabolic diseases is significantly influenced by the gut bacterial flora. The microbiota's synthesis of a wide range of metabolites and their interactions with host cell receptors, which may either activate or inhibit signalling pathways and have either positive or negative effects on the host's health, are some of the factors that determine this control.

Relation between Microbial Biomass and pH

One important factor in maintaining the gut microbiota is the pH of the environment. A donor-independent response to an increase or decrease in ambient pH was found in this study's evaluation of the effects of pH on the organisation of the gut microbiota luminal and mucosal communities as well as the synthesis of short chain fatty acids (SCFAs) in vitro [92]. According to *Jin and Kirk* (2018), this parameter influences microbial growth and metabolism as well as the availability of nutrients and enzyme activity in the extracellular environment [340,341]. Human physiology and microbial metabolism work together in the colon to create a pH gradient that rises from the proximal to distal colon over time [78]. The gut microbiota's fermentation and the production of metabolites like lactate and Short Chain Fatty Acids (SCFAs) are responsible for the proximal colon's low pH of about 5.7 [343-345]. Indeed, the concentration of SCFA and the pH of the surrounding environment are negatively correlated [228]. As the generated SCFAs are absorbed, or used, and bicarbonate is released by the mammalian cells, the pH in the colon increases (*Holzer* 2015). Because the proximal colon's use of carbohydrates restricts the distal colon's access to nutrients, the microbial community starts to break down the proteins and amino acids that are available, releasing urea and ammonia in the process, raising the pH of the surrounding environment to about 6.7 [315]. Gut microbial populations and their metabolisms are subject to selection pressures from pH and fermentable substrates. Using triplicate batch cultures that began with faecal slurry and were incubated with an initial pH of 6.0, 6.5, or 6.9 and 10 mM glucose, fructose, or cellobiose as the carbon substrate, and his colleagues assessed the relative contributions of pH, alkalinity, and substrate on microbial community structure, metabolism, and functional interactions. We examined fermentation products and 16S rRNA gene sequences. Microbial diversity was influenced by substrate type and ph. Insufficient alkalinity caused a pH reduction from 6.0 to about 4.5, which grouped pH 6.0 cultures together and separated them from pH 6.5 and 6.9 colonies, which only had slight pH drop. Fermentative metabolism was shown to reflect the influence of pH on the organisation of microbial communities. Regardless of the kind of substrate used, lactate buildup happened in pH 6.0 cultures whereas propionate and acetate accumulations were seen in pH 6.5 and 6.9 cultures. Lastly, the interactions between the communities that produce and consume lactate were influenced by pH. Cultures that began at pH 6.5 and 6.9 were dominated by *Veillonella*, *Bacteroides*, and *Escherichia*, which produced acetate and propionate, whereas cultures that began at pH 6.0 were dominated by lactate-producing *Streptococcus*. Lactate buildup resulted from acid suppression of lactate-consuming organisms.

Restoration of Gut

Including the correct items in your diet may be just as crucial for intestinal health. Your gut microbiota, which is made up of billions of bacteria and fungus, may be starved by the things you remove. When eating, people pay more attention to the nutrients their bodies require than they do to the nutrients their microbiota requires. Probiotic and prebiotic-rich foods support intestinal health. Probiotic microbes have been found in traditional fermented foods and medications [12,121,256]. The most popular of these as probiotic delivery systems are fermented dairy products, such as cheese, yoghurt, acidified milk, and drinking yoghurt. Their distinct physicochemical and nutritional properties enable them to buffer against the harsh acidic conditions of the stomach (pH 2-3) and maintain a viable number of probiotics in the lower gut (6 to 8 Log CFU/mL), which may aid in their potential therapeutic effects [13,158,302]. For generations, a significant portion of the human diet has consisted of fermented foods [54]. In addition, the shelf-life of fermented meals made from meat, milk, and plants is longer than that of fresh raw materials [259]. This is because the high water content and nutritious richness of fresh meals make them very perishable. In many parts of the world, including Asia and Western nations, fermented foods and beverages made from plants and animals are an essential part of the diet. They contain

nutrients that have the potential to help people stay healthy and avoid disease, but they also change in taste, texture, toxicity, and cooking time [157,254]. These foods naturally include substances that can block any harmful bacteria and spoilage organisms, such as organic acids, ethanol, or antibiotic chemicals [168]. Because LAB may create substances that are beneficial to both human and animal health, they play a significant role in food fermentation. Additionally, by preserving the equilibrium of the gut microbiota, LAB made from single or mixed cultures obtained from fermented foods are appropriate probiotics for enhancing the digestive system. Additionally, these microbes can strengthen the immune system's defences against harmful germs. The quality of diet, eating habits, and maternal milk are the primary determinants of general health. In the past, humans ate food that included a variety of living microbes. Nonetheless, the idea of cleanliness raised the bar for consuming hygienic food with few living microorganisms. The Western diet has led to a large decline in the consumption of fermented foods, which in turn has reduced the number of probiotic organisms that our predecessors were exposed to [129]. Cases of cancer, allergies, obesity, heart disease, and autoimmune diseases all naturally rise when the probiotic content of the Western diet declines [34]. By altering the gut microbiota and mucosal immunology, probiotic usage affects human physiology [65]. Numerous genera, including as *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Pediococcus*, and various yeasts, are utilised as probiotics [285]. When given in enough quantities, probiotics-live bacteria-have positive health effects. *Streptococcus thermophilus, Saccharomyces bourlardii, Akkermansia muciniphila, Faecalibacterium prausnitzii,* and *Lactococcus lactis* are the less popular probiotics [21,135,210]. They have a significant impact on the mucosal immune system, gut luminal environment, and mucosal barrier function. Dendritic cells, monocytes, epithelial cells, Natural Killer (NK) cells, B cells, and T cells (including T cells with regulatory characteristics) are among the many innate and adaptive immune cells that they significantly affect. Additionally, certain probiotic strains including *Bifidobacterium* and Lactobacilli, as well as prebiotics, may help close the spaces between intestinal cells, avoiding leaky gut syndrome. According to recent research, prebiotics and probiotics will play a significant role in medicine in the future because of their many health advantages. Prebiotics are one type of fibre that helps nourish these good bacteria. They are present in a variety of foods that are abundant in the Microbiome Diet, including radishes, asparagus, garlic, Jerusalem artichokes, onions, and leeks [295]. Numerous health advantages, including as better nutrition absorption, reduced risk of certain gastrointestinal illnesses, decreased possibility of obesity, metabolic stress, and deteriorating mental health, have been associated with prebiotic ingestion. By encouraging the development of beneficial bacteria while preventing the spread of potentially harmful species, prebiotics can help regulate the total bacterial variety of the gut. Prebiotics affect the gut's lymphoid tissue, which can alter immune responses and lower inflammation.

Impact of Gut on Immune System

The human body's greatest microbial population is found in the gastrointestinal system. Beginning in early childhood, the gut microbiota has a major influence on the maintenance of immunological tolerance and performs important functions in the development of the gut immune system. These microorganisms have a dynamic and interdependent relationship with the immune system. By offering a wide range of antigenic determinants and microbial metabolites that affect the initiation, maturation, and preservation of immunological function and homeostasis, they produce immune signals. Simultaneously, the innate and adaptive immune systems play a role in regulating a stable microbial environment between harmful and commensal microbes. As a result, the host immune system and the gut bacteria community cooperate to preserve immunological homeostasis. When such a condition is disturbed in vulnerable hosts, it can have a significant negative impact on human health and result in a number of autoimmune and auto-inflammatory diseases. The interaction between microbial populations and various immune system lineages in the gut has evolved together, significantly influencing intestinal immunity.

The human gut immune system is specifically designed to maintain balance within the gut microbiota. It achieves this by controlling the localization of microbes, regulating their composition, preventing pathogen invasion, controlling the growth of native bacteria, and eliminating harmful microbes. Additionally, it supports the growth of beneficial probiotics, all of which contribute to maintaining gut health and immune homeostasis [16,122]. Up to 30% of *Clostridium* clusters IV and XIV are found in a healthy gut microbiota, and many of them exhibit immunomodulatory properties [17]. The gut microbiome is made up of billions of viruses (virome) at 106-109 per gramme of faeces, trillions of bacteria (bacteriome) at 1012 per gramme of faeces, and fungi (mycobiome), which make up less than 1% of the total. Understanding how gut microbial populations, their metabolites, and immune system cells co-adapt is crucial to understanding how humans are exposed to bacteria and how to stay healthy [215]. The metabolites that the microorganisms create include tryptophan, sphingolipids, secondary bile salts, SCFAs, and other compounds that support the protection of gut walls [218]. In a healthy condition, the gut microbiota works with other inflammatory cells (neutrophils, lymphocytes) and antigen-presenting cells (DCs, tissue macrophages) to keep the host immunological defence system in balance. Here, we'll go over these metabolites' primary makeup and immunological ramifications.

The following processes collectively allow the gut immune system to have a significant impact on gut flora. First, the gut mucosal immune system's unique histological structure includes a wide range of immune responses to reduce host tissue exposure to unwanted microorganisms. For instance, immune effectors that stratify luminal microorganisms and decrease bacterial-epithelial cell interaction include mucus released by the colon antimicrobial peptides secreted by the small intestine and IgA secreted by B cells [297]. Severe infections and excessive pathogen development are avoided by this stratification [156,174,227].

Furthermore, penetrant bacteria's ability to enter intestinal tissues is restricted by morphological compartmentalisation. The

luminal side of the firmly linked epithelium barrier is where microorganisms are restricted. The lamina propria macrophages phagocytose and eliminate microorganisms when they breach this barrier [139]. They are also taken up by the DCs and sent to the mesenteric lymph nodes, where they are contained in the body's secondary lymphatic tissues.Second, the preservation of homeostasis and the variety of microbial communities depend heavily on host immunity [46]. Both the innate and adaptive immune systems support the development of advantageous microbial community members and aid in preserving a stable microbial community. The microbiota's makeup can be recognised and altered by the innate immune system [187]. Through its capacity to identify molecular patterns and trigger immunological responses via PRRs, such as TLRs, purinergic receptors, G protein-coupled receptors (GPCRs), Nod-like receptors (NLRs), and the aryl hydrocarbon receptor, the innate immune system preserves microbial equilibrium [153].

The Role of Gut Microbiota in Immune Homeostasis and Autoimmunity

The gut microbiota interacts closely with the host immune system. Certain members of the gut microbiota have been linked to autoimmune diseases. Thanks to revolutionary developments in "next-generation" sequencing technology, which have made it possible to characterise these intricate commensal communities with culture-independent microbial analysis, has the study of gut microbiota and autoimmunity become a more manageable field [117,188]. This has facilitated the characterization of complex commensal communities. Progress has been made in understanding cellular and molecular interactions between commensals and the mucosal immune system [235,304].

Furthermore, significant advancements have been achieved as researchers have started to identify the molecular and cellular relationships between commensals and the mucosal immune system, especially with the use of autoimmune animal models. Maintaining self-tolerance to prevent autoimmunity while also eradicating invasive infections is essential for the body's health and immune system balance. The gastrointestinal tract's gut microbiota offers the host vital health advantages, especially through immunological homeostasis regulation [128]. Furthermore, it is now clear that changes to these gut microbial populations can result in immunological dysregulation, which in turn can induce autoimmune diseases. Here, we summarise the developments in our knowledge of how the gut microbiota controls both innate and adaptive immunological homeostasis, which can influence the onset of systemic and intestinal autoimmune disorders [330]. In addition to helping us comprehend the pathophysiology of autoimmune illnesses, investigating the relationship between gut bacteria and the human immune system will provide the groundwork for the development of innovative immuno- or microbe-based treatments.

Numerous techniques have been employed to illustrate the pivotal function of gut microbiota signals in immune system development. Using Germ-Free (GF) models, in which animals are grown in a sterile environment without ever coming into contact with microbes, is one effective strategy [248]. These models demonstrate how the microbiome significantly affects both innate and adaptive immunity. As will be covered later, another strategy is to manipulate the microbiota with antibiotics or reconstitution, which offers important insights into its function in immunological homeostasis and autoimmune disorders [136,282,276]. Notably, the gut microbiota has a significant impact on systemic immune responses in addition to controlling the local intestine immune system [148]. In order to preserve immunological balance, this section examines how the gut microbiome influences both innate and adaptive immunity [214].

Microbiota and Innate Immune Homeostasis

Antigen-Presenting Cells (APCs)

Since they co-evolved with the microbiota, intestinal APCs are essential for defending the body against infection while preserving tolerance to the typical gut flora. For instance, compared to the spleen, the Dendritic Cells (DCs) in Peyer's patches generate more interleukin-10 (IL-10) [283]. Under normal circumstances, gut macrophages that are located close to the intestinal microbiota have a distinct "inflammation anergy" phenotype, which means that they do not release pro-inflammatory cytokines in response to microbial stimuli [149,150]. The Microbiota's Role in APC Developmentis as intestinal DCs are shown to be less common in Germ-Free (GF) animals; nevertheless, they can be recruited to the intestines by monocolonizing them with Escherichia coli [284]. A subgroup of DCs that express CD70 and CX3CR1 are also stimulated by ATP produced from microbes, aiding in the differentiation of Th17 cells [16]. The gut has the body's greatest concentration of tissue macrophages. Although GF mice have normal quantities of intestinal macrophages, GF pigs have lower numbers of these cells, and GF pigs also have lower amounts of systemic macrophages [224,219]. Additionally, GF mice lack macrophage activation markers such major histocompatibility complex class II and have impaired macrophage capabilities including phagocytosis and chemotaxis.

Neutrophils

Innate immunity depends on neutrophils, whose modulation is influenced systemically by the microbiome. For example, GF rats are neutropenic and have reduced phagocytic function, as well as impaired generation of nitric oxide and superoxide anion [230]. Normal immune function is not restored when GF rats are returned to a traditional setting. According to recent research, the Nucleotide Oligomerisation Domain 1 (NOD1) receptor recognises peptidoglycan from the gut microbiota, which increases neutrophil killing activity [56].

Other Innate Cell Types

Studies have identified two types of Natural Killer (NK) cells in the gut that express the NKp46 receptor. One resembles conventional NK cells, while the other produces less interferon-c (IFNc) and lacks perforin. These gut-specific NKp46+ cells also express the nuclear hormone receptor RORγt and IL-22 [266]. Since GF

mice lack IL-22-producing NKp46+ cells, it suggests that the gut microbiota plays a critical role in promoting the differentiation of these cells. Mast cells carry out regulatory tasks include regulating smooth muscle activity and blood flow and it comprising 2-3% of the GI tract's lamina propria cells, GF mice have greater blood mast cell percentages and lower intestine mast cell densities. According to another research, the microbiota stimulates mast cell migration into the gut by causing Intestinal Epithelial Cells (IECs) to produce CXCR2 ligands [33]. This mechanism is reliant on MyD88, a signalling protein in the TLR pathway.

Intestinal Epithelium are the main physical barrier dividing gut microorganisms from underlying tissue is the intestinal epithelium. IECs secrete cytokines, chemokines, and antimicrobial peptides, among other immunoregulatory functions, while often not being categorised as immune cells [267]. Reduced IEC proliferation and decreased antimicrobial gene expression were seen in mice treated with GF and antibiotics, indicating that the microbiota affects the immunoregulatory activities of IECs via controlling the expression of these factors. The main physical barrier separating the commensals that are kept in the intestinal lumen from the sterile tissue underneath is the intestinal epithelium, which is made up of a single layer of IECs. IECs have several immunoregulatory functions, including the release of cytokines, chemokines, and antimicrobial peptides, in addition to their mechanical protective role. However, they are often not categorised as immune cells. Mice treated with GF and broad-spectrum antibiotics showed decreased IEC growth and expression of their antimicrobial genes [165,250]. These findings imply that by controlling the expression of antimicrobial factors, the gut microbiota might influence the immunoregulatory functions of IECs.

