Hindawi
Advanced Gut & Microbiome Research
Volume 2022, Article ID 9976555, 16 pages
https://doi.org/10.1155/2022/9976555

Review Article

Potential Biotics for Nutritional Improvement of Health via Microbiome-Gut-Brain Axis

Madiha Khan Niazi[1] **and Farooq Hassan**[2]

[1]*University Institute of Diet and Nutritional Sciences, Faculty of Allied Health Sciences, The University of Lahore, Pakistan*
[2]*Assistant Director Standards Development and Dissemination (Tibb), Punjab Healthcare Commission-Lahore, Pakistan*

Correspondence should be addressed to Madiha Khan Niazi; dr.madihaniazi@gmail.com

Received 15 October 2022; Revised 10 November 2022; Accepted 16 November 2022; Published 24 November 2022

Academic Editor: Jiong Yu

Copyright © 2022 Madiha Khan Niazi and Farooq Hassan. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

People's dietary consumption is significantly influenced by biological, social, and psychological behaviours; as a result, complexes regarding their health arise. Due to the nutraceutical advantages of functional foods and supplements, a variety of fermented foods and beverages are now available to consumers. The properties of probiotics, prebiotics, postbiotics, and paraprobiotics are discussed in this overview along with their importance to diet and long-term health. Several synbiotic products, which are complimentary blends of chosen, defined probiotic cultures and prebiotic substrates, have drawn consumers' attention in the nutraceutical sector recently. Probiotics and symbiotic preparations are distinct from the traditional fermented foods eaten in various cultures, even if they might be thought of as possible biotics in food. Because they are prepared with seasonal raw ingredients obtained from regional agricultural techniques, fermented foods are affordable and a staple diet component in many nations. All of the biotics mentioned in this article are meant to increase the number of good microbes in the gut, which has been shown to be crucial for the microbiome-gut-brain axis, which affects the activity of the vagus nerve.

1. Introduction

The term "microbiota" did not appear until the turn of the 20th century. Numerous microorganisms, such as bacteria, viruses, and yeast, have been shown to cohabit in different parts of the human body (gut, skin, lung, and oral cavity). An estimated 150 times more genetic information exists in the human microbiota, also referred to as "the hidden organ," than in the total human genome. Despite the terms "microbiota" and "microbiome" being frequently confused, there are some distinctions between the two. The term "microbiota" refers to the living microorganisms that can be found in specific habitats, such as the oral and intestinal microbiota. In addition to the bacterial population, the term "microbiome" also refers to the structural components, metabolites, and environmental factors of all ambient microorganisms [1]. The microbiome is more extensive than the microbiota in this regard. In this review, we primarily concentrate on how the microbiome affects human health and disease. Every location has a unique microbiota from other locations (depicted in Figure 1). It is thought that the gut microbiota is crucial for preserving human health [2]. Among the many functions that gut bacteria perform are vitamin generation, pathogen defence, immune response induction, and food fermentation. Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia are the six phyla that make up the gut microbiota. These phyla are often broken down into Firmicutes and Bacteroidetes [3]. The fungi Candida, Saccharomyces, Malassezia, and Cladosporium have received the most research attention (gut mycobiota) [4]. In addition to bacteria and fungus, the human gut microbiota also consists of viruses, phages, and archaea, particularly M. smithii. Although less well known than in the stomach, the microbiota is localized in many places, including the oral cavity, lung, vagina, and skin. According to estimates, the oral microbiota of humans is the second-largest microbial community. Oral bacteria can be found in a variety of places, including saliva, the tongue, tooth surfaces, gums, the buccal mucosa, the palate, and subgingival/supragingival plaque. These ecosystems are prone

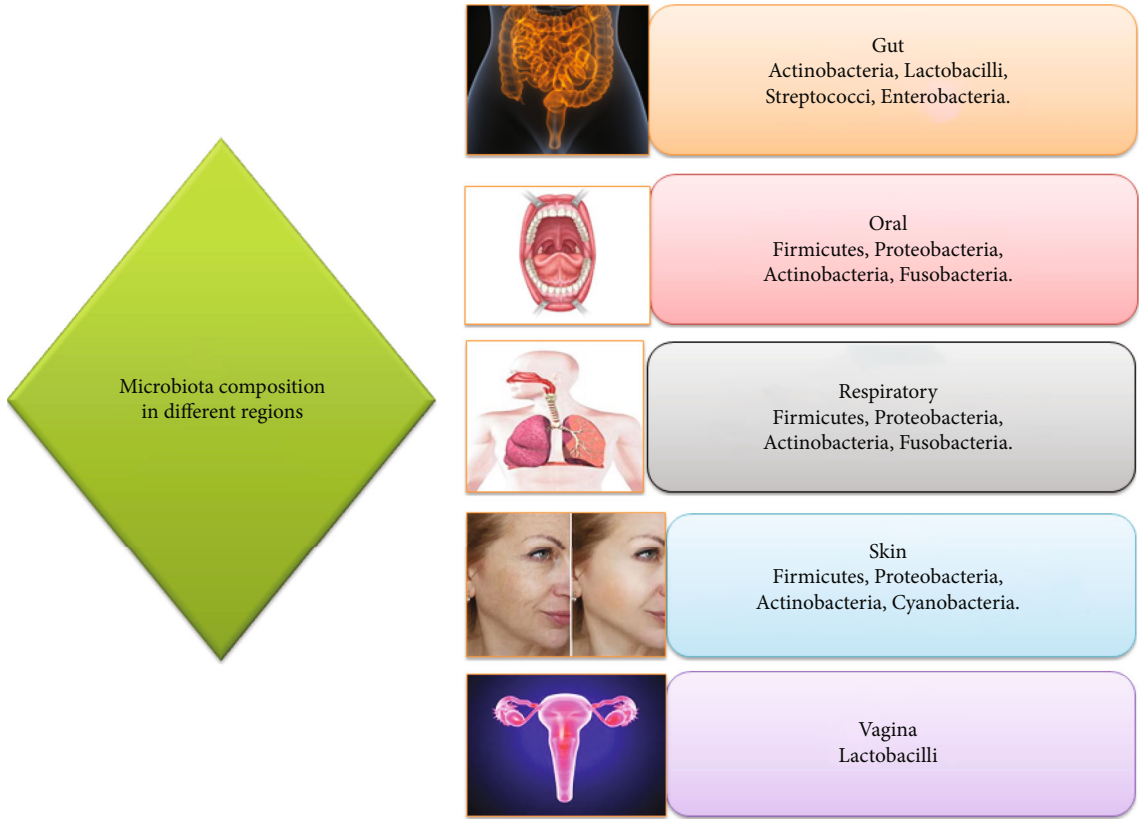

Figure 1: Human microbiota composition in different locations.

to significant and abrupt changes in activity and composition because of factors like pH fluctuations, gene mutations, and bacterial interactions. The microbiota compositions of the seven sites are essentially comparable, notwithstanding a few small scale variations. Firmicutes, Proteobacteria, Bacteroidetes, Actinobacteria, and Fusobacteria are frequently the most prevalent bacteria in the oral microbiota. Although it was once thought that human lungs in good health were sterile, multiple studies have shown that bacteria can also be found in lung tissues. Actinobacteria, Bacteroidetes, Firmicutes, and Proteobacteria dominated the lung microbiota. Microbial movement, emigration, and reproductive rates affect the composition of the lung microbiota [5]. Location affects the number, diversity, and distribution of glands and hair follicles on human skin. Physical and chemical variations result in diverse microbiota compositions in various skin types. Actinobacteria, Bacteroidetes, Cyanobacteria, Firmicutes, and Proteobacteria make up the majority of the skin microbiota.

Recently, there has been a lot of focus on the connection between the microbiota and diseases like cancer, diabetes, and neurological issues. The control of the microbiota in the human body may be crucial to the treatment of disease. In this article, we cover the body of research on the human microbiota's contributions to the development of disease, the regulation of health conditions, and potential clinical uses in the treatment of disorders.