Microbiota and Adaptive Immune Homeostasis

Numerous microbial species have been shown to be important regulators of distinct adaptive immune system branches. The mutualistic interaction between the microbiota and the host is shaped by the antigen-specific adaptive immune responses. In the mucosa, the immune system's T cells and B cells have position-specific phenotypes and functions that are influenced by the microbiota. Because of their prevalence and intimate relationship with the immunological tissues of the gut, these reactions mainly target the gut bacteria. The variety and functionality of immune cells, particularly B cells and T cells, are greatly impacted when bacteria colonize mammalian hosts. This involves the differentiation of T cells that carry the CD4 antigen and B cells that produce IgA, especially TH17 cells and Treg cells, which are essential parts of the intestinal lamina propria's effector T cells (Teff). Furthermore, a brief discussion will be given to the reciprocal interactions between lymphocytes and the microbiota, which have not received much attention. It's crucial to remember that the majority of knowledge on these immune-microbiota interactions is derived from research conducted on mice in controlled environments, where they are not exposed to pathogenic microorganisms or the microbiota present in wild populations [42,43]. A constitutive increase in highly differentiated innate and adaptive immune cells, including effector memory T cells that carry the CD8 antigen, is observed in laboratory mice when they are housed with free-living wild mice9 [30]. Compared to mice housed in certain pathogen-free settings, the immunological profiles of these mice are substantially more similar to those of adult humans. Therefore, variations in the species' microbiotas may be a contributing factor in certain mice studies' inability to forecast how humans would react to treatment [140].

T cell

The intestinal lamina propria is home to the majority of CD4+ T cells, which are essential for immunological responses. They develop into subtypes (Th1, Th2, Th17, Treg) upon activation, and each is controlled by distinct transcription factors and cytokines [17,180]. Tregs support immunological tolerance, Th1 and Th2 cells aid in infection responses, while Th17 cells are associated with inflammation. Allergies and autoimmune illnesses might result from an imbalance in these reactions. The gut microbiota influences the development of these T-cell subtypes [98,112,113,134]. In Germ-Free (GF) mice, the absence of microbiota leads to a reduction in intestinal CD4+ T cells and a Th2-skewed immune response. Specific bacteria like *Bacteroides* fragilis promote Th1 responses, while Segmented Filamentous Bacteria (SFB) induce Th17 cells. Studies also suggest that Clostridia species can help develop Tregs, and the microbiota maintains immune homeostasis by limiting the conversion of Tregs. Other T-cell types, such CD8+ T cells and γδ T cells, which both functions less well in GF mice, are also impacted by microbiota. All things considered, the gut microbiota is crucial in forming the immune system, and variations in the microbial makeup affect health consequences via controlling the development of T cells [114].

B cell

Immunoglobulin A (IgA) is mostly secreted by gut-associated B lymphocytes, especially those found in Peyer's patches. Every day, the gut secretes about 0.8 grammes of IgA per metre, which is a far greater production rate than any other Ig classes. Both the quantity and cellularity of Peyer's patches are diminished in Germ-Free (GF) mice, which results in decreased intestinal plasma cells and IgA levels. Mucosal IgA synthesis is largely influenced by the gut microbiota; in GF mice, high secretory IgA levels must be induced by a high dosage of live bacteria [59,60,61,82]. Mucosal IgA, on the other hand, targets the present microbiota mainly because it lacks a memory response. The spleen of GF mice has smaller and fewer germinal centres, which are where affinity maturation and B cell differentiation take place. As a result, while natural IgM levels stay normal, serum levels of natural IgG are drastically decreased. It's interesting to note that GF rats' blood levels of IgE, an allergy-associated Ig isotype, are elevated both globally and locally in the gut [240]. The Th2-predisposed immunological response in GF animals, which might encourage the induction of IgE, a hallmark of Th2-driven humoral immunity, is consistent with this rise in IgE.

Microbiota and Autoimmunity

It is possible to propose a "commensalocentric" theory of maintaining general health since the commensal microbiota has such a profound impact on immune system regulation and other facets of mammalian health. The immune system responds to self-tissues and cells as though they were infections, a condition known as autoimmunity. The commensal microbiota can influence the innate and adaptive arms of immune responses as well as the processes of "innate-adaptive connection," hence either promoting or inhibiting autoimmune reactions [53]. The "specific lineage hypothesis" states that certain microbial lineages influence immunity and autoimmunity, whereas the "balanced signal hypothesis" states that many lineages can shift the homeostatic balance that controls host/microbiota equilibrium in favour of either decreased or increased host response. Finding ways to prevent and cure autoimmune diseases requires a thorough understanding of the intricate relationships between the host and microbiome. It is not unexpected that some gut microbiota members have been connected to autoimmune disorders given the significant impact the microbiota has on the innate and adaptive immune systems. The significance of gut bacteria in autoimmune illnesses connected to the gastrointestinal tract has received a lot of interest. Interestingly, as was previously mentioned, the gut microbiota affects several systemic immunological components and plays a function that extends beyond the local gut immune system. As a result, new research has also uncovered how gut microbiome affects extraintestinal illnesses. We specifically highlight research that demonstrates how alterations in a single microbial species and/or worldwide commensal ecosystems may tilt the scales in favour of a protective or pathogenic immune response, hence affecting the course of autoimmune disorders.

Impact of Microbiota on various diseases

It has been demonstrated that the human microbiome is an essential component of human health. Dysbiosis is marked by several abnormalities in the human microbiome. It has been suggested that the microbiome should be considered "essential organ" of the human body because of the magnitude of its impact [97]. There are a number of extrinsic variables that can lead to dysbiosis in the gut microbiome. These factors include the ingestion of antibiotics, dietary components, psychological and physiological stress, and host characteristics. Dysbiosis is a disorder that impairs the proper functioning of gut microbiota, which is essential for host health. This disturbance leads to the production of microbial extracts, which can be harmful for the host and induce various diseases [35]. An excess of pathogenic bacteria or fungi is commonly accompanied by dysbiosis. This is often followed by a considerable reduction of microbial community or essential functional groups, as well as host immunological response, paving the way for the 34 disease [207]. Enough research has been done to demonstrate that dysbiosis of the microbiota in the gut is the underlying factor of a wide variety of disorders. The following is a discussion of various diseases and the microbiome-based therapies that are available for treating them (Figure 5).

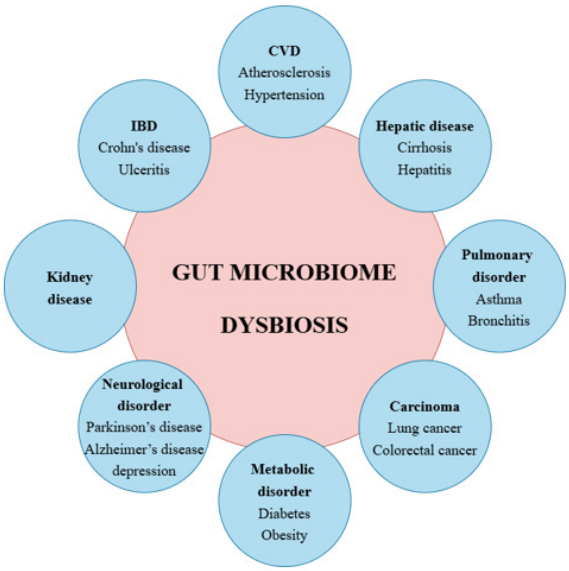

Figure 5: Various diseases caused by dysbiosis of human microbiota.

Inflammatory Bowel Syndrome

Inflammatory Bowel Disease (IBD) is an illness that spans multiple diagnoses, including Crohn's disease or CD and ulcerative colitis or UC, and is distinguished by recurrent and persistent inflammation of the GI system [167]. The inflammatory bowel disease or IBD is a chronic gut pathogenic disorder. There is a distinction between the two diseases in terms of the clinical manifestations of inflammation and the intestinal localisation. Both diseases are characterised by symptoms such as diarrhoea, rectal hemorrhage, abdominal discomfort, letharginess, and shedding pounds [182]. It

is characterised by extensive transmural ulcerations and can occur anywhere along the gastrointestinal tract. Patients who have CD experience patchy inflammation, which can occur anywhere throughout the GI tract [95]. Patients with ulcerative colitis often have ulcerations that are more superficial and are confined to the mucosa of the colon, as well as inflammation that typically spans the entire length of the large intestine, from rectum to colon [95,96]. A number of environmental factors, such as smoking, nutrition, drugs, strain, removal of appendex, geography, and social standing, have been proven to have an effect on the advancement and intensity of the condition [67]. Frequent episodes of diarrhoea, fever, and abdominal pain are all symptoms that are associated with CD and UC. However, the interaction between host factors and gut microbiota indicates a significant deal of potential in the development of disease. The underlying mechanism of this disease development is still not fully understood [35]. The immune system's interaction with the microbiota of the gastrointestinal tract is the root cause of severe inflammation. The heightened sensitivity of T-lymphocytes residing in the gut microbiota to non-pathogenic antigens is the fundamental cause of Inflammatory Bowel Disease (IBD) [94].

A variety of research has shown the antibodies production that target specific antigens derived from commensal bacteria and autoantigens, including anti-Saccharomyces cerevisiae, perinuclear anti-neutrophil cytoplasmic antibody, and anti-Pseudomonas fluorescens-associated sequence 12 [77,177,178,212]. Dysbiosis and the reduction of microbiomes, that is crucial for maintaining the integrity of the mucosal barrier of the gut, are both caused by a lack of tolerance towards the gut microbiome in patients with IBD who also have an abnormal immune response.

Impaired functions lead to an increase in the exposure between epithelial cells and the microbiota of the gut, which in turn stimulates the local immune system and contributes to severe inflammation in the gut tissues. Pathogenesis of inflammatory bowel disease may be influenced by dysbiosis of the gut [225]. In patients with Inflammatory Bowel Disease (IBD), a common trait that is found is a decline in the number of guts *Firmicutes*, like Faecalibacterium prausnitzii and Roseburia sp. [131,202,286,325] By decreasing the levels of pro-inflammatory cytokines (IL-12 and IFN-g) and boosting the levels of anti-inflammatory IL-10, these bacteria have a major impact on the anti-inflammatory defence mechanism [286]. *Firmicutes* are responsible for the production of butyrate, which serves as the principal energy substrate within colonocytes. Reduced levels of *Firmicutes* have the potential to generate local inflammation by lowering levels of anti-inflammatory cytokine, which is an essential component in the regulation of mucosal immunity. This could also lead to impairment in the function of the intestinal barrier due to a lack in short-chain fatty acids [202,89,239]. In the treatment of IBD, the probiotic F. prausnitzii is utilised as a medicinal agent. The dysbiotic traits that are noticed in people with inflammatory bowel disease include an increase in the percentage of pathogenic gut bacteria, such as species of Enterobacteriaceae and *Bacteroides* fragilis, both of which have increased levels of endotoxic LPS in their external layers [68]. According to study by *Feagan, et al* and *Christensen, et al*, many anti-inflammatory therapies, such as Antibodies (Ab), which target pro-inflammatory mediators (including anti-TNF-alpha, anti-IL12, and anti-IL23), have been shown to be effective in reducing inflammation [88,55].

Cardiovascular Diseases (CVD)

The major cause of illness and death across the globe is Cardiovascular Diseases (CVDs), which include coronary heart disease, cerebrovascular disease, peripheral arterial disease, and other similar conditions. In spite of the fact that conditions such as atherosclerosis, hypertension, obesity, diabetes, dyslipidaemia, and mental illness are among the general risk factors, there is a growing body of research that suggests microbiota play a role in maintaining cardiovascular health, and that its dysregulation may contribute to cardiovascular diseases [185]. Numerous studies have shown that Genetically Modified Organisms (GM) and the metabolic products they produce interact with the host in a variety of different ways, which can have an effect on the development and occurrence of Cardiovascular Disease (CVD). The metabolic products of the gut microbiome, which include Trimethylamine Oxide (TMAO), bile acids, and Short-Chain Fatty Acids (SCFAs), have been shown to play a role in Cardiovascular Disease (CVD) by a significant number of researches [52].

Hypertension stands out as a prevalent risk factor for cardiovascular disease. Hypertension is linked to modifications in gut function, shifts in gut microbial communities, and variations in gut-brain axis. In individuals with hypertension, there was a significant reduction in microbial richness, diversity, and evenness [194], while the *Firmicutes*/*Bacteroidetes* ratio showed a notable increase [194]. The gut microbiota, recognised as the largest endocrine organ in the body, has a significant impact on the cardiovascular system and plays a role in the development of cardiovascular diseases. The gut microbiota plays a crucial role in the metabolism of choline, phosphatidylcholine, and carnitine, ultimately leading to the production of trimethylamine-N-oxide (TMAO). TMAO has been proposed to not only regulate the equilibrium of cholesterol and bile acid concentrations, while also linked to the onset of early atherosclerosis and an elevated risk of long-term mortality of cardiovascular diseases [255]. Mechanistically, TMAO can activate the expression of inflammatory cytokines IL-6, IL-8, and TNF-α by MAPK and NF-κB signalling pathway. NF-κB is recognised as a crucial mediator that governs the activation, differentiation, and effector function of inflammatory immune cells. The dysregulation of NF-κB likely plays a role in the pathogenesis of atherosclerosis by facilitating the recruitment of monocytes [137]. Another inflammation mediator, Lipopolysaccharide (LPS), also referred to as endotoxin, is a component of Gram-negative bacteria primarily found in the gut and oral cavity. Recent studies indicate that LPS can trigger vascular oxidative stress, resulting in endothelial dysfunction and vascular inflammation. A retrospective analysis by *Yoshida, et al.* indicated that individuals with cardiovascular diseases exhibit elevated faecal LPS levels in comparison to those without such conditions. The variations in the structures of lipid A moieties of LPS across dif-

ferent bacteria are noteworthy, as they may influence the activity of LPS [338]. The gut microbiota has the capability to metabolise polysaccharides and proteins into Short-Chain Fatty Acids (SCFAs), which are another class of metabolites associated with Cardiovascular Diseases (CVDs). The majority of SCFAs are acetates, butyrates, or propionates [213].

Epidemiologic studies indicate that sufficient dietary fibre intake may be associated with a reduced risk of cardiovascular disease, potentially due to lower levels of low-density lipoprotein. Prebiotics are fibres, primarily oligosaccharides, which undergo selective fermentation by specific bacteria, mainly from the Lactobacilli and Bifidobacteria genera. This process leads to alterations in the composition and function of the GI microflora, ultimately providing benefits to the host's well-being and health [106]. A randomised trial demonstrated that the intake of live *Lactobacillus* plantarum led to a diversification of homogeneous gut microbial flora and was linked to a decrease in the occurrence of cardiovascular disease events.

Respiratory Diseases

Respiratory diseases encompass a range of conditions impacting the lungs and the broader respiratory system and can be managed using probiotics [100]. This category includes chronic illnesses such as asthma, Chronic Obstructive Pulmonary Disease (COPD), and pulmonary fibrosis, as well as acute conditions like pneumonia. Comprehensive investigations have indicated that oral, lung, and gut microbiota are linked to the onset of respiratory diseases. COPD and asthma rank as the two most commonly diagnosed chronic respiratory conditions. COPD is characterised as a disease state marked by airflow limitation linked to chronic bronchitis or emphysema. Asthma is a complex condition marked by persistent inflammation of the airways, which leads to an exaggerated response to various environmental stimuli. It is associated with symptoms such as wheezing, difficulty breathing, and a sensation of tightness in the chest [138]. The chronic inflammation triggered by lung microbiota could be a crucial factor in the onset of chronic respiratory diseases [145]. The gut microbiota plays a significant role in modulating pro-inflammatory and autoimmune responses, contributing to various inflammation-related diseases. Numerous investigations have established a connection between early-life gut microbiota dysbiosis and a heightened risk of developing asthma in later years, a phenomenon referred to as the gut-lung axis [23]. Gut microbiota dysbiosis in early life may contribute to the onset of respiratory diseases, as gut microbiota is crucial for the maturation of immune cells and resistance to pathogens [287]. The studies by *Roussos, et al.* and *Rutten, et al.* have shown that individuals with chronic gastrointestinal diseases exhibit a greater prevalence of chronic respiratory conditions such as asthma and COPD, although the underlying mechanisms remain ambiguous [260,263,291] *Sprooten, et al.* reported that individuals experiencing acute COPD exacerbations exhibited heightened gastrointestinal permeability, indicating a potential role of gut microbiota in these exacerbations [291]. A further investigation revealed that elevated levels of gut microbiota-dependent circulating TMAO were linked to all-cause mortality in patients with COPD [233]. It is proposed that gut bacterial metabolites could play a role in asthma by influencing immune modulation [253].

The typical respiratory tract and gut microbiota serve as a defence against pneumonia by inhibiting the colonization of pathogenic bacteria and by influencing immune responses. Consequently, it is expected that the dysbiosis of respiratory tract microbiota is regarded as a risk factor for pneumonia.

The primary origin of microbes in the lower airways is the upper airways. Recent studies have indicated that a decrease in nasal microbiota diversity heightens the risk of pneumonia.

Notably, three microbiota profiles characterised by Lactobacilli, Rothia, and *Streptococcus* showed a significant correlation with pneumonia [71]. Changes in immune response resulting from microbiota dysbiosis could elevate the likelihood of pneumonia. Dysregulation of SCFA-producing bacteria may play a role in the development of pneumonia. *Segal, et al*. indicated a correlation between pulmonary SCFAs and an increase in anaerobic bacteria [274]. The interaction between pneumonia and microbiota is significantly influenced by gut microbiota. *Schuijt, et al*. discovered that the gut microbiota serves a protective function against S. pneumoniae infection [271]. In patients with COVID-19, a reduction in the abundance of various gut commensals was noted, including Bifidobacteria, Eubacterium rectale, and Faecalibacterium prausnitzii. The dysbiosis of gut microbiota showed a positive correlation with disease severity, accompanied by increased levels of inflammatory cytokines and blood markers including CRP, aspartate aminotransferase, and lactate dehydrogenase. Consequently, in contrast to chronic respiratory diseases, the gut-lung axis could offer enhanced protection for the host against pneumonia through the modulation of the immune response [142].

Colorectal Cancer

The global mortality rate of Colorectal Cancer (CRC) ranks as the fourth leading cause of cancer-related deaths [15]. Cancer is a condition marked by the swift multiplication of atypical cells that expand without restraint, potentially affecting nearly every area of the body. In 2020, cancer stands as a primary contributor to global mortality, resulting in more than 10 million fatalities [90]. The process of carcinogenesis is complex and influenced by multiple factors. It is well recognised that tobacco, bacteria and viruses, obesity, alcohol, and radiation significantly contribute to the risk of developing cancer [109]. Research indicates that an imbalance in gut microbiota can initiate inflammation and immune responses that are indirectly associated with the development of cancer [140].

Grivennikov, et al. indicated that microbial products could lead to the deterioration of the epithelial barrier, subsequently triggering inflammation associated with tumours and facilitating the initiation and progression of Colorectal Cancer (CRC) [119]. *Chen, et al.* proposed that both commensal and pathogenic bacteria contribute to the progression of CRC through three mechanisms: 1) taking advantage of defects in the tumour surface barrier, 2) invading healthy

colonic tissue and triggering local inflammation, and 3) generating genotoxic metabolites that lead to the oncogenic transformation of colonic epithelial cells [51]. The primary bacteria identified as contributors to CRC include *Enterococcus faecalis, Escherichia coli, Bacteriodes fragilis, Streptococcus bovis, Fusobacterium nucleatum,* and *Helicobacter pylori* [66] (Table 1).

The fadA of F. nucleatum is a distinctive adhesin that facilitates its adhesion to and invasion of human epithelial cells, triggering an inflammatory response [126] and promoting cell proliferation [261]. The bacteria in question have the capability to generate genotoxic substances, including colibactin, B. fragilis toxin, and typhoid toxin, which lead to damage in host DNA [170,171,172]. Probiotics that utilise lactic acid-producing bacteria, such as *Lactobacillus* and *Bifidobacterium*, demonstrate a protective effect against colon cancer by decreasing tumour incidence and tumour loads. They are suggested to have a direct anti-proliferative effect on tumour cells by preventing carcinogen-induced DNA damage. This occurs partly through the inhibition of carcinogen and mutagen formation, reduction of the activity of pro-carcinogenic enzymes like ornithine decarboxylase, and enhancement of anti-tumor immunity, which is evidenced by an increase in natural killer cells, MHC class II antigen-presenting cells, and CD4-CD8C T cells [83,281].

Neurological Disorders

Neurological disorders are conditions that affect both the central and peripheral nervous systems. These conditions can cause damage to the brain, spinal cord, cranial and peripheral nerves, the autonomous nervous system, nerve roots, and neuromuscular plaque. There are a number of situations that can result in bleeding in the brain, such as diseases that affect the blood vessels, disorders that are brought on by problems with the development of the nervous system, injuries to the spinal cord or brain, and brain tumours [81]. Dysbiosis of the human gut microbiome has been linked to a wide range of neurological illnesses [32,80,93,102,163]. These findings were published in a number of different studies. For a variety of population subsets, it was known that neuropsychiatric and neurodegenerative illnesses of the brain, in addition to a great number of other comorbidities, were responsible for causing significant mortality [316].

Neuropsychiatric Illnesses

Microbiota in the gut are thought to play a significant part in the process of influencing neuronal behaviour through the gut-brain axis [127]. Some studies believe that gut-induced stress, along with a disrupted gut microbiome and a variety of other factors, plays a significant role in the development of depression, anxiety, and other psychological disorders. This is despite the fact that the direct mechanism by which gut bacteria influence neuropsychiatric disorders has not been studied. When compared with faecal samples from healthy controls, faecal samples from individuals with major depressive disorder have been shown to have a higher number of *Bacteroidetes*, *Protobacteria, and Actinobacteria*, while having a lower number of *Firmicutes*. This was demonstrated by *Jiang, et al.* [152]. There are mental and neurological disorders that afflict twenty-five percent of the world's population, including anxiety and depression (Neuropsychiatric Disorders). In fact, 85% of people who suffer from depression and 90% of persons who suffer from anxiety disorders both feel significant levels of anxiety. This suggests that these two clinical illnesses are quite closely associated to one another [41,205]. Extensive research has been conducted to study the connection between anxiety and depression and alterations in the stability and composition of the microbiota in the gut [27]. Additionally, patients who suffer from anxiety problems have been shown to exhibit fascinating alterations in the microbiota of their faeces. They made the observation that patients who suffered from Generalised Anxiety Disorder (GAD) had lower levels of microbial diversity and richness. This was found to be correlated with lower levels of short-chain fatty acid producers like Eubacterium rectale and Fecalibacterium, as well as higher levels of Ruminococcus, Escherichia, Shigella, and Fusobacterium [151]. When compared to a placebo, the administration of probiotics comprising *Bifidobacterium bifidum, Lactobacillus acidophilus*, and *Lactobacillus casei* to individuals suffering from major depressive disorder resulted in a significant reduction in the severity of depression symptoms [9]. According to *Bravo, et al., Lactobacillus rhamnosus* has been found to release GABA and activate GABA receptors in the brain, namely GABA Aα2 and GABA B1b receptors. With this, it has been demonstrated that *Lactobacillus rhamnosus* can reduce the severity of depression and anxiety-like behaviours in mice [40]. According to the findings of a number of pre-clinical researches, the presence of gut dysbiosis in mice models of Autism Spectrum Disorder (ASD) was found to generate significant neurological abnormalities. Comparing children with autism to controls revealed that certain species, such as *Clostridium* and *Ruminococcus*, were distinct from one another [91]. A correlation was found between the severity of autism in children and the presence of symptoms of gastrointestinal pain, as demonstrated by *Adams, et al.* [7,159,160]. Children who have been diagnosed with autism spectrum disorder benefited from improved gastrointestinal function and lower behavioural ASD scores, according to the findings of a pilot study that was carried out by Kang and colleagues and utilised faecal transplantation of standardised gut flora [146].

Neurodegenerative Disorders

Neurodegenerative disorders are largely distinguished by the process of neuron elimination. Alzheimer's disease and Parkinson's disease can be considered to be the most prevalent forms of neurodegenerative illnesses [176].

Parkinson's disease

The neurodegenerative ailment known as Parkinson's Disease (PD) is a prevalent condition that manifests itself through a variety of motor symptoms. These symptoms include tremor, muscle rigidity, slowness of movement, and irregular gait [294] (Sveinbjornsdottir, 2016). Parkinson's Disease (PD), which affects more than 1% of the elderly population and 0.3% of the general population worldwide, is the second most prevalent neurodegenerative disorder after Alzheimer's diseases [306]. Parkinson's disease is

a progressive neurodegenerative ailment marked by the loss of voluntary movement control due to significant dysfunction in the substantia nigra and striatum. The deterioration of dopaminergic neurones, the buildup of phosphorylated α-synuclein (αSyn), mitochondrial dysfunction, an overproduction of reactive oxygen species, and an increase in microglial activation are among these changes [36]. Growing data reveals a substantial disparity in gut microbiome makeup between Parkinson's disease and healthy populations, however findings vary among investigations [189,84,85]. Numerous investigations indicated a considerable rise in the prevalence of *Bifidobacterium*, Pasteurella, and *Enterococcus* in the gut microbiota of Parkinson's disease patients [137,141,238], while the quantity of *Brautella, Prevotella*, and *Faecococcus* diminished [270,29,132,133]. Although an increase in *Bifidobacterium* has been observed in Parkinson's Disease (PD), research indicates that a subsequent decline in *Bifidobacterium* may serve as a predictor for the potential deterioration of PD stage. This suggests that the rise in *Bifidobacterium* in Parkinson's disease may indicate a mechanism of protective action against neurological deterioration. Consequently, it may be deduced that a probiotic intervention utilising *Bifidobacterium* may inhibit the advancement of Parkinson's disease to more severe phases [105]. Nevertheless, the prevalence of *Lactobacillus* in patients with PD showed significant variation across various studies. The findings are not entirely unexpected, as the genetic makeup is influenced by numerous factors including varying lifestyles, dietary habits, age, geographical location, body mass index, and racial background [189].

Alzheimer's Diseases

Alzheimer's Disease (AD) is a long-lasting and unchangeable neurodegenerative condition, representing the most prevalent type of dementia among older adults. Individuals with AD exhibit significant CNS impairments in learning, memory, and behavioural functions, resulting in severe challenges in daily activities [44,45,326]. Alzheimer's disease results from the accumulation of aggregates formed by polymerised β-amyloid precursor protein (Aβ) in both soluble multimeric and insoluble amyloid deposits within the brain. This accumulation initiates a series of pathological processes that culminate in neurofibrillary tangles, aggregates of hyperphosphorylated tau proteins, the development of neurofibrillary lesions, and ultimately leads to dementia [269]. In comparison to the control group, the stool samples from patients with Alzheimer's disease exhibited elevated levels of *Bacteroidetes*, alongside reduced levels of *Firmicutes* and *Actinobacteria*. In a study by *Vogt, et al*. (2017), it was observed that patients with Alzheimer's disease exhibited reduced abundances of the *Firmicutes* families *Ruminococcaceae*, *Turicibacteraceae,* and *Clostridiaceae* [314]. In the analysis of faecal microbiomes and faecal SCFAs across different ages of AD-affected mice and wild-type mice, significant increases in *Proteobacteria* and *Verrucomicrobia* were noted, alongside notable decreases in *Butyricicoccus* and *Ruminococcus* in AD mice. This suggests a clear alteration in microbiota composition and diversity. The reduced levels of SCFAs suggest modifications in various metabolic pathways [195]. The involvement of intestinal microflora in the development of AD in patients starts with an imbalance in the gut-brain axis. A growing body of research suggests that AD is closely linked to inflammation caused by GM [196-197]. The information presented indicates that gut microbiome dysbiosis can enhance neuroinflammation during the progression of Alzheimer's disease and alter the dynamic equilibrium of the gut microbiome, suggesting a potential innovative approach for therapy in Alzheimer's disease. The modulation of gut microbiota could hold significant potential for therapeutic strategies in addressing disorders of the nervous system [52] (Table 1).

Table 1: Human gut dysbiosis associated with various diseases.

Disease	Bacteria that Decreases	Bacteria that Increases	Ref.
Colorectal cancer	*↓Prevotella, ↓Ruminococcus spp., ↓Pseudobutyrivibrio ruminis*	*↑Acidaminobacter, ↑Phascolarctobacterium, ↑Citrobacter farmer,*	*Jing, et al,* 2021 *Khoruts. et al,* 2010
Obesity	*↓Bacteridetes ↓Methanobrevibacter smithii*	*↑Enterobacteria, ↑Ruminococcus gnavus*	*Hamilton, et al,* 2012
IBD: Chron's disease	*↓Bacteroides, ↓Faecalibacterium prausnitzii ↓Bifidobacterium adolescentis*		*Kassam, et al*, 2013
Ulcerative cholitis	*↓Bifidobacteria, ↓Roseburia hominis ↓Faecalibacterium prausnitzii, ↓Lachnospiraceae, ↓Ruminococcaceae*		
Diabetes: Diabetes type1	*↓Lactobacillus, ↓Bifidobacterium, ↓Blautia coccoides, ↓Eubacterium rectal, ↓Prevotella,*	*↑Clostridium, ↑Bacteroides, ↑Veillonella*	*Gough, et al,* 2011
Diabetes type2	*↓Firmicutes↓Clostridia, ↓Lactobacillus, ↓Eubacterium rectale,*	*↑Bacteroids-Prevotella Verses Clostridiacocoides, ↑Betaproteo bacteria, ↑Bacteroidetes/ Firmicutes ratio*	*Van, et al,* 2013

CVD		↑*Clostridium*, ↑*Lactobacillales*, ↑*Enterobacteriaceae spp*, ↑*Chryseomonas*, ↑*Helicobacter* ↑*Firmicutes*, ↑*Bacteroides*	*Marrs, et al,* 2021
Hepatic disease	↓*Alistipes*, ↓*Bilophila*, ↓*Veillonella*, ↓*Faecalibacterium*, ↓*Ruminococcus*, ↓*Bifidobacterium*, ↓*Prevotella* ↓*Coprococcus,*	↑*Clostridium,* ↑*Bacteroidetes,* ↑*Betaproteobacteria,* ↑*Lactobacillus spp.,* ↑*Collinsella*, ↑*Corynebacteriu*, ↑*Prevotellaceae*, ↑*Ruminococcaceae*, ↑ *Sarcina*, ↑*Sutterellaceae*, ↑*Enterobacteriaceae*, ↑*Bacteroidaceae*	*Paramsothy, et al,* 2017

Metabolic Disorders

Obesity

Obesity and its metabolic implications constitute significant public health issues, with over 1.9 billion adults classified as overweight and more than 650 million as obese [328] (World Health Organisation, 2020). Numerous studies have shown that Gut Mirobiome (GM) significantly contributes to the development of obesity [70]. GM dysbiosis is common in obesity, characterised by diminished gut microbiome variety and richness in fat individuals. The makeup of gut microbiota is significantly affected by dietary practices. A high-fat diet alters the gut microbiota, resulting in increased *Firmicutes* and *Proteobacteria* and reduced *Bacteroidetes* numbers. The *Firmicutes* to *Bacteroides* ratio is associated with body weight, with obese individuals exhibiting a higher ratio. Obesity may also result from *Clostridium* difficile infections. Obesity is influenced by a chronic inflammatory state caused by gut bacteria or their metabolites, which govern the microbiota-brain-gut axis [223]. The prevalence of *Akkermansia muciniphila, Faecalibacterium prausnitzii,* and *Bacteroides* diminished, whilst the prevalence of Phylum *Firmicutes* dramatically escalated [309]. GM have the capability to ferment indigestible carbohydrates into significant metabolites, including Short-Chain Fatty Acids (SCFAs) and succinate. Recent studies reveal that these metabolites significantly contribute to obesity and associated comorbidities. Short-Chain Fatty Acids (SCFAs) modulate energy equilibrium and inhibit obesity by diminishing appetite and enhancing energy expenditure [47]. Conjugated Linoleic Acid (CLA) is a significant fatty acid that contributes to obesity prevention. Four strains of *Bifidobacterium* breve, one strain of *Bifidobacterium bifidum*, and one strain of *Bifidobacterium* pseudolongum were capable of synthesising various isomers of conjugated linoleic acid and conjugated linolenic acid from dietary supplements. *Bacteroides* spp., present in the gut microbiome, has been documented to contribute to obesity prevention [31]. The aforementioned researches have elucidated the function and mechanism of GM and its metabolites in the onset and progression of obesity, which hold substantial importance for the prevention and treatment of obesity.