2. Biotics Related to Nutrition and Health

Probiotics, prebiotics, and synbiotics are all considered biotics or those that influence health through diet. The subsections below have discussed each of these.

2.1. Probiotic. The word "probiotics" is derived from the Greek word "pro life, " which means "for life" [6]. The hosts will profit if these active, nonpathogenic microorganisms are available in large enough quantities. Kollath first uttered the phrase in 1953. He claimed that a number of organic and inorganic chemicals could aid in the recovery of health in malnourished people. The term "probiotic" was originally used in 1954 by scientist Ferdinand Vergin, who was investigating the impact of antibiotics and related substances on the gut microbial population at the time he discovered the beneficial effects of probiotics on the gut microbiota. In a 1962 science article by Lily and Stillwell, probiotics were described as "substances generated by one bacteria which supports the growth of another." Probiotics are "other chemicals" in addition to bacteria that keep the balance of germs in the intestine, according to Parker's definition of the word from 1974. Roy Fuller revised the concept of probiotics in 1989, dropping the phrase "other substances." His assertion that probiotics are "live microbial feed supplements that positively influence the host animal by boosting its gut microbial balance" is the basis of the generally

accepted definition of probiotics [7]. Probiotics are currently referred to as "living bacteria that, when eaten in sufficient numbers, provide the host with health benefits" by both the Food and Drug Administration (FDA) and the World Health Organization (WHO).

2.2. The Mechanism of Action of Probiotics. Although the particular mechanism by which probiotics benefit the host cell is unknown, they do so. Probiotics have the ability to alter gut pH and boost the immune system. Additionally, they may be used to treat various medical conditions, such as inflammatory bowel disease. This facilitates the colonisation of bacteria in the gut [8]. Probiotics produce antimicrobial compounds that compete with one another for attachment sites and are released into the environment. [9].

2.3. The Health Benefits of Probiotics. The same probiotic strain that has been shown to have the desired therapeutic effect must be employed for a good clinical outcome. Using probiotic microorganisms like Lactobacillus rhamnosus GG and Saccharomyces boulardi can prevent diarrhoea brought on by antibiotics. Use Saccharomyces boulardii and Lactobacillus rhamnosus GG to prevent the growth of Clostridium difficile (CDI). After the initial CDI, Saccharomyces boulardii and Lactobacillus rhamnosus GG prevent recurrence. Helicobacter pylori can be totally eliminated by combining Lactobacillus rhamnosus GG, Saccharomyces boulardii, and Lactobacillus acidophilus. VSL#3 and Escherichia coli Nissle 1917 are useful for the treatment of ulcerative colitis. Effective treatments for Crohn's disease include Lactobacillus rhamnosus GG (LGG) and Lactobacillus johnsonii LA1. Bifidobacterium infantis is given to patients with irritable bowel syndrome. For acute pancreatitis, Lactobacillus plantarum can be used orally. Treatments for necrotizing enterocolitis include Lactobacillus acidophilus and Bifidusbacterium species. The multiorgan dysfunction syndrome is treated with VSL (MODS). In cases of allergies, immunological reaction, and ventilator-associated pneumonia, Lactobacillus rhamnosus GG is administered. The International Scientific Association of Probiotics and Prebiotics (ISAPP), which states that a probiotic must be alive when supplied, have a health benefit, and be given at an effective dose, is the greatest source for this information [10]. Depending on the population of living things, different amounts of probiotic food and supplement should be taken. Daily dosing of 107 to 1011 live bacteria has been shown in clinical tests to have beneficial therapeutic effects. It is noteworthy to note that to maintain the same quantity of live bacteria in the lower intestine, in a dairy medium, 100 times fewer live bacteria must be given than in a freeze-dried supplement [11]. According to several studies, bacteria with a high propensity to survive in the upper GI tract can more easily pass through dairy [12].

2.4. Prebiotics. Prebiotics were initially introduced in 1995 by Gibson and Roberfroid. Prebiotics are "a non-digestive food component that benefits the host by specifically promoting the proliferation and/or activity of one or a restricted number of bacteria in the colon, and improves human health," according to their definition. The calorie content of the food or food item is not increased by probiotics. With regard to the "selectively fermented material that allows specific changes; both in the composition and/or activity in the gut microbiota that impart benefits onto host well-being and health," Gibson and Roberfroid proposed an alternative hypothesis [13, 14]. This definition, which also incorporates the prebiotic index definition, is compatible with the terms "prebiotic" and "bifidogenic". This definition states that in order to be accepted, proposed prebiotics must successfully complete the in vitro and in vivo tests listed below.

According to Anadón et al. [15], the inability to digest food is brought on by three factors:

(i) Low pH resistance to stomach acid

(ii) Fermentation by the intestinal microbiota and

(iii) Targeted stimulation of intestinal bacterial activity and growth

Prebiotics are nonviable food components that modify the gut flora for the advantage of the host, in accordance with FAO/WHO recommendations. Prebiotics and probiotics can function alone or in tandem. The different bacterial species and strains are impacted by diverse prebiotics. These nondigestible dietary supplements boost health by enhancing probiotics like Lactobacilli and Bifidobacteria in quantity and activity. Because the digestive enzymes cannot break down prebiotics while they are in the gut, they enter the large intestine intact. These give the probiotic bacteria that are already present in the stomach food. By encouraging the growth of helpful bacteria while inhibiting the growth of harmful (pathogenic) ones, effective prebiotics can change the composition of the gut microbiota. Prebiotics keep the colon's pH at the ideal level, which is necessary for probiotics to thrive. They promote the growth of the probiotics, which helps the immune system. They prevent the spread of germs and all of its negative effects. They increase peristalsis while reducing gas generation. Additionally, they encourage the beneficial microflora's expansion and procreation. These prebiotics serve as food for the probiotics. A dietary substrate needs to go through selective fermentation to see if it might be a prebiotic. Particularly, prebiotics change the microbiota in ways that are advantageous to the host's health. Prebiotics, like other low digestible carbohydrates that also have an osmotic effect in the GIT, increase intestinal gas production if they are digested by the natural flora at the place where they exert their prebiotic influence [16, 17]. Inulin and transgalactooligosaccharides are the two prebiotics that are most regularly employed (TOS). The most often utilised plant-based prebiotics as food supplements are inulin, fructo-oligosaccharides, lactulose, dietary fiber, and gums. Some naturally occurring foods that include these two include garlic, onions, leeks, shallots, asparagus, spinach, Jerusalem artichokes, chicory, peas, beans, lentils, oats, and bananas [6]. Oligosaccharide is one of the most well-known prebiotics. Additional prebiotics that are often employed include fructo-oligosaccharides (FOS), mannanoligosaccharides (MOS), inulin, lactulose,

and xylooligosaccharides (XOS). One of these is xylooligosaccharides, which are widely available.

2.5. Mechanism for Action. The GIT's gut bacteria are a component of an ecosystem. Bifidobacterium and Lactobacillus are two examples of helpful bacteria, whereas Salmonella species, Clostridium perfringens, Helicobacter pylori, etc. are instances of harmful bacteria. Prebiotics are dietary components that are either totally or only partially absorbed. They benefit the host by encouraging the growth of advantageous bacteria in the colon as opposed to dangerous ones. By boosting the amount of minerals in the colon, such as calcium and magnesium, creating short-chain fatty acids (SCFA) and lactic acid as a byproduct of fermentation, and supporting the host immune system (IgA production, cytokine regulation, etc.), prebiotics aid probiotic bacteria in growing [18]. The probiotic's mode of action may benefit from prebiotics. Lactobacilli and Bifidobacteria are the two probiotic species that have been used as prebiotic targets the most frequently to date. Their outstanding success in the probiotic sector provides compelling evidence in favour of this. Prebiotics can currently be added to a variety of foods, including dairy products, beverages, health drinks, spreads, infant formula and weaning foods, cereals, bakery goods, confections, chocolates, chewing gum, savoury goods, sauces, soups, dressings, meat products, dried instant foods, canned foods, food supplements, animal feeds, and pet foods [19].