Diabetes

Diabetes is a systemic metabolic disorder marked by elevated Blood Glucose Levels, encompassing Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), and Gestational Diabetes Mellitus (GDM). T1DM results from an autoimmune attack on pancreatic β cells, whereas T2DM is defined by the body's inability to adequately manufacture or utilise insulin. Gestational Diabetes Mellitus (GDM) is a highly widespread complication of pregnancy, linked to an elevated risk of metabolic diseases in both mothers and foetuses. The association between microbiota and Diabetes Mellitus (DM) has been thoroughly investigated, and the link between microbiota dysbiosis and the onset of DM is well known [142]. In Type 1 Diabetes Mellitus, the microbiota is a compelling area of research owing to its significant association with chronic inflammation and immunological response. Numerous studies indicate that the oral and faecal microbiota compositions are unique in patients with Type 1 Diabetes Mellitus (T1DM). *Groot, et al.* discovered that *Christensenella* and *Bifidobacterium* were abundant in faecal samples [69,72]. Patients with T1DM may display reduced amounts of Butyrate-Producing Bacteria, which are crucial for mitigating chronic inflammation and preserving intestinal homeostasis.

The gut microbiota has been associated with the development of Type 2 Diabetes Mellitus (T2DM). Multiple investigations have verified that the composition of gut microbiota is modified in people with T2DM [143,144,147]. *Larsen, et al.* indicated that the prevalence of *Firmicutes* and Clostridia was dramatically less in T2DM patients relative to the control group. Moreover, the ratios of *Bacteroidetes* to *Firmicutes* and the *Bacteroides-Prevotella* group to the *C. coccoides-E*. rectale group exhibited a favourable correlation with blood glucose levels [179]. *Almugadam, et al.* demonstrated that the prevalence of Short-Chain Fatty Acid-Producing Bacteria, Facalibacterium and Roseburia, was dramatically reduced in individuals with Type 2 Diabetes Mellitus (T2DM) [11]. Antidiabetic medications enhanced the diversity and richness of Gut Microbiota, enriching the gut ecology with Beneficial Bacteria [110].

In Gestational Diabetes Mellitus (GDM), multiple researches

have indicated that gut microbiota influences insulin resistance and inflammation during pregnancy. Metabolic problems frequently occur in women with Gestational Diabetes Mellitus (GDM), characterised by increased insulin resistance and diminished insulin production [246]. Pregnancy induces significant alterations in gut microbiota composition, perhaps contributing to the onset of Gestational Diabetes Mellitus (GDM). A favourable link has been observed between insulin and *Collinsella, gastrointestinal polypeptide* and *Coprococcus*, and adipokine with *Ruminococcaceae* and *Lachnospiraceae* [111]. *Koren, et al.* found that gut microbiota altered from the first to the third trimester, exhibiting increased diversity and decreased richness [169]. Research demonstrated that patients with gestational diabetes mellitus exhibited an elevated *Firmicutes* to *Bacteroidetes* ratio, a significant factor contributing to obesity and exacerbating inflammation [58]. The prevalence of SCFA-producing bacteria was markedly diminished in GDM pregnancies relative to healthy controls, suggesting that the increased blood glucose levels may result from alterations in microbiota [63].

Liver Diseases

Liver illnesses continue to be a primary source of morbidity and mortality globally. Nonalcoholic fatty liver disease/nonalcoholic steatohepatitis (NAFLD/NASH) and alcoholic liver disease (ALD) are the predominant chronic liver disorders that frequently result in liver cirrhosis and carcinoma [232]. Cirrhosis is the terminal phase of all chronic liver disorders, marked by tissue fibrosis and the alteration of normal liver architecture into aberrant nodules. The liver obtains 70% of its blood supply from the intestine through the portal vein, rendering it consistently exposed to gut-derived elements such as bacterial components, endotoxins (including lipopolysaccharide, flagellin, and lipoteichoic acid), and peptidoglycans. Numerous hepatic cells, such as Kupffer cells, sinusoidal cells, biliary epithelial cells, and hepatocytes, have innate immune receptors termed pathogen-recognition receptors that react to the continuous input of microbial-derived products from the gut [6]. The makeup of gut microbiota differs between patients with NAFLD and healthy individuals. The quantity of *Lactobacillus*, Dorea and *Streptococcus* in the intestines of NAFLD patients increased, whereas the levels of *Ruminococcus, Prevotella* and *Flavobacterium* diminished [249,346]. GM metabolites originating from saccharolytic and proteolytic fermentation may influence the gut-liver axis through many mechanisms, thereby contributing to the pathophysiology of NAFLD [47].

Kidney Diseases

Approximately 9% of the worldwide population is afflicted by chronic kidney disease (CKD). Co-morbidities such as diabetes, hypertension, and heart disease are regarded as significant risk factors for chronic kidney disease (CKD). Chronic Kidney Disease (CKD) is physiologically defined as a reduction in Glomerular Filtration Rate (GFR) of less than 60 ml/min per 1.73 m^2 or the presence of albuminuria for three or more months. The primary characteristics identified in CKD patients are the progressive decline of kidney function and irreversible alterations in renal structure. The functionality of the gut-kidney axis is rooted in the interconnectedness of metabolic and immune pathways [242]. The metabolic pathway primarily centres on the production by gut microbiota [318]. A variety of investigations have been carried out to connect the qualitative and quantitative alterations in intestinal microbiota with the development of Chronic Kidney Disease (CKD) and End-Stage Renal Disease (ESRD) [119,204]. Factors including enhanced protein absorption decreased dietary fibre consumption, delayed intestinal transit, and regular oral administration of iron supplements and antibiotics have led to modifications in the intestinal microbial environment, which in turn has resulted in systemic inflammation and the buildup of uremic toxins. Inflammation and uremic toxins play significant roles in the advancement of CKD and its related complications [236]. A comparative study of faecal samples has revealed differences between healthy subjects and CKD patients, indicating that CKD patients exhibit a reduced abundance of the Actinobacteria phylum and Akkermansia genera. A clinical study involving 73 subjects has revealed 31 phylotypic differences between CKD and control groups. The predominant phylotypes identified in CKD patients include *Bacteroides, Parabacteroides, R. gnavus, R. torques, Flavonifractor, Weissella, Ruminiclostridium, Erysipelatoclostridium, Eggerthella*, and *Sellimonas* [200]. Patients with ESRD exhibit an increase in Actinobacteria, *Proteobacteria*, and *Firmicutes*, alongside a decrease in *Bifidobacteria* and *Lactobacilli* when compared to the control group [236].

Conclusion

The gut microbiome plays a crucial role in maintaining overall health by influencing various physiological processes. Effective health management by the gut microbiome includes modulating digestion, synthesizing essential vitamins, and maintaining gut barrier integrity. The gut is fundamental for health due to its role in hosting a vast array of beneficial microorganisms known as normal flora, which aid in immune function, pathogen resistance, and metabolic processes.

The benefits of normal flora are vast; they not only help in nutrient absorption and production of vital compounds but also play a pivotal role in protecting against infections by outcompeting harmful microbes. Microbial succession, the dynamic changes in microbial composition over time, is essential in establishing and maintaining a healthy microbiota, especially from birth through adulthood. Understanding the complex ecosystem of the microbiome highlights its significance in human health. The restoration of gut health, often through probiotics, prebiotics, and dietary changes, can reverse dysbiosis and support a balanced microbiome, leading to improved health outcomes. Finally, the impact of the gut on the immune system underscores the importance of maintaining gut health for robust immune function, as a well-balanced gut microbiota is integral to the development and regulation of the immune response. In conclusion, the growing body of evidence underscores the significant impact of gut microbiota on a wide range of diseases. Inflammatory Bowel Diseases (IBD) highlight the crucial role of dysbiosis in triggering chronic inflammation and gut dysfunction.

Similarly, respiratory diseases, such as asthma and Chronic Obstructive Pulmonary Disease (COPD), have been linked to microbiota alterations, suggesting a potential therapeutic role for microbiota modulation. Colorectal cancer, often influenced by gut microbial imbalances, further emphasizes the need for a deeper understanding of the microbiome's involvement in carcinogenesis. Neurological disorders, including Parkinson's and Alzheimer's diseases, show a complex relationship with the gut-brain axis, with altered gut microbiota influencing disease progression and offering potential for microbiota-based interventions. Metabolic disorders, such as obesity, diabetes, and liver disease, are also closely associated with gut microbial composition. Dysbiosis may contribute to metabolic dysfunctions by affecting insulin sensitivity, fat metabolism, and inflammation. Overall, the microbiome plays a critical role in the pathophysiology of various diseases, and further research into microbial therapies holds promise for personalized treatment strategies across a wide array of health conditions. In conclusion, the gut microbiome is a cornerstone of health, influencing everything from digestion and immunity to overall well-being. Future research and therapeutic strategies should continue to focus on maintaining and restoring a healthy microbiome to promote optimal health.

Authors Contribution

APG conceptualized the topic and framed the outlines of this review paper, Anchal collected all literature related to impact of gut microbiome on diseases while Rashmi collected all literature related to gut microbiome, normal flora, microbial succession etc. All authors collectively prepared the manuscript, reviewed and designed the figures.

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Conflict of Interest

The authors declare that they have no conflict of interest.

References

1. AboNahas HH, Darwish AM, Abd El kareem HF, AboNahas YH, Mansour SA, et al. (2022) "Trust Your Gut: The Human Gut Microbiome in Health and Disease," in Microbiome-Gut-Brain Axis, eds R. Z. Sayyed and M. Khan (Singapore: Springer) 53-96.
2. Ackerman DL, Craft KM, Doster RS, Weitkamp JH, Aronoff DM, et al. (2018) Antimicrobial and antibiofilm activity of human milk oligosaccharides against Streptococcus agalactiae, Staphylococcus aureus, and Acinetobacter baumannii. ACS Infect. Dis 4: 315-324.
3. Ackerman DL, Craft KM, Townsend SD (2017) Infant food applications of complex carbohydrates: structure, synthesis, and function. Carbohydr. Res 437: 16-27.
4. Ackerman DL, Doster RS, Weitkamp JH, Aronoff DM, Gaddy JA, et al. (2017) Human milk oligosaccharides exhibit antimicrobial and antibiofilm properties against Group B Streptococcus. ACS Infect. Dis 3: 595-605.
5. Adak A, Khan MR (2019) An insight into gut microbiota and its functionalities. Cell Mol Life Sci 76: 473-493.
6. Adams DH, Eksteen B, Curbishley SM (2008) Immunology of the gut and liver: a love/hate relationship. Gut 57: 838-848.
7. Adams JB, Johansen LJ, Powell LD, Quig D, Rubin RA et al. (2011) Gastrointestinal flora and gastrointestinal status in children with autism--comparisons to typical children and correlation with autism severity. BMC Gastroenterol 11: 22.
8. Adolph TE, Mayr L, Grabherr F, Schwärzler J, Tilg H, et al. (2019) Pancreas-Microbiota Cross Talk in Health and Disease. Annual review of nutrition 39: 249-266.
9. Akkasheh G, Kashani Poor Z, Tajabadi Ebrahimi M, Jafari P, Akbari H, et al. (2016) Clinical and metabolic response to probiotic administration in patients with major depressive disorder: A randomized, double-blind, placebo-controlled trial. Nutrition 32(3): 315-320.
10. Almgren M (2018) Benefits of skin-to-skin contact during the neonatal period: governed by epigenetic mechanisms? Genes Dis 5: 24-26.
11. Almugadam BS, Liu Y, Chen SM, Wang CH, Shao CY, et al. (2020) Alterations of Gut Microbiota in Type 2 Diabetes Individuals and the Confounding Effect of Antidiabetic Agents. J Diabetes Res 28: 7253978.
12. Anal AK (2019) Quality ingredients and safety concerns for traditional fermented foods and beverages from Asia: a review. Fermentation 5(1).
13. Araújo EA, dos Santos Pires AC, Pinto MS, Jan G, Carvalho AF, et al. (2012) Probiotics in dairy fermented products. In: Rigobelo, E.C. (Ed.), Probiotics. Rennes: CC pp 129-148.
14. Aresti Sanz J, El Aidy S (2019) Microbiota and gut neuropeptides: a dual action of antimicrobial activity and neuroimmune response. Psychopharmacology 236(5): 1597-1609.
15. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, et al. (2017) Global patterns and trendsin colorectal cancer incidence and mortality, Gut 66: 683-691.
16. Atarashi K, Nishimura J, Shima T, Umesaki Y, Yamamoto M, et al. (2008) ATP drives lamina propria T(H)17 cell differentiation. Nature 455(7214): 808-812.
17. Atarashi K, Tanoue T, Shima T, Imaoka A, Kuwahara T, et al. (2011) Induction of colonic regulatory T cells by indigenous Clostridium species. Science 331(6015): 337-341.
18. Azad MB, Bridgman SL, Becker AB, Kozyrskyj AL (2014) Infant antibiotic exposure and the development of childhood overweight and central adiposity. International journal of obesity 38(10): 1290-1298.
19. Bäckhed F, Roswall J, Peng Y, Feng Q, Jia H, et al. (2015) Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life. Cell host & microbe 17(5): 690-703.
20. Bakhshinejad B, Ghiasvand S (2017) Bacteriophages in the human gut: our fellow travelers throughout life and potential biomarkers of heath or disease. Virus Res 240: 47-55.
21. Ballan R, Battistini C, Xavier Santos D, Saad SMI (2020) Interactions of probiotics and prebiotics with the gut microbiota. Progress in Molecular Biology and Translational Science 171: 265-300.
22. Barbian ME, Owens JA, Naudin CR, Denning PW, Patel RM, et al. (2022) Butyrate supplementation to pregnant mice elicits cytoprotection against colonic injury in the offspring. Pediatric research 92(1): 125-134.
23. Barcik W, Boutin RCT, Sokolowska M, Finlay BB (2020) The role of lung and gut microbiota in the pathology of asthma. Immunity 52: 241-255.
24. Barlow JT, Leite G, Romano AE, Sedighi R, Chang C, et al. (2021) Quantitative sequencing clarifies the role of disruptor taxa, oral microbiota, and strict anaerobes in the human small-intestine microbiome. Microbiome 9(1): 214.

25. Barr JJ (2017) A bacteriophages journey through the human body. Immunological reviews 279(1): 106-122.

26. Bassis CM, Tang AL, Young VB, Pynnonen MA (2014) The nasal cavity microbiota of healthy adults. Microbiome 2: 27.

27. Bastiaanssen TFS, Cowan CSM, Claesson MJ, Dinan TG, Cryan JF, et al. (2019) Making sense of the microbiome in psychiatry. Int. J. Neuropsychopharmacol 22: 37-52.

28. Beaumont M, Goodrich JK, Jackson MA, Yet I, Davenport ER, et al. (2016) Heritable components of the human fecal microbiome are associated with visceral fat. Genome biology 17(1): 189.

29. Bedarf JR, Hildebrand F, Coelho LP, Sunagawa S, Bahram M, et al. (2017) Functional implications of microbial and viral gut metagenome changes in early stage L-DOPA-naïve Parkinson's disease patients. Genome Med 9(1): 39.

30. Beura LK, Hamilton SE, Bi K, Schenkel JM, Odumade OA, et al. (2016) Normalizing the environment recapitulates adult human immune traits in laboratory mice. Nature 532(7600): 512–516.

31. Bhattacharjee A (2012) Oral Micro-Particulate Colon Targeted Drug Delivery System For The Treatment Of Crohn's Disease: A Review.

32. Bibbo S, Dore MP, Pes GM, Delitala G, Delitala AP, et al. (2017) Is there a role for gut microbiota in type 1 diabetes pathogenesis? Ann. Med 49: 11-22.

33. Bischoff SC (2009) Physiological and pathophysiological functions of intestinal mast cells. Seminars in immunopathology, 31(2): 185-205.

34. Bisht N, Garg AP (2023) Health management using probiotics. J Adv Pediatr Child Health 6: 001-006.

35. Bisht N, Garg AP (2019) Isolation, Characterization and Probiotic Value of Lactic Acid Bacteria from Milk and Milk Products, An International J of Biological Sciences (BiotechToday) 9(2): 54-63.