2.6. Use as Medicine. Prebiotics primarily possess antibacterial, anticancer, and hypolipidemic characteristics; however, there is only weak evidence that they can be helpful for those who have diabetes [19]. It also modifies glucose levels and guards against osteoporosis. It works well for treating inflammatory bowel diseases as well as constipation. Through mineral absorption and mineral balance, it enhances mineral absorption in the colon and has advantageous effects on lipids. For a baby who is not getting mother's milk, supplemental infant formula is beneficial.

2.7. Synbiotics. Probiotics and prebiotics are both present in synbiotic products. This expression alludes to cooperation or synergy [20]. Gibson came up with the concept when considering the advantages of combining prebiotics and probiotics. He asserted that a probiotic and prebiotic taken separately might not be as effective at avoiding GIT disorders as the combination. As a result, synbiotics were created, in which the probiotic bacterium is assisted in surviving and growing by the prebiotic component. Prebiotics act as a source of nutrition for probiotics, allowing them to remain inside the GIT for longer than they otherwise could. This is supported by data indicating enhanced probiotic bacteria survival after passing through the upper digestive tract. Probiotics have been proven to be affected by H2O2, pH, organic acids, oxygen, moisture, and stress, especially in dairy products like yoghurt [21]. Additionally, synergism promotes the creation of probiotics and aids in the more successful colon implantation of live microbial dietary supplements. For the greatest probability of surviving in the GIT, a probiotic needs both food and a prebiotic fuel. Prebiotics must, however, particularly encourage the growth of probiotics rather than other bacteria for them to have a positive impact on human health. The most prevalent instance of a synbiotic is when FOS is combined with bacteria belonging to the genera Lactobacillus or Bifidobacterium (fructooligosaccharides).

2.8. Mechanism of Action. Probiotics are more effective when combined with synbiotics, which also offer some health benefits. Prebiotics boost the efficiency of probiotics when combined with probiotics, which control the metabolic activity in the intestine. Strong intestinal biostructure, a sizable population of beneficial bacteria, and the inability of prospective pathogens to proliferate in the digestive tract are all indications of this. Synbiotics reduce the number of unwanted metabolites while also rendering nitrosamines and cancer-causing substances inactive. Additionally, short-chain fatty acids, ketones, carbon disulfides, and methyl acetate levels are all greatly reduced by synbiotics, all of which are good for one's health [22]. These products halt intestinal breakdown processes such as diarrhoea and constipation.

2.9. Reactions to Drugs. For instance, synbiotics have anticancer, antiallergenic, and antidiarrhoeal characteristics and can act as antimicrobials in pyogenic inflammation. Additionally, they can be utilised to enhance immune system management, increase brain function, lower blood sugar and lipid levels, prevent osteoporosis, avoid nosocomial infections following surgery, and improve liver function in cirrhotic individuals. Science has previously provided evidence for these behaviours through testing. One study found that the liver creates and maintains hepatic triacylglycerols (IHTG), which encourages steatosis, when metabolic wastes such ethanol, SFCAs, and lipopolysaccharides (LPSs) translocate there (fatty liver). Adult subjects who received a synbiotic supplement containing inulin as a prebiotic and five probiotics—Lactobacillus plantarum, Lactobacillus delbrueckii spp. bulgaricus, Lactobacillus acidophilus, Lactobacillus rhamnosus, and Bifidobacterium bifidum—significantly lessened the severity of nonalcoholic steatohepatitis. Giving a probiotic supplement decreased the risk of getting sick (Lactobacillus casei, Lactobacillus rhamnosus, Streptococcus thermophilus, Bifidobacterium breve, Lactobacillus acidophilus, Bifidobacterium longum, prebiotics, probiotics, synbiotics, and its importance in the management of diseases). In nonalcoholic fatty liver disease, nuclear factor-B (NF-B) is either decreased or blocked, which causes the production of tumour necrosis factor (TNF-), which promotes insulin resistance and the absorption of inflammatory cells [20, 23].

2.10. Biotoxins May Be Present in Fermented Foods. Numerous studies have shown that food fermentation results in a wide variety of foods with positive dietary and health effects. Foods that have undergone a gradual, controlled microbial cultivation process and their enzymatic activity on uncooked substrates either from plant or animal sources are frequently referred to as fermented foods (Table 1) [24]. Aside from

Table 1: Fermented utilising a substrate comprised of both plant and animal sources.

Components used for fermentation	Fermented substrates sustaining growth and activity of cultures
Milk/cheese + cultures	Fermented dairy products
Vegetable + cultures	Fermented vegetable products
Cereals + cultures	Fermented cereal foods
Root vegetables + cultures	Fermented root crop foods
Legumes + cultures	Fermented legume foods
Meat + cultures	Fermented meat foods
Fruits + cultures	Fermented undistilled beverages
Fish + cultures	Fermented fish products

prebiotic fibers derived from grains, beans, vegetables, and specialised LAB strains that serve as fermenting bacteria, foods prepared with agricultural substrates from a variety of sources also contain these substances. Fresh vegetables are harder to digest than fermented leafy, tuber, and root vegetables. Microorganisms used in fermentation also contribute to increased food safety by acting in an allelopathic manner against dangerous bacteria and fungal contaminants. This helps to preserve food so that it can be stored. Organoleptic qualities, such as flavours, textures, and aromas, are added to foods created utilising microbial cultures [24]. A number of fermentation-process variables are changed to produce each unique sensory profile, including the development of specific microbe cultures, the use of raw fruits or vegetables, and the preservation of suitable environmental conditions during fermentation. Food fermentation substrates frequently include sizable levels of prebiotic carbohydrates. Other carbohydrates such as psyllium, galactomannan, arabino-OSs, lactose, and resistant starch can also have prebiotic effects [16]. IMOSs are well-known functional foods in Asia and are employed as prebiotics in the functional food markets of the United States and Europe [25]. Dietary fibers are prevalent in fermented foods manufactured from grains, beans, lentils, and vegetables [26] and support the growth of the intestinal bacteria required for fermentation. When taken, these medications have beneficial impacts on the gut flora. Another advantage is that fruits, vegetables, and legumes include fiber, which promotes the development of the bacteria that are present in food that has undergone fermentation [27, 28]. Probiotics can create metabolites that may serve as protective barriers for the gut by absorbing prebiotics from food during the course of their prolonged stay in the GIT. In a study, it was shown that inulin-type fructans, which are frequently found in fermented foods, cause specific alterations in the microbiota of the human gut [29]. The promotion of Bifidobacterium adolescentis and Faecalibacterium prausnitzii by the inulin present in plant materials used in fermentation has shown a nutraceutical benefit on the human gut microbiota [30]. The prebiotic qualities of these OSs have been corroborated by comparable in vitro experiments, where OSs produced from tapioca starch are routinely employed for food fermentation [31]. Foods that have been fermented utilising a substrate comprised of both plant and animal sources are displayed in Table 1 [32–35].