36. Blandini F, Nappi G, Tassorelli C, Martignoni E (2000) Functional changes of the basal ganglia circuitry in Parkinson's disease. Prog. Neurobiol 62: 63-88.

37. Bode L (2012) Human milk oligosaccharides: every baby needs a sugar mama. Glycobiology 9: 1147-1162.

38. Bokulich NA, Chung J, Battaglia T, Henderson N, Jay M, et al. (2016) Antibiotics, birth mode, and diet shape microbiome maturation during early life. Science translational medicine 8(343): 343ra82.

39. Booijink CC, El Aidy S, Rajilić Stojanović M, Heilig HG, Troost FJ, et al. (2010) High temporal and inter-individual variation detected in the human ileal microbiota. Environmental microbiology 12(12): 3213-3227.

40. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, et al. (2011) Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci U S A 108(38): 16050-5.

41. Bui E, Fava M (2017) From depression to anxiety, and back. Acta Psychiatr. Neurol. Scand 136: 341-342.

42. Bull MJ, Plummer NT (2014) Part 1: The Human Gut Microbiome in Health and Disease. Integrative medicine (Encinitas, Calif.) 13(6): 17-22.

43. Bunker JJ, Flynn TM, Koval JC, Shaw DG, Meisel M, et al. (2015) Innate and Adaptive Humoral Responses Coat Distinct Commensal Bacteria with Immunoglobulin A. Immunity 43(3): 541-553.

44. Burns A, Iliffe S (2009) Alzheimer's disease. Bmj 338: b158.

45. Byndloss MX, Olsan EE, Rivera Chávez F, Tiffany CR, Cevallos SA, et al. (2017) Microbiota-activated PPAR-γ signaling inhibits dysbiotic Enterobacteriaceae expansion. Science 357(6351): 570-575.

46. Campbell C, Dikiy S, Bhattarai SK, Chinen T, Matheis F, et al. (2018) Extrathymically Generated Regulatory T Cells Establish a Niche for Intestinal Border-Dwelling Bacteria and Affect Physiologic Metabolite Balance. Immunity 48(6): 1245-1257.e9.

47. Canfora EE, Meex RCR, Venema K, Blaak EE (2019) Gut microbial metabolites in obesity, NAFLD and T2DM. Nat. Rev. Endocrinol. 15 (5): 261-273.

48. Cani PD (2018) Human gut microbiome: hopes, threats and promises Gut 67: 1716-1725.

49. Carlsson J, Gothefors L (1975) Transmission of Lactobacillus jensenii and Lactobacillus acidophilus from mother to child at time of delivery. Journal of Clinical Microbiology 1(2): 124-128.

50. Caugant DA, Høiby EA, Magnus P, Scheel O, Hoel T, et al. (1994) Asymptomatic carriage of Neisseria meningitidis in a randomly sampled population. Journal of clinical microbiology 32(2): 323-330.

51. Chen J, Pitmon E, Wang K (2017) Microbiome, inflammation and colorectal cancer. Semin Immunol 32: 43-53.

52. Chen Y, Zhou J, Wang L (2021) Role and Mechanism of Gut Microbiota in Human Disease. Frontiers in Cellular and Infection Microbiology 11: 625913.

53. Chervonsky AV (2013) Microbiota and autoimmunity. Cold Spring Harb Perspect Biol 5(3): a007294.

54. Chilton SN, Burton JP, Reid G (2015) Inclusion of fermented foods in food guides around the world. Nutrients 7: 390-404.

55. Christensen KR, Steenholdt C, Buhl SS, Ainsworth MA, Thomsen OØ, et al. (2015) Systematic information to healthcare professionals about vaccination guidelines improves adherence in patients with inflammatory bowel disease in anti-tnfa therapy, Am. J. Gastroenterol 110: 1526-1532.

56. Clarke TB, Davis KM, Lysenko ES, Zhou AY, Yu Y, et al. (2010) Recognition of peptidoglycan from the microbiota by Nod1 enhances systemic innate immunity. Nat Med 16: 228-231.

57. Coppa GV, Bruni S, Morelli L, Soldi S, Gabrielli O et al. (2004) The first prebiotics in humans: human milk oligosaccharides. J. Clin. Gastroenterol. 38(6 Suppl) S80-S83.

58. Cortez RV, Taddei CR, Sparvoli LG, Ângelo AGS, Padilha M, et al. (2019) Microbiome and its relation to gestational diabetes. Endocrine 64(2): 254-264.

59. Crabbé PA, Bazin H, Eyssen H, Heremans JF. (1968) The normal microbial flora as a major stimulus for proliferation of plasma cells synthesizing IgA in the gut. The germ-free intestinal tract. Int Arch Allergy Appl Immunol 34: 362-375.

60. Craft KM, Thomas HC, Townsend SD (2018) Interrogation of human milk oligosaccharide fucosylation patterns for antimicrobial and antibiofilm trends in Group B Streptococcus. ACS Infect, Dis 4: 1755-1765.

61. Craft KM, Townsend SD (2019) Mother knows best: deciphering the antibacterial properties of human milk oligosaccharides. Acc. Chem. Res 52: 760-768.

62. Craft KM, Townsend SD (2019) 1-Amino-2'-fucosyllactose inhibits biofilm formation by Streptococcus agalactiae. The Journal of antibiotics, 72(6): 507-512.

63. Crusell MKW, Hansen TH, Nielsen T, Allin KH, Rühlemann MC, et al. (2018) Gestational diabetes is associated with change in the gut microbiota composition in third trimester of pregnancy and postpartum. Microbiome 6(1): 89.

64. Cryan JF, de Wit H (2019) The gut microbiome in psychopharmacology and psychiatry. Psychopharmacology, 236(5): 1407-1409.

65. Curk MC, Hubert JC, Bringel F (1996) Lactobacillus paraplantarum sp. now., a new species related to Lactobacillus plantarum. Int J Syst Bacteriol 46(2): 595-8.

66. Dai Z, Zhang J, Wu Q, Chen J, Liu J, et al. (2019) The role of microbiota in the development of colorectal cancer. Int J Cancer 145(8): 2032-2041.

67. Danese S, Sans M, Fiocchi C (2004) Inflammatory bowel disease: the role of environmental factors. Autoimmun Rev 3(5): 394-400.

68. Darfeuille Michaud A, Neut C, Barnich N, Lederman E, Di Martino P, et al. (1998) Presence of adherent Escherichia coli strains in ileal mucosa of patients with Crohn's disease. Gastroenterology 115(6): 1405-13.

69. de Groot PF, Belzer C, Aydin Ö, Levin E, Levels JH, et al. (2017) Distinct fecal and oral microbiota composition in human type 1 diabetes, an observational study. PLoS One 12(12): e0188475.

70. De La Cuesta Zuluaga J, Corrales Agudelo V, Velasquez Mejia EP, Carmona JA, Abad JM, et al. (2018) Gut microbiota is associated with obesity and cardiometabolic disease in a population in the midst of Westernization. Sci. Rep 8(1): 11356.

71. de Steenhuijsen Piters WA, Huijskens EG, Wyllie AL, Biesbroek G, van den Bergh MR, et al. (2016) Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients. ISME J 10(1): 97-108.

72. De Vadder F, Kovatcheva Datchary P, Goncalves D, Vinera J, Zitoun C, et al. (2014) Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. Cell 156(1-2): 84-96.

73. de Vos WM, Tilg H, Van Hul M, Cani PD (2022) Gut microbiome and health: mechanistic insights. Gut 71(5): 1020-1032.

74. Depommier C, Everard A, Druart C, Plovier H, Van Hul, et al. (2019) Supplementation with Akkermansia muciniphila in overweight and obese human volunteers: a proof-of-concept exploratory study. Nature medicine 25(7): 1096-1103.

75. Dibb WL (1990) The normal microbial flora of the outer ear canal in healthy Norwegian individuals. NIPH Ann 13(1): 11-6.

76. Dieterich W, Schink M, Zopf Y (2018) Microbiota in the Gastrointestinal Tract. Medical sciences (Basel, Switzerland) 6(4): 116.

77. Dominguez Bello MG, Costello EK, Contreras M, Magris M, Hidalgo G, et al. (2010) Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proceedings of the National Academy of Sciences of the United States of America 107(26): 11971-11975.

78. Donaldson GP, Lee SM, Mazmanian SK (2016) Gut biogeography of the bacterial microbiota. Nat Rev Microbiol 14: 20-32.

79. Dreizen S, McCredie KB, Bodey GP, Keating MJ (1986) Microbial mucocutaneous infections in acute adult leukemia. Results of an 18-year inpatient study. Postgraduate medicine 79(8): 107-118.

80. DuanY, Prasad R, Feng D, Beli E, Li Calzi, et al. (2019) Bone marrow-derived cells restore functional integrity of the gut epithelial and vascular barriers in a model of diabetes and ACE2 deficiency. Circ. Res 125: 969-988.

81. Dugger BN, Dickson DW (2017) Pathology of neurodegenerative diseases. Cold Spring Harb. Perspect. Biol 9: a028035.

82. Durkin HG, Chice SM, Gaetjens E, Bazin H, Tarcsay L, et al. (1989) Origin and fate of IgE-bearing lymphocytes. II. Modulation of IgE isotype expression on Peyer's patch cells by feeding with certain bacteria and bacterial cell wall components or by thymectomy. J Immunol 143: 1777-83.

83. Dzidic M, Boix Amoros A, Royo MS, Mira A, Collado MC, et al. (2018) Gut Microbiota and Mucosal Immunity in the Neonate, Med. Sci 6(3): 56.

84. Elfil M, Kamel S, Kandil M, Koo BB, Schaefer SM, et al. (2020) Implications of the Gut Microbiome in Parkinson's Disease. Mov Disord 35 (6): 921-933.

85. Enav H, Bäckhed F, Ley RE (2022) The developing infant gut microbiome: a strain-level view. Cell Host Microbe 30: 627-638.

86. FH Karlsson, I Nookaew, D Petranovic, J Nielsen (2011) Prospects for systems biology and modeling of the gut microbiome, Trends Biotechnol 29: 251-258.

87. Falony G, Joossens M, Vieira Silva S, Wang J, Darzi Y, et al. (2016) Population-level analysis of gut microbiome variation. Science 352(6285): 560-564.

88. Feagan BG, Rutgeerts P, Sands BE, Hanauer S, Colombel JF, et al. (2013) Vedolizumab as induction and maintenance therapy for ulcerative colitis. N Engl J Med 369(8): 699-710.

89. Feng Y, Wang Y, Wang P, Huang Y, Wang F, et al. (2018) ShortChain Fatty Acids Manifest Stimulative and Protective Effects on Intestinal Barrier Function Through the Inhibition of NLRP3 Inflammasome and Autophagy, Cell Physiol. Biochem 49: 190-205.

90. Ferlaysss J (2020) Global Cancer Observatory: Cancer Today. Lyon: International Agency for Research on Cancer.

91. Finegold SM, Molitoris D, Song Y, Liu C, Vaisanen ML, et al. (2002) Gastrointestinal microflora studies in late-onset autism. Clin Infect Dis 35(Suppl 1): S6-S16.

92. Firrman J, Liu L, Mahalak K, Tanes C, Bittinger K, et al. (2022) The impact of environmental pH on the gut microbiota community structure and short chain fatty acid production. FEMS Microbiol Ecol 98(5): fiac038.

93. Frank DN, St Amand AL, Feldman RA, Boedeker EC, Harpaz N, et al. (2007) Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. Proc Natl Acad Sci U S A 104(34): 13780-13785.

94. Franzosa EA, Sirota Madi A, Avila Pacheco J, Fornelos N, Haiser HJ, et al. (2019) Gut microbiome structure and metabolic activity in inflammatory bowel disease. Nat Microbiol 4(2): 293-305.

95. Fujimura K E, Slusher N A, Cabana M D, Lynch S V (2010) Role of the gut microbiota in defining human health. Expert Rev Anti Infect Ther 8(4): 435-454.

96. Fujiwara D, Wei B, Presley L L, Brewer S, McPherson M, Lewinski M A, et al. (2008) Systemic control of plasmacytoid dendritic cells by CD8+ T cells and commensal microbiota. J Immunol 180(9): 5843-5852.

97. G Lippi, E Danese, C Mattiuzzi, Camilla Mattiuzzi, Emmanuel J Favaloro (2017) The Intriguing Link between the Intestinal Microbiota and Cardiovascular Disease, SeminThromb Hemost 43(6): 609-613.

98. Gäbele E, Dostert K, Hofmann C, Wiest R, Schölmerich J, Hellerbrand C, et al. (2011) DSS induced colitis increases portal LPS levels and enhances hepatic inflammation and fibrogenesis in experimental NASH. J Hepatol 55(6): 1391-1399.

99. Gabriel I, Olejek A, Stencel Gabriel K, Wielgos M (2018) The influence of maternal vaginal flora on the intestinal colonization in newborns and 3-monthold infants. J Matern Fetal Neonatal Med 31(11): 1448-1453.

100. Garg Amar P, Afeefa Ateequ, Neha Bisht, Bajeerao Patil (2024) Management of asthma using probiotics. Expl Asthma Allergy 2: 9-32.

101. Gao W, Salzwedel A P, Carlson A L, Xia K, Azcarate Peril M A, Styner M A, Thompson A L, et al. (2019) Gut microbiome and brain functional connectivity in infants-a preliminary study focusing on the amygdala. Psychopharmacology (Berl) 236(5): 1641-1651.

102. Gavin P G, Mullaney J A, Loo D, Cao K L, Gottlieb P A, Hill M M, et al. (2018) Intestinal Metaproteomics Reveals Host-Microbiota Interactions in Subjects at Risk for Type 1 Diabetes. Diabetes Care 41(10): 2178-2186.

103. Geerlings S Y, Kostopoulos I, De Vos W M, Belzer C (2018) *Akkermansia muciniphila* in the Human Gastrointestinal Tract: When, Where and How?. Microorganisms 6(3): 75.

104. Gentile C L, Weir T L (2018) The gut microbiota at the intersection of diet and human health. Science 362(6416): 776-780.

105. Gerhardt S, Mohajeri M H (2018) Changes of Colonic Bacterial Composition in Parkinson's Disease and Other Neurodegenerative Diseases. Nutrients 10(6): 708.

106. Gibson GR, Probert HM, Loo JV, Rastall RA, Roberfroid MB (2004) Dietary modulation of the human colonic microbiota: updating the concept of prebiotics. Nutr Res Rev 17(2): 259-275.

107. Girma A, Aemiro A, Workineh D, Tamir D (2023) Magnitude, Associated Risk Factors, and Trend Comparisons of Urinary Tract Infection among Pregnant Women and Diabetic Patients: A Systematic Review and Meta-Analysis. J Pregnancy: 8365867.

108. Gohir W, Ratcliffe E M, Sloboda D M (2015) Of the bugs that shape us: maternal obesity, the gut microbiome, and long-term disease risk. Pediatr Res 77(1-2): 196-204.

109. Golemis EA, Scheet P, Beck TN, Scolnick EM, Hunter DJ, Hawk E, et al. (2018) Molecular mechanisms of the preventable causes of cancer in the United States. Genes Dev 32(13-14): 868-902.

110. Gomes J M G, Costa J A, Alfenas R C G (2017) Metabolic endotoxemia and diabetes mellitus: a systematic review. Metabolism 68: 133-144.

111. Gomez Arango LF, Barrett HL, McIntyre HD, Callaway LK, Morrison M, Dekker Nitert M (2016) Connections Between the Gut Microbiome and Metabolic Hormones in Early Pregnancy in Overweight and Obese Women. Diabetes 65(8): 2214-2223.

112. Goodman T, Lefrancois L (1989) Intraepithelial lymphocytes. Anatomical site, not T cell receptor form, dictates phenotype and function. J Exp Med 170(5): 1569-1581.

113. Goraya M U, Li R, Mannan A, Gu L, Deng H, Wang G (2022) Human circulating bacteria and dysbiosis in non-infectious diseases. Front Cell Infect Microbiol 12: 932702.

114. Gough E, Shaikh H, Manges AR (2011) Systematic review of intestinal microbiota transplantation (fecal bacteriotherapy) for recurrent Clostridium difficile infection. Clin Infect Dis 53(10): 994-1002.

115. Greenfield S, Sheehe PR, Feldman HA (1971) Meningococcal carriage in a population of ''normal'' families. J Infect Dis 123(1): 67-73.

116. Grice E A, Segre J A (2011) The skin microbiome. Nat Rev Microbiol 9(4): 244-253.

117. Grice E A, Kong H H, Conlan S, Deming C B, Davis J, Young A C, et al. (2009) Topographical and temporal diversity of the human skin microbiome. Science 324(5931): 1190-1192.

118. Grimoud J, Durand H, Courtin C, Monsan P, Ouarné F, Theodorou V, et al. (2010) *In vitro* screening of probiotic lactic acid bacteria and prebiotic glucooligosaccharides to select effective synbiotics. Anaerobe 16(5): 493-500.

119. Grivennikov SI, Wang K, Mucida D, Stewart CA, Schnabl B, Jauch D, et al. (2012) Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth. Nature 491(7423): 254-258.

120. Gueimonde M, Sakata S, Kalliomäki M, Isolauri E, Benno Y, Salminen S (2006) Effect of maternal consumption of lactobacillus GG on transfer and establishment of fecal bifidobacterial microbiota in neonates. J Pediatr Gastroenterol Nutr 42(2): 166-170.

121. Guimarães J T, Balthazar C F, Silva R, Rocha R S, Graça J S, Esmerino E A, et al. (2020) Impact of probiotics and prebiotics on food texture. Curr Opin Food Sci 33: 38-44.

122. Kayama H, R Okumura, Kiyoshi Takeda (2020) Takeda Interaction between the microbiota, epithelia, and immune cells in the intestine. Annu Rev Immuno 38: 23-48.

123. Hakansson A, Molin G (2011) Gut microbiota and inflammation. Nutrients 3(6): 637-682.

124. Hall AB, Tolonen AC, Xavier RJ (2017) Human genetic variation and the gut microbiome in disease. Nat Rev Genet 18(11): 690-699.

125. Hamilton MJ, Weingarden AR, Sadowsky MJ, Khoruts A (2012) Standardized frozen preparation for transplantation of fecal microbiota for recurrent Clostridium difficile infection. Am J Gastroenterol 107(5): 761-767.

126. Han YW, Shi W, Huang GT, Kinder Haake S, Park NH, Kuramitsu H, et al. (2000) Interactions between periodontal bacteria and human oral epithelial cells: Fusobacterium nucleatum adheres to and invades epithelial cells. Infect Immun 68(6): 3140-3146.

127. Hao W Z, Li X J, Zhang P W, Chen J X (2020) A review of antibiotics, depression, and the gut microbiome. Psychiatry Res 284: 112691.

128. Hapfelmeier S, Lawson M A, Slack E, Kirundi J K, Stoel M, Heikenwalder M, et al. (2010) Reversible microbial colonization of germ-free mice reveals the dynamics of IgA immune responses. Science 328(5986): 1705-1709.

129. Harish K, Varghese T (2006) Probiotics in humans-evidence based review. Calicut Med J 4(4): e3.

130. Harper Owen R, Dymock D, Booth V, Weightman A J, Wade W G (1999) Detection of unculturable bacteria in periodontal health and disease by PCR. J Clin Microbiol 37(5): 1469-1473.

131. Hayes C L, Dong J, Galipeau H J, Jury J, McCarville J, Huang X, et al. (2018) Commensal microbiota induces colonic barrier structure and functions that contribute to homeostasis. Sci Rep 8(1): 14184.

132. Heintz Buschart A, Pandey U, Wicke T, Sixel Döring F, Janzen A, Sittig Wiegand E, et al. (2018) The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov Disord 33(1): 88-98.

133. Hejran, Abdul Bari (2023) The Health Benefits of Normal Flora in Human Bod." Vestnik Torajgyrov Universiteta. Himiko-Biologičeskaâ Seriâ.

134. Helgeland L, Dissen E, Dai KZ, Midtvedt T, Brandtzaeg P, Vaage JT (2004) Microbial colonization induces oligoclonal expansions of intraepithelial CD8 T cells in the gut. Eur J Immunol 34(12): 3389-3400.

135. Hill C, Guarner F, Reid G, Gibson G R, Merenstein D J, Pot B, et al. (2014) Expert consensus document: The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. Nat Rev Gastroenterol Hepatol 11(8): 506-514.

136. Hill D A, Hoffmann C, Abt M C, Du Y, Kobuley D, Kirn T J, et al. (2010) Metagenomic analyses reveal antibiotic-induced temporal and spatial changes in intestinal microbiota with associated alterations in immune cell homeostasis. Mucosal Immunology, 3(2): 148-158.

137. Hill Burns EM, Debelius JW, Morton JT, Wissemann WT, Lewis MR, Wallen ZD, et al. (2017) Parkinson's disease and Parkinson's disease medications have distinct signatures of the gut microbiome. Mov Disord 32(5): 739-749.

138. Hilty M, Burke C, Pedro H, Cardenas P, Bush A, Bossley C, et al. (2010) Disordered microbial communities in asthmatic airways. PLoS One 5(1): e8578.

139. Hine A M, Loke P (2019) Intestinal Macrophages in Resolving Inflammation. J Immunol 203(3): 593-599.

140. Honda K, Littman D R (2016) The microbiota in adaptive immune homeostasis and disease. Nature 535(7610): 75-84.

141. Hopfner F, Künstner A, Müller SH, Künzel S, Zeuner KE, Margraf NG, et al. (2017) Gut microbiota in Parkinson disease in a northern German cohort. Brain Res 1667: 41-45.

142. Hou K, Wu ZX, Chen XY, Wang JQ, Zhang D, Xiao C, et al. (2022) Microbiota in health and diseases. Signal Transduct Target Ther 7(1): 135.

143. Hou K, Zhang S, Wu Z, Zhu D, Chen F, Lei ZN, et al. (2022) Reconstruction of intestinal microecology of type 2 diabetes by fecal microbiota transplantation: Why and how. Bosn J Basic Med Sci 22(3): 315-325.

144. Hsiao EY, McBride SW, Hsien S, Sharon G, Hyde ER, McCue T, et al. (2013) Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. Cell 155(7): 1451-1463.

145. Huang YJ, Nelson CE, Brodie EL, Desantis TZ, Baek MS, Liu J, et al. (2011) Airway microbiota and bronchial hyperresponsiveness in patients with suboptimally controlled asthma. J Allergy Clin Immunol 127(2): 372-381.e1-3.

146. Ilhan Z E, Marcus A K, Kang D W, Rittmann B E, Krajmalnik Brown R (2017) pH-Mediated Microbial and Metabolic Interactions in Fecal Enrichment Cultures. mSphere 2(3): e00047-17.

147. Integrative HMP (iHMP) Research Network Consortium (2019) The Integrative Human Microbiome Project. Nature 569(7758): 641-648.

148. Ivanov I I, Atarashi K, Manel N, Brodie E L, Shima T, Karaoz U, et al. (2009) Induction of intestinal Th17 cells by segmented filamentous bacteria. Cell 139(3): 485-498.

149. Iwasaki A, Kelsall BL (1999) Freshly isolated Peyer's patch, but not spleen, dendritic cells produce interleukin 10 and induce the differentiation of T helper type 2 cells. J Exp Med 190(2): 229-239.

150. Jiang C, Xie C, Li F, Zhang L, Nichols RG, Krausz KW, et al. (2015) Intestinal farnesoid X receptor signaling promotes nonalcoholic fatty liver disease. J Clin Invest 125(1): 386-402.

151. Jiang HY, Zhang X, Yu ZH, Zhang Z, Deng M, Zhao JH, et al. (2018) Altered gut microbiota profile in patients with generalized anxiety disorder. J Psychiatr Res.104: 130-136.

152. Jiang H, Zongxin Ling, Yonghua Zhang, Hongjin Mao, Zhanping Ma, Yan Yin, et al. (2015) Altered fecal microbiota composition in patients with major depressive disorder. Brain Behav Immun 48: 186-194.

153. Jiang M, Zhang J, Wan X, Ding Y, Xie F (2023) Conjunctival sac flora and drug susceptibility analysis in normal children in East China. BMC Ophthalmol 23(1): 248.

154. Jin Q, Kirk M (2018) pH as a primary control in environmental microbiology: 1. Thermodynamic perspective. Front Environ Sci 6: 21.

155. Jing Y, Yu Y, Bai F, Wang L, Yang D, Zhang C, Qin C, Yang M, Zhang D, Zhu Y, Li J, Chen Z. (2021), Effect of fecal microbiota transplantation on neurological restoration in a spinal cord injury mouse model: involvement of brain-gut axis. Microbiome 9(1): 59.

156. Johansson M E, Phillipson M, Petersson J, Velcich A, Holm L, Hansson G C (2008) The inner of the two Muc2 mucin-dependent mucus layers in colon is devoid of bacteria. Proc Natl Acad Sci U S 105(39): 15064-15069.

157. Kabak B, Dobson AD (2011) An introduction to the traditional fermented foods and beverages of Turkey. Crit Rev Food Sci Nutr 51(3): 248-260.

158. Kalicka D, Znamirowska A, Pawlos M, Buniowska M, Szajnar K (2019) Physical and sensory characteristics and probiotic survival in ice cream sweetened with various polyols. Int J Dairy Technol 72(3): 456-465.

159. Kang DW, Adams JB, Gregory AC, Borody T, Chittick L, Fasano A, et al. (2017) Microbiota Transfer Therapy alters gut ecosystem and improves gastrointestinal and autism symptoms: an open-label study. Microbiome 5(1): 10.

160. Karlsson C, Ahrné S, Molin G, Berggren A, Palmquist I, Fredrikson GN, et al. (2010) Probiotic therapy to men with incipient arteriosclerosis initiates increased bacterial diversity in colon: a randomized controlled trial. Atherosclerosis 208(1): 228-233.

161. Karlsson F H, Tremaroli V, Nookaew I, Bergström G, Behre C J, Fagerberg B, et al. (2013) Gut metagenome in European women with normal, impaired and diabetic glucose control. Nature 498(7452): 99-103.

162. Kassam Z, Lee CH, Yuan Y, Hunt RH (2013) Fecal microbiota transplantation for Clostridium difficile infection: systematic review and meta-analysis. Am J Gastroenterol 108(4): 500-508.

163. Kasselman L J, Vernice N A, DeLeon J, Reiss A B (2018) The gut microbiome and elevated cardiovascular risk in obesity and autoimmunity. Atherosclerosis 271: 203-213.

164. Khoruts A, Dicksved J, Jansson JK, Sadowsky MJ (2010) Changes in the composition of the human fecal microbiome after bacteriotherapy for recurrent Clostridium difficile-associated diarrhea. J Clin Gastroenterol 44(5): 354-360.

165. Khoury K A, Floch M H, Hersh T (1969) Small intestinal mucosal cell proliferation and bacterial flora in the conventionalization of the germfree mouse. J Expe Med 130(3): 659-670.

166. Kim N, Yun M, Oh Y J, Choi H J (2018) Mind-altering with the gut: Modulation of the gut-brain axis with probiotics. J Microbiol 56(3): 172-182.

167. Kochar B, Orkaby A R, Ananthakrishnan A N, Ritchie C S (2021) Frailty in inflammatory bowel diseases: an emerging concept. Therp Adv Gastroenterol 14: 17562848211025474.

168. Kok CR, Hutkins R. (2018) Yogurt and other fermented foods as sources of health-promoting bacteria. Nutr Rev 76(Suppl 1): 4-15.

169. Koren O, Goodrich JK, Cullender TC, Spor A, Laitinen K, Bäckhed HK, et al. (2012) Host remodeling of the gut microbiome and metabolic changes during pregnancy. Cell 150(3): 470-480.

170. Kostic AD, Gevers D, Pedamallu CS, Michaud M, Duke F, Earl AM, et al. (2012) Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome Res 22(2): 292-298.

171. Kunii J, Takahashi K, Kasakura K, Tsuda M, Nakano K, Hosono A, et al. (2011) Commensal bacteria promote migration of mast cells into the intestine. Immunobiology 216(6): 692-697.

172. Kuwahara T, Ogura Y, Oshima K, Kurokawa K, Ooka T, Hirakawa H, et al. (2011) The lifestyle of the segmented filamentous bacterium: a non-culturable gut-associated immunostimulating microbe inferred by whole-genome sequencing. DNA Research: Inter J Rapid Publication Rep Genes Genom 18(4): 291-303.

173. Lagier J C, Khelaifia S, Alou M T, Ndongo S, Dione N, Hugon P, et al. (2016) Culture of previously uncultured members of the human gut microbiota by culturomics. Nature Microbiology 1: 16203.

174. Lakshmanan MD, SM Nair, BS (2023) Prabhu Mammalian Antimicrobial Peptides, Antimicrobial Peptides Elsevier. 171-195.

175. Lambeth SM, Carson T, Lowe J, Ramaraj T, Leff JW, et al. (2015) Composition, Diversity and Abundance of Gut Microbiome in Prediabetes and Type 2 Diabetes. Journal of diabetes and obesity 2(3): 1-7.

176. Lamptey RNL, Chaulagain B, Trivedi R, Gothwal A, Layek B, et al. (2022) Review of the Common Neurodegenerative Disorders: Current Therapeutic Approaches and the Potential Role of Nanotherapeutics. Int J Mol Sci 23: 1851.

177. Landers CJ, Cohavy O, Misra R, Yang H, Lin YC, et al. (2002) Selected loss of tolerance evidenced by Crohn's disease-associated immune responses to auto- and microbial antigens. Gastroenterology 123(3): 689-699.

178. Landman C, Quévrain E (2016) Gut microbiota: description, role and pathophysiologic implications. Rev. Med. Interne 37(6): 418-423.

179. Larsen N, Vogensen FK, van den Berg FW, Nielsen DS, Andreasen AS, et al. (2010) Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 5(2): e9085.

180. Lathrop SK, Bloom SM, Rao SM, Nutsch K, Lio CW, et al. (2011) Peripheral education of the immune system by colonic commensal microbiota. Nature 478(7368): 250-254.

181. Lau K, Srivatsav V, Rizwan A, Nashed A, Liu R, et al. (2017). Bridging the Gap between Gut Microbial Dysbiosis and Cardiovascular Diseases. Nutrients 9(8): 859.

182. Le Berre C, Ananthakrishnan AN, Danese S, Singh S, Peyrin Biroulet L, et al. (2020) Ulcerative colitis and Crohn's disease have similar burden and goals for treatment. Clin. Gastroenterol. Hepatol 18(1): 14-23.

183. Lebeer S, Vanderleyden J, De Keersmaecker SC (2008) Genes and molecules of lactobacilli supporting probiotic action. Microbiology and Molecular Biology Reviews 72(4): 728-64.

184. Lee SH, Starkey PM, Gordon S (1985) Quantitative analysis of total macrophage content in adult mouse tissues. Immunochemical studies with monoclonal antibody F4/80. J Exp Med 161(3): 475-489.

185. Leite GGS, Weitsman S, Parodi G, Celly S, Sedighi R, et al. (2020) Mapping the Segmental Microbiomes in the Human Small Bowel in Comparison with Stool: A REIMAGINE Study. Digestive diseases and sciences 65(9): 2595-2604.

186. Lema I, Araújo JR, Rolhion N, Demignot S (2020) Jejunum: The understudied meeting place of dietary lipids and the microbiota. Biochimie 178: 124-136.

187. Levy M, Kolodziejczyk, AA, Thaiss CA, Elinav E (2017) Dysbiosis and the immune system. Nature reviews. Immunology, 17(4): 219-232.

188. Ley RE, Bäckhed F, Turnbaugh P, Lozupone CA, Knight RD, et al. (2005) Obesity alters gut microbial ecology. Proceedings of the National Academy of Sciences of the United States of America 102(31): 11070-11075.

189. Li C, Cui L, Yang Y, Miao J, Zhao X, et al. (2019) Gut Microbiota Differs Between Parkinson's Disease Patients and Healthy Controls in Northeast China. Front Mol Neurosci 12: 171.