2.11. The Microbiome's Development. Vertical microbiota transmission through the placenta, amniotic fluid, and meconium causes it to first take shape [36–38]. According to two studies on animals, maternal stress during pregnancy reduces the Bifidobacterium community in the gut microbiota of fetuses [38, 39]. According to two separate researches, the distribution strategy affects both the initial microbiome and the gut microbiota. Children born vaginally have more germs in their intestines than babies born by cesarean section [36, 37]. The first week of life is when the very active process of gastric colonisation begins. This vital period of birth and GI development determines the immunity and health of newborns. Numerous stress-related illnesses, such as late-onset sepsis, cardiovascular disease, and atopic disease, have been linked to the underdevelopment of the microbiota during this time [40]. Early suppertime may also affect how the gut flora evolves. Studies have shown that breastfeeding affects IgA levels directly, the variety of Bifidobacterium species in the stomach, and IL-6 levels indirectly. In the intestines and other mucosal membranes, IgA, a sizable percentage of a secretory immunoglobulin, provides immunity. On the other hand, the proinflammatory cytokine IL-6 typically demonstrates both acute and chronic inflammation. Gamma-aminobutyric acid (GABA), an inhibitory modulator of several brain pathways, is produced in high quantities by the neonatal microbiome [41], which is primarily made up of the Lactobacillus genus and Bifidobacterium species. Breastmilk's ability to increase levels of IgA and Bifidobacterium species while lowering IL-6 levels and, consequently, inflammation makes older people less likely to suffer gastroenteritis. For the first four weeks of life, 13 infants who were exclusively breastfed had a lower total bacterial species count. [39] In addition to lactose, breast milk also contains more than a thousand other nondigestible substances in the form of oligosaccharides. According to [42] researchers, the nondigestible carbohydrates in breast milk are a crucial source of energy for bacterial fermentation [36]. In terms of health benefits, preterm infants who had been shown to have a unique bacterial makeup, predominating in proteobacteria rather than Bifidobacterium and Lactobacillus, responded to breast milk similarly. According to the finding that preterm neonates fed breast milk only showed an increase in Bifidobacterium, nondigestible carbohydrates in breast milk are likely to produce an environment that is better adapted for certain species [43]. Giving up nursing is the key diet change that leads to a microbiota that is more comparable to that of an adult. It has been suggested that the age at which a child is weaned is less important than the age at which they are weaned from breast milk to solid food because the microbiota growth patterns of children weaned from breast milk up to age four resembled those of children weaned at an earlier age [44]. The relationship between a person's diet and gut flora is critical throughout all stages of life. Dietary changes can drastically modify the makeup of the gut's bacterial flora in as little as 24 hours [43]. The

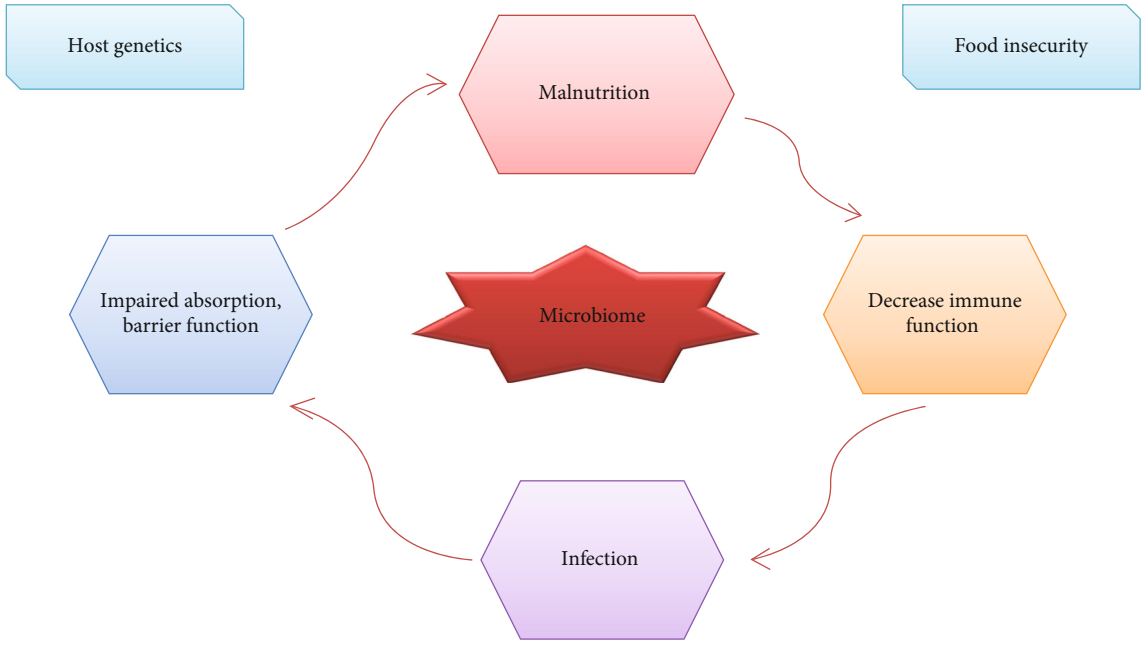

Figure 2: Childhood malnutrition and the intestinal microbiome.

equilibrium of bacteria returns if the meal change is merely transient. As long as all of the organisms that live in the gut have a symbiotic relationship, the human host can continue to function normally. The production of amino acids and vitamins, intestinal homeostasis, a healthy immune system, and a regular metabolism is all supported by symbiotic bacteria [37].

2.12. Lessons from Child Malnutrition. Through a number of mechanisms, such as the fermentation of nutritional components that would otherwise be indigestible, the de novo synthesis of micronutrients, the stimulation of hunger through interactions with the central nervous system, and the alteration of the host's nutrient assimilation and metabolism, gut microbes have an effect on the nutritional status of the host. Attempts to prevent or treat child malnutrition, one of the most important current global health challenges, could benefit from making use of this potential. Children who suffer from severe acute malnutrition usually develop their microbiotas more slowly and have less diversity in their microbial communities. (Figure 2) [45, 46].

Children's relative microbiota immaturity in Bangladesh [47] and Malawi reflects anthropometric measurements [48]. Mice that consume immature faeces from children who have the kwashiorkor virus lose more weight than mice that consume immature faeces from the disadvantaged child's healthy-weight sibling. There have not been any drugs created specifically to replace microbes or microbial services that are known to be absent in the relevant populations. Instead, the choice of drug was based on how each trial turned out. The next step is to select a medication that affects the microbiota in addition to targeting the microbiome [49].

In some parts of the world, it might not be the greatest idea to treat malnourished children with a single over-the-counter drug. Many of these issues may be resolved by concentrating on the gut microbiota and associated illnesses utilising locally developed nutritional approaches. The development and testing of therapeutic foods are described in a groundbreaking study that begins with the detection of bacteria that discriminate against age and growth in Bangladeshi children. Growing clinical evidence supports the effectiveness of drugs that target the microbiota. Future research will be required to identify the precise therapies that will be most helpful for the forthcoming wave of therapeutic refeeding initiatives. These medications must be produced in a manner that is resource-efficient, secure, and respectful to regional customs [50].

2.13. The Microbiota-Gut-Brain Axis. The gut-brain axis has been proven to be crucial for preserving homeostasis since the development of brain imaging in the 1980s, and [51] researchers now agree that this axis is bidirectional. Stomach distension activates crucial brain connections, but gastrointestinal disorders like irritable bowel syndrome also use these similar pathways (IBS). It has recently become evident that the gut microbiota regulates the gut-brain axis in an essential manner [52]. A number of animal models and studies on humans have been used to model the gut-brain axis [53].

3. The Role of Microbiota in the Evolution of Disease

A complex ecology made up of billions of bacteria is known as the microbiota. The majority of microbiota-related research today focuses on the connection between changes in microbiota composition, and various disease states as a result of enhanced sequencing techniques and analytics. Exogenous modifications to the microbiota population's homeostasis may be the cause of illnesses and the disruption of body functioning. A growing body of research suggests

that the microbiota may have a role in the development of CVDs, cancer, respiratory diseases, diabetes, IBD, brain disorders, chronic renal diseases, and liver problems. In this section, we largely concentrate on the bacterial component of the microbiota due to the paucity of information indicating the contribution of nonbacterial species to the genesis of disease [54].

3.1. Cardiovascular Issues. Cardiovascular diseases (CVDs) are the leading cause of morbidity and mortality worldwide. There is growing evidence that the microbiota may play a role in maintaining cardiovascular health. Research on microbiota transplantation, microbiota-dependent pathways, and downstream metabolites suggests that the microbiome may have an effect on the host's health [55].

3.1.1. Dental Bacteria. There is a link between periodontitis and atherosclerosis. Some bacteria have the ability to penetrate the endothelium and phagocytic cells in an atheroma, leading to pathogenic alterations and the appearance of the lesion. Intensive periodontal therapy can lower IL-6 and CRP levels as well as systolic blood pressure, lipid profiles, and other systemic inflammatory indicators [56–58].

3.1.2. Gut Microbiota. The dysbiosis of the human microbiota has an impact on several disorders (TMAO). TMAO has the ability to functionally activate the signalling pathways for nuclear factor-B (NF-B) and mitogen-activated protein kinase (MAPK). Patients with CVD have higher faecal LPS levels than those without CVD, according to Yoshida et al. The gut microbiota can transform proteins and polysaccharides into short-chain fatty acids (SCFAs), a different class of metabolites that have been linked to CVDs. Propionates are thought to regulate the balance between regulatory and effector T cells, which is crucial in preventing organ deterioration caused by hypertension [59, 60].

3.2. Cancer. Any organ in the body can be harmed by cancer, which is characterised by the unchecked and rapid proliferation of abnormal cells. The World Health Organization has classified over 100 compounds as human carcinogens, and it is anticipated that over 10 million people would die from cancer worldwide in 2020. [61] Gene changes that impact cell growth or metabolism are frequently responsible for the onset of cancer. Despite the complexity of carcinogenesis, the leading causes of cancer are tobacco, bacteria and viruses, obesity, alcohol, and radiation [62]. The identification of H. influenzae type b (H. influenzae) as a strong cancer-causing agent has brought about a significant increase in interest in the long-ignored role of microorganisms in cancer. It turns discovered that the microbiota significantly affects the development of cancer, primarily through influencing host metabolism, immune system activity, and the proliferation and demise of host cells. Pylori played a role in the rise of stomach cancer in 1994 [63].

3.2.1. The Oral Microbiota. Periodontitis has been linked to oral, gastric, pancreatic, oral, and genitourinary cancers. High antibody levels to P. gingivalis are associated with a twofold-increased risk of pancreatic cancer compared to low antibody levels. Oncogenes like Cyclin D-1 and c-Myc are more frequently created when the Wnt/catenin pathway is improperly activated. Furthermore, P. gingivalis may increase levels of cytokines including IL-8, TGF, and TNF, which may cause chronic inflammation [64, 65].

3.2.2. Respiratory Microbiota. Lung cancer patients had higher concentrations of Actinomyces, Veillonella, Streptococcus, Megasphaera, and Mycobacterium than did healthy controls [66]. In contrast, Peters et al. found no connection between the microbiome of tumour tissue and lung cancer recurrence [67].

3.2.3. Gut Microbiota. There is growing evidence that the gut flora may have an impact on the onset and progression of CRC. According to Grivennikov et al., microbial substances could weaken the epithelial barrier, which would then let the tumour to produce inflammation and promote the growth of CRC [68]. According to hypothesis, the gut microbiota may affect signalling pathways like E-cadherin/-catenin and TLR4/M to cause CRC. Dysbiosis of the gut flora is real, according to studies. B. faecalis coli and S. f. fragilis Bobo H., these microbes, have the ability to produce genotoxic substances such as nucleatum, pylori [69], colibactin, and B. Both the toxins produced by fragilis and typhoid damage the host's DNA, particularly intestinal F. Numerous CRC studies focused on nucleatum [70].

3.3. Diabetes Mellitus. Diabetes mellitus (DM) is a group of conditions that impact how the body manages glucose. The three kinds of DM are type 1 diabetes mellitus (T1DM), type 2 diabetes mellitus (T2DM), and gestational diabetes mellitus (GDM). T1DM, as opposed to T2DM, results from the body's autoimmune response to pancreatic cells, which explains why there is a problem with how well the body generates or uses insulin. One of the most prevalent pregnancy issues, GDM increases the chance that both the mother and the foetus will experience metabolic abnormalities. The relationship between dysbiosis in the microbiota and the onset of DM in relation to the microbiome has been the subject of numerous investigations.

3.3.1. Type 1 Diabetic Mellitus. The bacteria that generate SCFA butyrate, which is necessary for lowering chronic inflammation and maintaining intestinal homeostasis, may be present in reduced concentrations in T1DM patients. The majority of the study on the microbiome in T1DM was done using animal models; thus, more human studies are needed [71–73].

3.3.2. Type 2 Diabetic Mellitus. T2DM's onset has been linked to the gut microbiome. There may be underlying molecular mechanisms in the gut microbiota that affect inflammation, glucose metabolism, and gut permeability and cause T2DM. Antidiabetic medication has the ability to improve the diversity and richness of the gut flora [74].

3.3.3. The Oral Microbiota Might Affect T2DM. Many studies have shown that the oral microbiota of T2DM patients and healthy controls differs significantly. Xiao et al. found that

T2DM-related alterations to the oral microbiota and increased levels of the interleukin (IL)-17 were present. When transferred to GF mice, the changed oral microbiome is even more detrimental, demonstrating how DM can make periodontal disease worse. The microbiota in the gut can be impacted by bacteria from the mouth, which could also have an impact on the immune system [75].

3.3.4. Gestational Diabetes. Numerous studies have demonstrated that the gut microbiota during pregnancy contributes to GDM's inflammatory state and insulin resistance. The development of GDM may also be affected by major changes in the gut flora that occur during pregnancy. Women with GDM usually have metabolic abnormalities include increased insulin resistance and downregulated insulin production [76]. It was demonstrated that the Firmicutes to Bacteroidetes ratio, a critical factor that encourages obesity and exacerbates GDM, was elevated in GDM patients. From the first to the third trimesters, the gut microbiota changed, becoming more diverse and less rich, according to Romano-Keeler and Weitkamp. [77]. The gut microbiota may be important in the development of GDM and may also have an impact on GDM infants, claimed by Ponzo et al. [78] who found that proinflammatory bacterial abundance was higher in GDM newborns than in healthy controls. Other studies supported the result that the gut microbiota of the GDM infants included more proinflammatory bacteria than healthy controls [79].

3.4. Respiratory Conditions. Pneumonia, pulmonary fibrosis, asthma, and chronic obstructive pulmonary disease are a few chronic conditions that affect the lungs and other parts of the respiratory system (COPD). The start of respiratory infections may be influenced by oral, lung, and intestinal bacteria, according to numerous researches. This section will discuss the most important research relating the microbiome to the emergence of respiratory illnesses.

3.4.1. Chronic Respiratory Disease. There is growing evidence that the lung microbiome may play a direct role in the development of chronic respiratory diseases. Atypical fungal patterns [80], higher bacterial loads and diversity, increased Proteobacteria abundance, decreased Bacteroidetes and Firmicutes abundance, and increased Proteobacteria abundance are all observed in the sputum samples of asthma patients [81]. Children with high SCFA levels are less likely to develop asthma as adults. Chronic respiratory conditions may be influenced by the aspiration and systemic inflammation brought on by oral bacteria. Periodontitis is linked to higher levels of CRP and IL-6 [82], two indicators of systemic inflammation [83].

3.4.2. Gut Microbiota. It can induce a number of inflammation-related illnesses since it is a potent proinflammatory and autoimmune response modulator. Numerous studies have linked the gut-lung axis, commonly known as dysbiosis of the gut microbiota, to a higher chance of developing asthma in later life. The gut-lung axis has been carefully studied and analyzed in chronic respiratory diseases. It is believed that dysbiosis of the gut microbiome throughout adolescence may result in the emergence of respiratory disorders since gut microbiota is essential for immune cell maturation and pathogen resistance. [84–86] Sokolowska et al., Roussos et al., and Rutten et al. demonstrated that people with chronic GI illnesses had a higher prevalence of chronic respiratory diseases including asthma and COPD, despite the fact that the precise causes are still unknown. Individuals with acute COPD exacerbations demonstrated increased GI permeability, which may suggest that the gut microbiota is implicated in exacerbations, according to Sprooten et al. [87]. Another study discovered that in COPD patients, greater levels of gut microbiota-dependent circulating TMAO were associated with all-cause mortality [88]. According to Arrieta et al. [89], Veillonella, Faecalibacterium, and Lachnospira were demonstrated to be much less prevalent in infants at risk of developing asthma. Asthma may be influenced by the immune regulation brought on by gut bacterial metabolites, according to a theory. For instance, children with high amounts of SCFAs are less likely to develop asthma in the future, per a 2019 study by Roduit et al. [90]. SCFAs have been discovered to reduce inflammation in allergic asthma models and to promote the formation of peripheral regulatory T cells, according to Arpaia et al. and Cait et al. [91, 92]. In addition to bacterial metabolites, abnormally homing lymphocytes can also contribute to asthma [93]. Under normal circumstances, lymphocytes are thought to exhibit tissue specificity to the site where they initially come into contact with the antigen. IBD patients' intestinal lymphocytes may be to blame for the appearance of inflammation in organs other than the gut despite their recognised lack of tissue specificity. Innate lymphocytes were drawn from the stomach to the lungs in response to IL-25's proinflammatory signals, according to the research of Huang et al. [94]. The gut-lung axis may interact in both directions, according to some research, which is interesting to note. Perrone et al. [95] found that pneumonia reduced intestinal epithelial proliferation and caused intestinal epithelial apoptosis in mice [96].