190. Li F, Wang M, Wang J, Li R, Zhang Y, et al. (2019) Alterations to the Gut Microbiota and Their Correlation With Inflammatory Factors in Chronic Kidney Disease. Front Cell Infect Microbiol 12(9): 206.

191. Li Y, Ye Z, Zhu J, Fang S, Meng L, et al. (2022) Effects of Gut Microbiota on Host Adaptive Immunity Under Immune Homeostasis and Tumor Pathology State. Front Immunol 10(13): 844335.

192. Li D, Wang P, Wang P, Hu X, Chen F, et al. (2019) Targeting the gut microbiota by dietary nutrients: A new avenue for human health. Critical reviews in food science and nutrition 59(2): 181-195.

193. Li J, Jia H, Cai X, Zhong H, Feng Q, et al. (2014) An integrated catalog of reference genes in the human gut microbiome. Nature biotechnology 32(8): 834-841

194. Li J, Zhao F, Wang Y, Chen J, Tao J, et al. (2017) Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome 5(1): 14

195. Liu T, Zhang L, Joo D, Sun SC (2017) NF-κB signaling in inflammation. Signal Transduct. Target. Ther. 2: 17023.

196. Lloyd Price J, Abu Ali G, Huttenhower C (2016) The healthy human microbiome. Genome medicine 8(1): 51.

197. Lloyd Price J, Arze C, Ananthakrishnan AN, Schirmer M, Avila Pacheco J, et al. (2019) Multi-omics of the gut microbial ecosystem in inflammatory bowel diseases. Nature 569(7758): 655-662.

198. Lloyd Price J, Mahurkar A, Rahnavard G, Crabtree J, Orvis J, et al. (2017) Strains, functions and dynamics in the expanded Human Microbiome Project. Nature 550(7674): 61-66.

199. Lucas VS, Beighton D, Roberts GJ (2000). Composition of the oral streptococcal flora in healthy children. J Dent 28(1): 45-50.

200. Lun H, Yang W, Zhao S, Jiang M, Xu M, et al. (2019) Altered gut microbiota and microbial biomarkers associated with chronic kidney disease. Microbiologyopen 8(4): e00678.

201. Ma J, Prince AL, Bader D, Hu M, Ganu R, et al. (2014) High-fat maternal diet during pregnancy persistently alters the offspring microbiome in a primate model. Nature communications 5: 3889.

202. Machiels K, Joossens M, Sabino J, De Preter V, Arijs I, et al. (2014) A decrease of the butyrate-producing species Roseburia hominis and Faecalibacterium prausnitzii defines dysbiosis in patients with ulcerative colitis. Gut 63(8): 1275-1283.

203. Mackie RI, Sghir A, Gaskins HR (1999) Developmental microbial ecology of the neonatal gastrointestinal tract. Am J Clin Nutr 69(5): 1035S-1045S.

204. Mafra D, Fouque D (2015) Gut microbiota and inflammation in chronic kidney disease patients. Clin Kidney J 8(3): 332-334.

205. Maiuolo J, Gliozzi M, Musolino V, Carresi C, Scarano F, et al. (2021). The contribution of gut microbiota- brain axis in the development of brain disorders. Front Neurosci 15: 616883.

206. Makris AP, Karianaki M, Tsamis KI, Paschou SA (2021) The role of the gut-brain axis in depression: endocrine, neural, and immune pathways. Hormones (Athens, Greece) 20(1): 1-12.

207. Manichanh C, Rigottier Gois L, Bonnaud E, K Gloux, E Pelletier, et al. (2006) Reduced diversity of faecal microbiota in Crohn's disease revealed by a metagenomic approach. Gut 55(2): 205-211.

208. Marcobal A, Barboza M, Froehlich JW, Block DE, German JB, et al. (2010) Consumption of human milk oligosaccharides by gut-related microbes. Journal of agricultural and food chemistry 58(9): 5334-5340.

209. Mariño E, Richards JL, McLeod KH, Stanley D, Yap YA, et al. (2017), Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes. Nat Immunol 18(5): 552-562.

210. Markowiak P, Śliżewska K (2017) Effects of probiotics, prebiotics, and synbiotics on human health. Nutrients 9(9): 1021.

211. Marrs T, Walter J (2021) Pros and cons: Is faecal microbiota transplantation a safe and efficient treatment option for gut dysbiosis? Allergy 76(7): 2312-2317.

212. Martin CR, Osadchiy V, Kalani A, Mayer EA (2018) The Brain-Gut-Microbiome Axis, Cell Mol. Gastroenterol. Hepatol 6(2): 133-148.

213. Mathewson ND, Jenq R, Mathew AV, Koenigsknecht M, Hanash A, et al. (2016) Gut microbiome-derived metabolites modulate intestinal epithelial cell damage and mitigate graft-versus-host disease. Nat Immunol 17(5): 505-513.

214. Mazmanian SK, Liu CH, Tzianabos AO, Kasper DL (2005) An immunomodulatory molecule of symbiotic bacteria directs maturation of the host immune system. Cell 122(1): 107-118.

215. McCarville JL, Chen GY, Cuevas VD, Troha K, Ayres JS, et al. (2020). Microbiota Metabolites in Health and Disease. Annual review of immunology 38: 147-170.

216. Menni C, Lin C, Cecelja M, Mangino M, Matey Hernandez ML, et al. (2018) Gut microbial diversity is associated with lower arterial stiffness in women. European heart journal 39(25): 2390-2397.

217. Mennitti LV, Oliveira JL, Morais CA, Estadella D, Oyama LM, et al, (2015) Type of fatty acids in maternal diets during pregnancy and/or lactation and metabolic consequences of the offspring. The Journal of nutritional biochemistry 26(2): 99-111.

218. Michaels M, Madsen KL (2023) Immunometabolism and microbial metabolites at the gut barrier: Lessons for therapeutic intervention in inflammatory bowel disease. Mucosal immunology 16(1): 72-85.

219. Mikkelsen HB, Garbarsch C, Tranum Jensen J, Thuneberg L (2004) Macrophages in the small intestinal muscularis externa of embryos,

newborn and adult germ-free mice. J Mol Histol 35(4): 377-387.

220. Milani C, Duranti S, Bottacini F, Casey E, Turroni F, et al. (2017) The First Microbial Colonizers of the Human Gut: Composition, Activities, and Health Implications of the Infant Gut Microbiota. Microbiology and molecular biology reviews : MMBR, 81(4): e00036-17.

221. Mirowski GW, Bettencourt JD, Hood AF (1997) Oral infections in the immunocompromised host. Seminars in cutaneous medicine and surgery 16(4): 249-256.

222. Mitsuyama M, Ohara R, Amako K, Nomoto K, Yokokura T, et al. (1986) Ontogeny of macrophage function to release superoxide anion in conventional and germfree mice. Infect Immun 52(1): 236-239.

223. Moran CP, Shanahan F (2014) Gut microbiota and obesity: role in aetiology and potential therapeutic target, Best Pract. Res. Clin. Gastroenterol 28(4): 585-597.

224. Mørland B, Midtvedt T (1984) Phagocytosis, peritoneal influx, and enzyme activities in peritoneal macrophages from germfree, conventional, and ex-germfree mice. Infect Immun 44: 750-752.

225. Nagao Kitamoto H, Shreiner AB, Gillilland MG 3rd, Kitamoto S, Ishii C, et al. (2016), Functional Characterization of Inflammatory Bowel Disease-Associated Gut Dysbiosis in Gnotobiotic Mice. Cell Mol Gastroenterol Hepatol 2(4): 468-481.

226. Neu J, Rushing J (2011) Cesarean versus vaginal delivery: long-term infant outcomes and the hygiene hypothesis. Clin Perinatol 38(2): 321-331.

227. Nogueira AR, Shoenfeld Y (2019) Microbiome and autoimmune diseases: cause and effect relationship. Current opinion in rheumatology 31(5): 471-474.

228. Nugent SG, Kumar D, Rampton DS, Evans DF (2001) Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. Gut 48(4): 571-577.

229. Nygren E, Gonzales Strömberg L, Logenius J, Husmark U, Löfström C, et al. (2023) Potential sources of contamination on textiles and hard surfaces identified as high-touch sites near the patient environment. PloS one 18(7): e0287855.

230. Ohkubo T, Tsuda M, Tamura M, Yamamura M (1990) Impaired superoxide production in peripheral blood neutrophils of germ-free rats. Scand J Immunol 32(6): 727-729.

231. Opstelten JL, Plassais J, van Mil SW, Achouri E, Pichaud, M, et al. (2016). Gut Microbial Diversity Is Reduced in Smokers with Crohn's Disease. Inflammatory bowel diseases 22(9): 2070-2077.

232. Osna NA, Donohue TM, Kharbanda KK (2017) Alcoholic liver disease: pathogenesis and current management. Alcohol Res. 38(2): 147-161.

233. Ottiger M, Nickler M, Steuer C, Bernasconi L, Huber A, et al. (2018) Gut, microbiota-dependent trimethylamine-N-oxide is associated with long-term all-cause mortality in patients with exacerbated chronic obstructive pulmonary disease. Nutrition 45: 135-141.e1.

234. Owaga E, Hsieh RH, Mugendi B, Masuku S, Shih CK, et al. (2015) Th17 Cells as Potential Probiotic Therapeutic Targets in Inflammatory Bowel Diseases. International journal of molecular sciences 16(9): 20841-20858.

235. Palmer C, Bik EM, DiGiulio DB, Relman DA, Brown PO, et al. (2007) Development of the human infant intestinal microbiota. PLoS biology 5(7): e177.

236. Pan W, Kang Y (2018) Gut microbiota and chronic kidney disease: implications for novel mechanistic insights and therapeutic strategies. Int Urol Nephrol 50(2): 289-299

237. Paramsothy S, Kamm MA, Kaakoush NO, Walsh AJ, van den Bogaerde J, et al. (2017), Multidonor intensive faecal microbiota transplantation for active ulcerative colitis: a randomised placebo-controlled trial. Lancet 389(10075): 1218-1228.

238. Peng C, Gathagan RJ, Covell DJ, Medellin C, Stieber A, et al. (2018) Cellular milieu imparts distinct pathological α-synuclein strains in α-synucleinopathies. Nature 557(7706): 558-563.

239. Peng L, He Z, Chen W, Holzman IR, Lin J, et al. (2007) Effects of butyrate on intestinal barrier function in a caco-2 cell monolayer model of intestinal barrier, Pediatr. Res 61(1): 37-41.

240. Pereira P, Forni L, Larsson EL, Cooper M, Heusser C, et al. (1986) Autonomous activation of B and T cells in antigen-free mice. Eur J Immunol 16(6): 685-688.

241. Petrillo F, Pignataro D, Lavano MA, Santella B, Folliero V, et al. (2020) Current Evidence on the Ocular Surface Microbiota and Related Diseases. Microorganisms 8(7): 1033.

242. Pluznick JL (2020) The gut microbiota in kidney disease. Science 369(6510): 1426-1427.

243. Poretsky R, Rodriguez R LM, Luo C, Tsementzi D, Konstantinidis KT, et al. (2014) Strengths and limitations of 16S rRNA gene amplicon sequencing in revealing temporal microbial community dynamics. PloS one 9(4): e93827.

244. Proal AD, Albert PJ, Marshall TG (2014) Inflammatory disease and the human microbiome, Discov Med 17(95): 257-265.

245. Qin J, Li R, Raes J, Arumugam M, Burgdorf KS, et al. (2010) A human gut microbial gene catalogue established by metagenomic sequencing. Nature 464(7285): 59-65.

246. Radzicka S, Pietryga M, Iciek R, Brązert J (2018) The role of visfatin in pathogenesis of gestational diabetes (GDM). Ginekol. Pol 89: 518-521.

247. Rajilić Stojanović M, de Vos WM (2014) The first 1000 cultured species of the human gastrointestinal microbiota. FEMS Microbiol Rev 38(5): 996-1047.

248. Rakoff Nahoum S, Paglino J, Eslami Varzaneh F, Edberg S, Medzhitov R, et al. (2004) Recognition of commensal microflora by toll-like receptors is required for intestinal homeostasis. Cell 118(2): 229-241.

249. Raman M, Ahmed I, Gillevet PM, Probert CS, Ratcliffe NM, et al. (2013) Fecal microbiome and volatile organic compound metabolome in obese humans with nonalcoholic fatty liver disease. Clin Gastroenterol Hepatol 11(7): 868-75.e1-3.

250. Reikvam DH, Erofeev A, Sandvik A, Grcic V, Jahnsen FL, et al. (2011) Depletion of murine intestinal microbiota: effects on gut mucosa and epithelial gene expression. PloS one 6(3): e17996.

251. Rinninella E, Raoul P, Cintoni M, Franceschi F, Miggiano GAD, et al. (2019) What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms 7(1): 14.

252. Riquelme E, Zhang Y, Zhang L, Montiel M, Zoltan M, et al. (2019) Tumor Microbiome Diversity and Composition Influence Pancreatic Cancer Outcomes. Cell 178(4): 795-806.e12.

253. Roduit C, Frei R, Ferstl R, Loeliger S, Westermann P, et al. (2019) High levels of butyrate and propionate in early life are associated with protection against atopy. Allergy 74(4): 799-809.

254. Rolle R, Satin M (2002) Basic requirements for the transfer of fermentation technologies to developing countries. Int J Food Microbiol 75(3): 181-187.

255. Roncal C, Martínez Aguilar E, Orbe J, Ravassa S, Fernandez Montero A, et al. (2019) Trimethylamine-N-Oxide (TMAO) Predicts Cardiovascular Mortality in Peripheral Artery Disease. Sci Rep 9(1): 15580.

256. Roobab U, Batool Z, Manzoor MF, Shabbir MA, Khan MR, et al. (2020) Sources, formulations, advanced delivery and health benefits of probiotics. Curr. Opin. Food Sci 32: 17-28.

257. Rooks MG, Garrett WS (2016) Gut microbiota, metabolites and host immunity. Nat Rev Immunol 16(6): 341-352.

258. Roscoe DL, Chow AW (1988) Normal flora and mucosal immunity of the head and neck. Infect Dis Clin North Am 2(1): 1-19.

259. Ross RP, Morgan S, Hill C (2002) Preservation and fermentation: Past, present and future. Int J Food Microbiol 79(1-2): 3-16.

260. Roussos A, Koursarakos P, Patsopoulos D, Gerogianni I, Philippou N, et al. (2003) Increased prevalence of irritable bowel syndrome in patients with bronchial asthma. Respir Med 97(1): 75-79.

261. Rubinstein MR, Wang X, Liu W, Hao Y, Cai G, et al. (2013) Fusobacterium nucleatum promotes colorectal carcinogenesis by modulating E-cadherin/β-catenin signaling via its FadA adhesin. Cell Host Microbe 14(2): 195-206.

262. Rutayisire E, Huang K, Liu Y, Tao F (2016) The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. BMC Gastroenterol 16(1): 86.

263. Rutten EPA, Lenaerts K, Buurman WA, Wouters EFM (2014) Disturbed intestinal integrity in patients with COPD: effects of activities of daily living. Chest 145(2): 245-252.

264. Salzman NH, Hung K, Haribhai D, Chu H, Karlsson Sjöberg J, et al. (2010) Enteric defensins are essential regulators of intestinal microbial ecology. Nature immunology 11(1): 76-83.

265. Sanchez Rodriguez E, Egea Zorrilla A, Plaza Díaz J, Aragón Vela J, Muñoz Quezada S, et al. (2020) The Gut Microbiota and Its Implication in the Development of Atherosclerosis and Related Cardiovascular Diseases. Nutrients 12(3): 605.

266. Sanos SL, Bui VL, Mortha A, Oberle K, Heners, C, et al. (2009). RORgammat and commensal microflora are required for the differentiation of mucosal interleukin 22-producing NKp46+ cells. Nature immunology 10(1): 83-91.

267. Satoh Takayama N, Vosshenrich CA, Lesjean Pottier S, Sawa S, Lochner M, et al. (2008) Microbial flora drives interleukin 22 production in intestinal NKp46+ cells that provide innate mucosal immune defense. Immunity 29(6): 958-970.

268. Schauber J, Gallo RL (2009) Antimicrobial peptides and the skin immune defense system. J. Allergy Clin Immunol 124(3 Suppl 2): R13-R18.