3.4.3. Oral Microbiota. Due to the contiguous anatomic structure and microaspiration, it has been linked to chronic respiratory illnesses [97]. The nasal microbiota and lung microbiota have more differences than the oral and lung microbiome, according to early investigations [98]. Through aspiration and systemic inflammation, it is postulated that the oral microbiota may contribute to chronic respiratory illnesses. It is likely that aspiration of oral bacteria into the lungs causes dysbiosis and inflammation of the lung microbiota. The abundance of oral bacteria Veillonella and Prevotella in bronchoalveolar lavage samples has been linked to subclinical inflammation, which is characterised by elevated neutrophils and lymphocytes, according to Segal et al. [99]. Fusobacterium and Porphyromonas, two periodontal pathogens, were specifically elevated in the bronchial microbiome of asthmatic individuals, according to an RCT [100]. Numerous inflammatory cytokines linked to periodontitis have also been found in chronic respiratory illnesses. TNF- was shown to be elevated in the sputum of COPD patients, according to Aaron et al. Significant research has

demonstrated that TNF- may promote the production of ROS in pulmonary tissues, along with the production of other adhesive and proinflammatory molecules such VCAM-1, ICAM-1, and RAGE. TNF- is thought to play a role in asthma as an inflammatory cytokine that attracts neutrophils and eosinophils [101]. High levels of CRP and IL-6, two markers of systemic inflammation, are associated with periodontitis. According to Thomas, there is a substantial correlation between CRP levels and the prevalence of asthma [102]. The oral-lung axis, however, still needs to be better understood and calls for additional research.

3.4.4. Pneumonia. By inhibiting the colonisation of harmful bacteria and controlling immune reactions, the normal respiratory tract and gut microbiota guard against pneumonia. The fact that dysbiosis of the respiratory tract microbiota is regarded as a risk factor for pneumonia is therefore not surprising. The primary source of microorganisms for the lower airways is the upper airways. Recent studies have demonstrated that pneumonia risk increased as nasal microbiota diversity decreased. Pneumonia was specifically substantially related with three microbiota profiles dominated by Lactobacilli, Rothia, and Streptococcus [103]. S. pneumonia, H. influenzae, and M. catarrhalis colonisation of the airways with pathogenic bacteria in newborns was linked to an increased risk of pneumonia and bronchiolitis [104]. Studies on the lower airway microbiome revealed that Prevotella and Veillonella, which are more prevalent, made HIV patients more susceptible to pneumonia. Additionally, pneumonia risk may rise as a result of altered immunological response brought on by microbial dysbiosis. For instance, deregulation of bacteria that produce SCFA may have a role in the emergence of pneumonia. According to Vissing et al. [105], elevated anaerobic bacteria were associated with lung SCFA levels. In fact, through inhibiting the IFN- and IL-17A pathways, SCFAs directly limit immunological response. Neutrophils quickly go to lung parenchyma and alveoli after bacterial infection. IFN- levels are crucial for host defense during pneumonia because the IFN- produced by neutrophils controls bacterial clearance [106]. Similar to this, Th17 cells and their specific IL-17A signalling are required for the immune response to pneumonia. By acting on non-immune cells during infection to trigger the synthesis of antimicrobial proteins, cytokines, and chemokines, IL-17A increases innate immunity during microbial infection. Inhibition of the IFN- and IL-17A pathways encourages lung bacterial growth and worsens inflammation. Salk et al. discovered a strong relationship between influenzae-specific lgA production and levels of Lactobacillus, Prevotella, Veillonella, Bacteroide, and Streptococcus [107]. Intriguing new findings suggest that commensal microbes may play a crucial role in the development of pneumonia. Studies on respiratory illnesses, particularly the global pandemic COVID-19, have increased in recent years. Microbial dysbiosis has been associated to COVID-19 mortality in recent studies. Fan et al. [108] investigated the lung microbiota characteristics of 20 deceased COVID-19 patients. Acinetobacter species, which are connected to mortality and antibiotic resistance, are thought to be an indicator of the dysbiosis of the lung microbiota. In addition, the most common fungus in the lung is more prevalent, and COVID-19 may result in significant dysbiosis of the lung microbiota, according to Han et al. [109]. Segal et al. [99] found a connection between microbiota in health and diseases and the enrichment of lower airways with oral bacteria Mycoplasma salivarium. According to Han et al., 13 signal transduction and targeted therapy had a subpar clinical outcome (7 : 135). However, there was insufficient proof to prove a connection between secondary respiratory infections and increased mortality. The gut microbiota is an additional crucial subject to discuss when looking at how bacteria and pneumonia interact. According to Schuijt et al. [110], the gut microbiota guards against S. pneumoniae infection. In comparison to the control group, S. pneumoniae infection in gut microbiota-deficient C57BL/6 mice resulted in greater bacterial dissemination, inflammation, organ damage, and mortality. The loss of gut microbiota was also associated with the activation of metabolic pathways, which leads in lower reactivity to inflammatory cytokines. To illustrate this, Felix et al. [111] showed how segmented filamentous commensal gut bacteria protected immunodeficient mice from S. pneumoniae infection. It appears likely that the bacteria promoted a shift in the lung's neutrophil phenotype from proinflammatory to proresolution, which is comparable to the effect of treatment with heat-inactivated S. pneumoniae. According to recent research, the gut flora of COVID-19 patients may indicate how serious the condition is [112]. In contrast to chronic respiratory disorders, the gut-lung axis may therefore enhance the host's defenses against pneumonia by controlling the immunological response.

3.4.5. Irritable Bowel Syndrome. In ulcerative colitis, the colon is constantly, extensively, and superficially inflamed (UC) [113]. Crohn's disease is characterised by discontinuous, transmural lesions that affect various areas of the GI tract (CD). IBD onset is influenced by both genetic and immunological dysregulation variables [114]. The oral-gut axis refers to the intimate connections between oral microorganisms and those in the GI tract. Although viruses and fungi may also be implicated in IBD, there has not been any proof of a connection to date. Research has revealed a link between IBD and oral diseases, even if the precise mechanisms are still not fully understood [115].

3.5. Brain Disorders. It was well recognised that some comorbidities, like neuropsychiatric and neurodegenerative brain illnesses, greatly raised mortality rates in a number of population categories. In several researches over the years, it has been shown that microbial diversity influences brain illnesses by changing the risk variables involved in their development. For instance, the findings of a meta-analysis study [116] show that depression raises the relative risk of mortality from all causes, and more precisely, that risk is 1.86 times higher in depressed patients than in nondepressed individuals. Depression has also been connected to HPA axis stimulation and inflammation brought on by the microbiota [117].

3.5.1. Gut Microbiota. In a number of animal models, preclinical research has demonstrated that the gut microbiome influences social interactions, repetitive behaviour, and cognitive function [118]. One possible idea describing how the gut microbiota influences neurological illnesses is stress-induced intestinal permeability, which permits endotoxins to enter the circulation. Major depressive disorder patients have lower levels of Firmicutes and higher levels of Bacteroidetes, Protobacteria, and Actinobacteria in their faeces when compared to healthy controls, according to new research by Jiang et al. [119]. The phylum Firmicutes includes two families, Lachnospiraceae and Ruminococcaceae, whose expression has been seen to decline and is thought to be related to several bacterial genera. The makeup of the gut microbiota, which is believed to have a large impact on the stress-regulated HPA axis pathway, is known to have a significant impact on both of the major brain illnesses, anxiety, and depression [120]. The gene expression of GF mice differs dramatically from that of control mice, according to an epigenetic study using GF animal models. Numerous studies have examined the notable differences seen in GF mice compared to the wild-type controls after this first discovery. While levels of neurotransmitters including norepinephrine, dopamine, and serotonin were discovered to be higher in the striatum of GF rats, dopaminergic turnover was found to be lower in the frontal cortex, striatum, and hippocampus of GF rats. Additional research using GF mouse models has shown a decrease in brain-derived neurotropic factor and nerve growth factor-inducible protein A in various brain regions [121].

3.5.2. Neurological Conditions. A number of neurological diseases, including Alzheimer's disease (AD), cerebrovascular stroke (CVS), Parkinson's disease (PD), and schizophrenia, among others, have been linked to the development of gut bacteria. Through regulating the host's innate immunity, gut bacteria have been demonstrated to play a role in the regulation of brain function [122]. Additionally, it is shown that the composition of the community differs according on the mode of delivery. Infants delivered vaginally are more diversified and have bacteria from the mother's genital tract that colonised them than children delivered via cesarean section [123]. Cesarean births resulted in less brain electrical activity, which is in line with in vivo studies on rats that revealed prepubertal abnormalities in the development of the cortex and hippocampus [124]. When presymptomatic PD is present, a study that used 16 s rRNA sequencing looked at 38 samples of human faeces. The findings revealed significant variations in the bacterial composition, with decreased Blautia, Faecalibacterium, and Ruminococcus and increased Escherichia and Streptococcus amyloid plaques and intracellular neurofibrillary tangles made of tau serving as the hallmarks of AD's pathological characteristics (NFT). The microbiomes of AD patients were substantially less varied than those of healthy controls, according to a research by Hung et al. [125]. Firmicutes, Bifidobacterium, Actinobacteria (a Bifidobacterium member), Bacteroidetes, and Proteobacteria were found to be decreased and elevated, respectively, in the AD group, according to this study [126]. Another preclinical investigation using mice revealed that Prevotellaceae and Peptococcaceae, the former of which is an essential part of the cecal microbiota, had undergone a significant alteration.

3.5.3. Neurological Issues Brought on by Mouth and Lungs Bacteria. Studies by Hicks et al. suggest that poor dental hygiene may influence the growth of complex communities on the tongue, below the gum line, and on the surface of teeth [127]. Analysis of the salivary microbiomes of these children has revealed significant differences between children with ASD, children who are developing normally, and children who do not have developmental abnormalities. Saliva from AD patients had decreased relative abundances of Rothia and higher relative abundances of Moraxella, Leptotrichia, and Sphaerochaeta when compared to healthy controls. This data demonstrates that AD patients may have higher rates of these illnesses than healthy people. Despite the extensive study being done on the affinity of microbial dysbiosis in many neurological illnesses, there is still no gold standard to link the changes in the microbial environment with the aetiology of these disorders. Mild cognitive impairment was shown to be associated with Pasteurellaceae and Lautropia mirabilis in a cohort study of 68 people, comprising AD and control groups [128]. To comprehend the breadth and complexity of the association between the microbiome and the emergence of a number of brain disorders, further preclinical and clinical studies with a microbiome focus are necessary.

3.6. Chronic Kidney Issues. The physiological signs of chronic kidney disease (CKD), which affects roughly 9% of the world's population, include a decrease in glomerular filtration rate (GFR) of less than 60 ml/min per 1.73 m2 or the presence of albuminuria for at least three months [129]. Renal function gradually deteriorating over time and permanent structural changes to the kidneys are the key symptoms of CKD [130].

3.6.1. Communication between the Gut Microbiota and the Renal Axis. Recently, there has been a lot of interest in the function of oral microbiome in mediating chronic systemic inflammatory dysregulation [131]. For their part in the onset of CKD, variations in microbial ecosystems have been the subject of much research. It has been established that kidney disease (CKD) is indirectly influenced by periodontitis, which modifies the oral microbiome by increasing systemic inflammation [132]. In human investigations employing biomarkers, elevated IgG levels brought on by the presence of periodontal pathogen species such as P. gingivalis, T. S. denticola, A. noxia actinomycetemcomitans, and V. parvula have been related to deteriorated kidney function. The death rate rose from 32% to 41% in CKD patients with periodontitis, according to a substantial 10-year cohort study. This is consistent with the findings of Bastos et al. [133] that pathogens such as Candida albicans, P. gingivalis, T. t., and forsythia are more common. To establish with certainty how the oral microbiota influences the onset of CKD, more information is required. In CKD patients, denticola was

discovered to be related to the onset of chronic periodontitis, demonstrating a two-way interaction between CKD and modifications in the oral microbiota. Interdependence between metabolic and immunological pathways is necessary for the gut-kidney axis to function properly [130]. The metabolic pathway is mainly focused on gut microbiota-produced compounds that mediate host physiological processes, whereas the immunological pathway depends on a variety of additional elements, such as monocytes, lymphocytes, and cytokines, which promote communication between the gut and kidney. Recently, the microbial ecology of the stomach has been connected to dysbiosis. According to a research by Vaziri et al. [134], uremic toxins and inflammation play significant roles in the development of CKD and its accompanying consequences. R. gnavus Torus is more prevalent in patients with CKD [135]. Patients with ESRD were shown to have higher prevalences of Actinobacteria, Proteobacteria, and Firmicutes than the control group. These results offer compelling proof that microbial dysbiosis mediates a variety of disruptions in the gut-renal system connection that contribute to the pathophysiology and progression of kidney diseases. Intestinal dysbiosis and intestinal barrier failure are related to uremia. Lower levels of two nephroprotective microbiome metabolites, butyrate, and vitamin K were found [136].

3.7. Chronic Liver Problems. One of the main causes of disease and mortality worldwide continues to be liver issues. The two most common chronic liver diseases that commonly result in liver cirrhosis and malignancy are alcoholic liver disease (ALD) and nonalcoholic fatty liver disease (NAFLD/NASH). Several liver conditions, such as benign steatosis and steatohepatitis that cause hepatocellular inflammation and damage, are included in NAFLD. [137] According to recent research, chronic liver problems may be influenced by the oral and intestinal microbiota. ALD may appear as a chronic disorder (steatosis and steatohepatitis) [138].

3.7.1. Diseases of the Liver and the Gut's Microbiota. The gut microbiota is essential for the metabolism of bile acids and may play a role in liver diseases. People with NASH exhibit higher levels of Lactobacillus, Parabacteroides, and Allisonella in their faeces compared to healthy controls, while having lower levels of Bacteroidetes [139]. By regulating chronic inflammation and immunological activation in the gut flora, many diseases can be avoided or postponed. Choline depletion and liver problems can be explained by a number of established pathways. The information that is now available suggests that gut microbiota may be important in liver diseases, but further research is required to establish a causal relationship [140].

3.7.2. Hepatitis and Oral Bacteria. As shown in a number of disorders, it has been proven that oral bacteria or their metabolites can move to other parts of the body. In a mouse model, P. gingivalis, one of the most common periodontal disorders, may have an impact on how NAFLD/NASH develops, according to Yoneda et al. [141]. Additionally, they found that compared to controls, NAFLD patients had a higher prevalence of P. gingivalis infection. Although there is no proven connection between periodontal and liver problems, current research suggests that periodontal bacteria may play a role in the emergence of NAFLD, NASH, and liver disease. Additionally, clinical evidence suggests that periodontitis may aid in the emergence of NAFLD/NASH [142].

Numerous mechanisms, such as oxidative stress, pathogen invasion, and proinflammatory mediators, help to support this process in the movement of periodontal bacteria and their metabolites into the systemic circulation [143]. Silva may occur in a gut with low intestinal permeability, according to Acharya et al. [144] and Santos et al. [145]. Cirrhotic people also exhibit petechiae, candidiasis, and xerostomia in addition to periodontitis. The development of oral illnesses in cirrhotic patients has also been linked to dysbiosis of the oral microbiota. This means that when bacteria and their waste products enter the bloodstream, they can penetrate and contribute to the dysbiosis of the gut microbiota, which ultimately assists in the development of liver diseases. HBV-associated oral pathogens such as Fusobacterium, Eubacterium, and Treponema can migrate to the liver and bind to innate T. [146].