269. Scheltens P, Blennow K, Breteler MM, de Strooper B, Frisoni GB, et al. (2016). Alzheimer's disease. Lancet (London, England), 388(10043): 505-517.

270. Scheperjans F, Aho V, Pereira PA, Koskinen K, Paulin L, et al. (2015) Gut microbiota are related to Parkinson's disease and clinical phenotype. Mov Disord 30(3): 350-358.

271. Schuijt TJ, Lankelma JM, Scicluna BP, de Sousa e Melo F, Roelofs JJ, et al. (2016) The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia. Gut 65(4): 575-583.

272. Schuster GS (1999) Oral flora and pathogenic organisms. Infectious disease clinics of North America 13(4): 757-774v.

273. Seekatz AM, Schnizlein MK, Koenigsknecht MJ, Baker JR, Hasler WL, et al. (2019) Spatial and Temporal Analysis of the Stomach and Small-Intestinal Microbiota in Fasted Healthy Humans. mSphere 4(2): e00126-19.

274. Segal LN, Clemente JC, Li Y, Ruan C, Cao J, et al. (2017) Anaerobic Bacterial Fermentation Products Increase Tuberculosis Risk in Antiretroviral-Drug-Treated HIV Patients. Cell Host Microbe 21(4): 530-537.e4.

275. Sekirov I, Russell SL, Antunes LC, Finlay BB (2010) Gut microbiota in health and disease. Physiol Rev 90(3): 859-904.

276. Sekirov I, Tam NM, Jogova M, Robertson ML, Li Y, et al. (2008) Antibiotic-induced perturbations of the intestinal microbiota alter host susceptibility to enteric infection. Infect immun 76(10): 4726-4736.

277. Sela DA, Chapman J, Adeuya A, Kim JH, Chen F, et al. (2008) The genome sequence of Bifidobacterium longum subsp. infantis reveals adaptations for milk utilization within the infant microbiome. Proc Natl Acad Sci USA 105(48): 18964-18969.

278. Sender R, Fuchs S, Milo R (2016) Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 14(8): e1002533.

279. Shao T, Hsu R, Rafizadeh DL, Wang L, Bowlus CL, et al. (2023) The gut ecosystem and immune tolerance. J autoimmun 141: 103114.

280. Shi N, Li N, Duan X, Niu H (2017) Interaction between the gut microbiome and mucosal immune system. Mil Med Res 4: 14.

281. Slavin J (2013) Fiber and prebiotics: mechanisms and health benefits. Nutrients 5(4):1417-1435.

282. Smith DG, Martinelli R, Besra GS, Illarionov PA, Szatmari I, et al. (2019) Identification and characterization of a novel anti-inflammatory lipid isolated from Mycobacterium vaccae, a soil-derived bacterium with immunoregulatory and stress resilience properties. Psychopharmacology 236(5): 1653-1670.

283. Smith K, McCoy KD, Macpherson AJ (2007) Use of axenic animals in studying the adaptation of mammals to their commensal intestinal microbiota. Semin immunol 19(2): 59-69.

284. Smythies LE, Shen R, Bimczok D, Novak L, Clements RH, Eckhoff DE, et al. (2010) Inflammation anergy in human intestinal macrophages is due to Smad-induced IkappaBalpha expression and NF-kappaB inactivation. J Biol Chem 285: 19593-19604.

285. Soemarie YB, Milanda T, Barliana MI (2021) Fermented foods as probiotics: A review. J Adv Pharm Technol Res 12(4): 335-339.

286. Sokol H, Pigneur B, Watterlot L, Lakhdari O, Bermúdez Humarán LG, et al. (2008) Faecalibacterium prausnitzii is an anti-inflammatory commensal bacterium identified by gut microbiota analysis of Crohn disease patients. Proc Natl Acad Sci USA 105 (43): 16731-16736.

287. Sokolowska M, Frei R, Lunjani N, Akdis CA, O'Mahony L (2018) Microbiome and asthma. Asthma Res Pract 4: 1.

288. Sommer F, Bäckhed F (2013) The gut microbiota--masters of host development and physiology. Nat rev Microbiol 11(4): 227-238.

289. Sonnenburg ED, Sonnenburg JL (2014) Starving our microbial self: the deleterious consequences of a diet deficient in microbiota-accessible carbohydrates. Cell metab 20(5): 779-786.

290. Sorbara MT, Pamer EG (2022) Microbiome-based therapeutics. Nat Rev Microbiol 20: 365-380.

291. Sprooten RTM, Lenaerts K, Braeken DCW, Grimbergen I, Rutten EP, et al. (2018) Increased Small Intestinal Permeability during Severe Acute Exacerbations of COPD. Respiration 95(5): 334-342.

292. Stenfors LE, Räisänen S (2002) Quantity of aerobic bacteria in the bony portion of the external auditory canal of children. Int j pediatr otorhinolaryngol 66(2): 167-173.

293. Svanborg C, Aniansson G, Mestecky J, Sabharwal H, Wold A (1991) Anti-adhesive molecules in human milk. Adv Exp Med Biol 310: 167-171.

294. Sveinbjornsdottir S (2016) The clinical symptoms of Parkinson's disease. J Neurochem. 139(Suppl 1): 318-324.

295. Swanson KS, Gibson GR, Hutkins R, Reimer RA, Reid G, et al. (2020) The International Scientific Association for Probiotics and Prebsssiotics (ISAPP) consensus statement on the definition and scope of synbiotics. Nat Rev Gastroenterol Hepatol 17(11): 687-701.

296. Swidsinski A, Loening-Baucke V, Verstraelen H, Osowska S, Doerffel Y (2008) Biostructure of fecal microbiota in healthy subjects and patients with chronic idiopathic diarrhea. Gastroenterology 135(2): 568-579.

297. Takeuchi T, Ohno H (2022) IgA in human health and diseases: Potential regulator of commensal microbiota. Front immunol 13: 1024330.

298. Tamburini S, Shen N, Wu HC, Clemente JC (2016) The microbiome in early life: implications for health outcomes. Nat med 22(7): 713-722.

299. Thaiss CA, Zmora N, Levy M, Elinav E (2016) The microbiome and innate immunity. Nature 535(7610): 65-74.

300. Thursby E, Juge N (2017) Introduction to the human gut microbiota. Biochemical j 474(11): 1823-1836.

301. Tlaskalová Hogenová H, Stepánková R, Hudcovic T, Tucková L, Cukrowska B, et al. (2004) Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immunol lett 93(2-3): 97-108.

302. Tomar O (2019) The effects of probiotic cultures on the organic acid content, texture profile and sensory attributes of Tulum cheese. Int J Dairy Technol 72(2): 218- 228.

303. Troost FJ, van Baarlen P, Lindsey P, Kodde A, de Vos WM, et al. (2008) Identification of the transcriptional response of human intestinal mucosa to Lactobacillus plantarum WCFS1 in vivo. BMC genomics 9: 374.

304. Turnbaugh PJ, Hamady M, Yatsunenko T, Cantarel BL, Duncan A, Ley RE, et al. (2009) A core gut microbiome in obese and lean twins. Nature 457(7228): 480-484.

305. Turnbaugh PJ, Ley RE, Hamady M, Fraser-Liggett CM, Knight R, et al. (2007) The human microbiome project. Nature, 449(7164): 804-810.

306. Tysnes OB, Storstein A (2017) Epidemiology of Parkinson's disease. J Neural Transm 124: 901-905.

307. Vaishampayan PA, Kuehl JV, Froula JL, Morgan JL, Ochman H, et al. (2010) Comparative metagenomics and population dynamics of the gut microbiota in mother and infant. Genome biol evol 2: 53-66.

308. Valdes AM, Walter J, Segal E, Spector TD (2018) Role of the gut microbiota in nutrition and health. BMJ 361: k2179.

309. Vallianou N, Stratigou T, Christodoulatos GS, Dalamaga M (2019) Understanding the Role of the Gut Microbiome and Microbial Metabolites in Obesity and Obesity-Associated Metabolic Disorders: Current Evidence and Perspectives. Curr. Obes. Rep. 8 (3): 317-332.

310. Van Baar ACG, Nieuwdorp M, Holleman F, Soeters MR, Groen AK, et al. (2018) The Duodenum harbors a Broad Untapped Therapeutic Potential. Gastroenterology 154(4): 773-777.

311. Van Baarlen P, Troost FJ, van Hemert S, van der Meer C, de Vos WM, et al. (2009) Differential NF-kappaB pathways induction by Lactobacillus plantarum in the duodenum of healthy humans correlating with immune tolerance. Proc Natl Acad Sci USA 106(7): 2371-2376.

312. van Baarlen P, Troost F, van der Meer C, Hooiveld G, Boekschoten M, et al. (2011) Human mucosal in vivo transcriptome responses to three lactobacilli indicate how probiotics may modulate human cellular pathways. Proc Natl Acad of Sci USA 108(Suppl 1): 4562-4569.

313. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, et al. (2013) Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 368(5): 407-415.

314. Vogt NM, Kerby RL, Dill-McFarland KA, Harding SJ, Merluzzi AP, et al. (2017) Gut microbiome alterations in Alzheimer's disease. Sci Rep 7(1): 13537.

315. Walker AW, Duncan SH, McWilliam Leitch EC, Child MW, Flint HJ (2005) pH and peptide supply can radically alter bacterial populations and short-chain fatty acid ratios within microbial communities from the human colon. Appl environ microbiol 71(7): 3692-3700.

316. Walker ER, McGee RE, Druss BG (2015) Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis. JAMA Psychiatry 72(4): 334-341.

317. Wan T, Wang Y, He K, Zhu S (2023) Microbial sensing in the intestine. Protein & cell 14(11): 824-860.

318. Wang IK, Lai HC, Yu CJ, Liang CC, Chang CT, et al. (2012) Real-time PCR analysis of the intestinal microbiotas in peritoneal dialysis patients. Appl Environ Microbiol 78(4):1107-11012.

319. Wang B, Yao M, Lv L, Ling Z, Li L (2017) The human microbiota in health and disease. Engineering 3(1): 71-82.

320. Wang J, Jia Z, Zhang B, Peng L, Zhao F (2020) Tracing the accumulation of in vivo human oral microbiota elucidates microbial community dynamics at the gateway to the GI tract. Gut 69(7): 1355-1356.

321. Wang M, Karlsson C, Olsson C, Adlerberth I, Wold AE, et al. (2008) Reduced diversity in the early fecal microbiota of infants with atopic eczema. J allergy and clin immunol 121(1): 129-134.

322. Wei B, Wingender G, Fujiwara D, Chen DY, McPherson M, et al. (2010) Commensal microbiota and CD8+ T cells shape the formation of invariant NKT cells. J immunol 184(3): 1218-1226.

323. Wells JM, Brummer RJ, Derrien M, MacDonald TT, Troost F, et al. (2017) Homeostasis of the gut barrier and potential biomarkers. Am j physiol Gastrointest liver physiol 312(3): G171-G193.

324. Williams AM, Probert CS, Stepankova R, Tlaskalova Hogenova H, Phillips A, et al. (2006) Effects of microflora on the neonatal development of gut mucosal T cells and myeloid cells in the mouse. Immunology 119(4): 470-478.

325. Willing BP, Dicksved J, Halfvarson J, Andersson AF, Lucio M, et al. (2010) A pyrosequencing study in twins shows that gastrointestinal microbial profiles vary with inflammatory bowel disease phenotypes. Gastroenterology 139(6): 1844-1854.

326. Wimo A, Maëlenn Guerchet, Gemma-Claire Ali, Yu-Tzu Wu, A Matthew Prina, et al. (2017), The worldwide costs of dementia 2015 and comparisons with 2010. Alzheimer's Dementia 13(1):1-7.

327. Wong JM, de Souza R, Kendall CW, Emam A, Jenkins DJ (2006) Colonic health: fermentation and short chain fatty acids. J Clin Gastroenterol 40(3): 235-243.

328. World Health Organization (2020) Obesity and overweight. World Obesity Federation. Available at: https://www.who.int/news-room/fact-sheets/detail/ obesity-and-overweight.

329. Wu Y, Wu J, Chen T, Li Q, Peng W, et al. (2018) Fusobacterium nucleatum Potentiates Intestinal Tumorigenesis in Mice via a Toll-Like Receptor 4/p21-Activated Kinase 1 Cascade. Dig Dis Sci 63(5): 1210-1218.

330. Wu HJ, Wu E (2012) The role of gut microbiota in immune homeostasis and autoimmunity. Gut microbes 3(1): 4-14.

331. Wu HJ, Ivanov II, Darce J, Hattori K, Shima T, et al. (2010) Gut-residing segmented filamentous bacteria drive autoimmune arthritis via T helper 17 cells. Immunity 32(6): 815-827.

332. Wu, H, Tremaroli V, Schmidt C, Lundqvist A, Olsson LM, et al. (2020) The Gut Microbiota in Prediabetes and Diabetes: A Population-Based Cross-Sectional Study. Cell metab 32(3): 379-390.e3.

333. Yan Q, Gu Y, Li X, Yang W, Jia L, et al. (2017) Alterations of the Gut Microbiome in Hypertension. Front Cell Infect Microbiol 7: 381.

334. Yang T, Richards EM, Pepine CJ, Raizada MK (2018) The gut microbiota and the brain-gut-kidney axis in hypertension and chronic kidney disease. Nat Rev Nephrol 14(7): 442-456.

335. Yang T, Santisteban MM, Rodriguez V, Li E, Ahmari N, et al. (2015) Gut dysbiosis is linked to hypertension. Hypertension 65 (6): 1331-1340.

336. Yassour M, Jason E, Hogstrom LJ, Arthur TD, Tripathi S, et al. (2018) Strain-Level Analysis of Mother-to-Child Bacterial Transmission during the First Few Months of Life. Cell host microbe 24(1): 146-154. e4.

337. Yatsunenko T, Rey FE, Manary MJ, Trehan I, Dominguez-Bello MG, et al. (2012) Human gut microbiome viewed across age and geography. Nature 486(7402): 222-227.

338. Yoshida N, Yamashita T, Kishino S, Watanabe H, Sasaki K, et al. (2020) A possible beneficial effect of Bacteroides on faecal lipopolysaccharide activity and cardiovascular diseases. Sci Rep 10(1): 13009.

339. Yu Y, Zhao F (2021) Microbiota-gut-brain axis in autism spectrum disorder. Journal of genetics and genomics=Yi chuan xue bao 48(9): 755-762.

340. Yu Y, Zhang B, Ji P, Zuo Z, Huang Y, et al. (2022) Changes to gut amino acid transporters and microbiome associated with increased E/I ratio in Chd8+/- mouse model of ASD-like behavior. Nat commun 13(1): 1151.

341. Zhang L, Wang Y, Xiayu X, Shi C, Chen W, et al. (2017) Altered gut microbiota in a mouse model of Alzheimer's disease. J. Alzheimers Dis 60: 1241-1257.

342. Zhang W, Wen K, Azevedo MS, Gonzalez A, Saif LJ, et al. (2008) Lactic acid bacterial colonization and human rotavirus infection influence distribution and frequencies of monocytes/macrophages and dendritic cells in neonatal gnotobiotic pigs. Vet immunol immunopathol 121(3-4): 222-231.

343. Zheng D, Liwinski T, Elinav E (2020) Interaction between microbiota and immunity in health and disease. Cell res 30(6): 492-506.

344. Zoetendal EG, Rajilic-Stojanovic M, de Vos WM (2008) High-Throughput diversity and functionality analysis of the gastrointestinal tract microbiota. Gut 57(11): 1605-1615.

345. Zoetendal EG, Raes J, van den Bogert B, Arumugam M, Booijink CC, et al. (2012) The human small intestinal microbiota is driven by rapid uptake and conversion of simple carbohydrates. ISME journal 6(7): 1415-1426.

346. Zou Y, Xue W, Luo G, Deng Z, Qin P, et al. (2019) 1,520 reference genomes from cultivated human gut bacteria enable functional microbiome analyses. Nat biotech 37(2): 179-185.

347. Zuo T, Wong SH, Lam K, Lui R, Cheung K, et al. (2018) Bacteriophage transfer during faecal microbiota transplantation in Clostridium difficile infection is associated with treatment outcome. Gut 67(4): 634-643.