4. Conclusion

Probiotics, prebiotics, and synbiotic supplements all support the eubiosis of the gut microflora. They greatly contribute to improving the host person's health by modifying gut pH, combating pathogens by creating antimicrobial chemicals, competing for pathogen binding and receptor sites, and activating immunomodulatory cells. For the probiotic to develop in the GIT, it needs both food and prebiotic fuel. Synbiotic usage of prebiotics and probiotics increases their impact on the host cell. The effects of probiotics, prebiotics, and synbiotics on conditions like diabetes, dyslipidemia, cardiovascular problems, hypertension, and cancer have been the subject of several studies up to this point. A fuller understanding of their role in these sickness states is needed to build a treatment that solely depends on food change. Hippocrates is reputed to have remarked, "Let food be thy medicine and medicine be thy food."

Conflicts of Interest

The authors declare that they have no conflicts of interest.

References

[1] G. Berg, D. Rybakova, D. Fischer et al., "Microbiome definition re-visited: old concepts and new challenges," *Microbiome*, vol. 8, no. 1, pp. 1–22, 2020.

[2] A. B. Shreiner, J. Y. Kao, and V. B. Young, "The gut microbiome in health and in disease," *Current Opinion In Gastroenterology*, vol. 31, no. 1, pp. 69–75, 2015.

[3] L. Laterza, G. Rizzatti, E. Gaetani, P. Chiusolo, and A. Gasbarrini, "The gut microbiota and immune system relationship in human graft-versus-host disease," *Mediterranean*

Journal Of Hematology And Infectious Diseases, vol. 8, no. 1, 2015.

[4] T. A. Auchtung, T. Y. Fofanova, C. J. Stewart et al., "Investigating colonization of the healthy adult gastrointestinal tract by fungi," *MSphere*, vol. 3, no. 2, article e00092, p. 18, 2018.

[5] R. P. Dickson and G. B. Huffnagle, "The lung microbiome: new principles for respiratory bacteriology in health and disease," *PLoS Pathogens*, vol. 11, no. 7, article e1004923, 2015.

[6] B. Bandyopadhyay and N. C. Mandal, "Probiotics, prebiotics and synbiotics-in health improvement by modulating gut microbiota: the concept revisited," *International Journal of Current Microbiology and Applied Sciences*, vol. 3, no. 3, pp. 410–420, 2014.

[7] R. Fuller and R. Fuller, "History and development of probiotics. InProbiotics," in *Probiotics*, pp. 1–8, Springer, 1992.

[8] P. Markowiak and K. Śliżewska, "Effects of probiotics, prebiotics, and synbiotics on human health," *Nutrients*, vol. 9, no. 9, pp. 1021–1051, 2017.

[9] A. Khalighi, R. Behdani, and S. Kouhestani, "Probiotics: a comprehensive review of their classification, mode of action and role in human nutrition," *Probiotics And Prebiotics In Human Nutrition And Health*, vol. 13, no. 10, p. 63646, 2016.

[10] C. Hill, F. Guarner, G. Reid et al., "The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic," *Nature Reviews Gastroenterology & Hepatology*, vol. 11, no. 8, pp. 506–514, 2014.

[11] N. J. Shah and O. C. Swami, "Role of probiotics in diabetes: a review of their rationale and efficacy," *Diabetes*, vol. 5, pp. 104–110, 2017.

[12] K. Kailasapathy and J. Chin, "Survival and therapeutic potential of probiotic organisms with reference to Lactobacillus acidophilus and Bifidobacterium spp," *Immunology And Cell Biology*, vol. 78, no. 1, pp. 80–88, 2000.

[13] G. R. Gibson, H. M. Probert, J. Van Loo, R. A. Rastall, and M. B. Roberfroid, "Dietary modulation of the human colonic microbiota: updating the concept of prebiotics," *Nutrition Research Reviews*, vol. 17, no. 2, pp. 259–275, 2004.

[14] M. Roberfroid, "Prebiotics: the concept revisited," *The Journal Of Nutrition*, vol. 137, no. 3, pp. 830S–837S, 2007.

[15] A. Anadón, M. R. Martínez-Larrañaga, I. Arés, and M. A. Martínez, "Prebiotics and probiotics: an assessment of their safety and health benefits," *Probiotics, Prebiotics, and Synbiotics*, vol. 1, p. 3, 2016.

[16] J. Slavin, "Fiber and prebiotics: mechanisms and health benefits," *Nutrients*, vol. 5, no. 4, pp. 1417–1435, 2013.

[17] J. Schrezenmeir and M. de Vrese, "Probiotics, prebiotics, and synbiotics—approaching a definition," *The American Journal of Clinical Nutrition*, vol. 73, no. 2, pp. 361s–364s, 2001.

[18] R. Nagpal, A. Kumar, M. Kumar, P. V. Behare, S. Jain, and H. Yadav, "Probiotics, their health benefits and applications for developing healthier foods: a review," *Fems Microbiology Letters*, vol. 334, no. 1, pp. 1–15, 2012.

[19] M. B. Roberfroid, F. Bornet, C. E. Bouley, and J. H. Cummings, "Colonic microflora: nutrition and health. Summary and conclusions of an International Life Sciences Institute (ILSI)[Europe] workshop held in Barcelona, Spain," *Nutrition Reviews*, vol. 53, no. 5, pp. 127–130, 1995.

[20] P. Markowiak-Kopeć and K. Śliżewska, "The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome," *Nutrients*, vol. 12, no. 4, p. 1107, 2020.

[21] K. Pandey, S. Naik, and B. Vakil, "Probiotics, prebiotics and synbiotics-a review," *Journal Of Food Science And Technology*, vol. 52, no. 12, pp. 7577–7587, 2015.

[22] A. N. Alamgir and A. N. M. Alamgir, "Vitamins, nutraceuticals, food additives, enzymes, anesthetic aids, and cosmetics," in *Therapeutic Use Of Medicinal Plants And Their Extracts: Volume 2*, vol. 74, pp. 407–534, Springer, 2018.

[23] S. Palai, C. M. Derecho, S. S. Kesh, C. Egbuna, and P. C. Onyeike, "Prebiotics, probiotics, synbiotics and its importance in the management of diseases," in *Functional Foods and Nutraceuticals: Bioactive Components, Formulations and Innovations*, pp. 173–196, Springer, 2020.

[24] J. P. Tamang, P. D. Cotter, A. Endo et al., "Fermented foods in a global age: east meets west," *Comprehensive Reviews in Food Science and Food Safety*, vol. 19, no. 1, pp. 184–217, 2020.

[25] D. Goffin, N. Delzenne, C. Blecker, E. Hanon, C. Deroanne, and M. Paquot, "Will isomalto-oligosaccharides, a well-established functional food in Asia, break through the European and American market? The status of knowledge on these prebiotics," *Critical Reviews In Food Science And Nutrition*, vol. 51, no. 5, pp. 394–409, 2011.

[26] Y. Brummer, M. Kaviani, and S. M. Tosh, "Structural and functional characteristics of dietary fibre in beans, lentils, peas and chickpeas," *Food Research International*, vol. 67, no. 67, pp. 117–125, 2015.

[27] S. Pathania and N. Kaur, "Utilization of fruits and vegetable by-products for isolation of dietary fibres and its potential application as functional ingredients," *Bioactive Carbohydrates and Dietary Fibre*, vol. 27, no. 27, article 100295, 2022.

[28] H. F. Zahid, C. S. Ranadheera, Z. Fang, and S. Ajlouni, "Utilization of mango, apple and banana fruit peels as prebiotics and functional ingredients," *Agriculture*, vol. 11, no. 7, p. 584, 2021.

[29] D. Vandeputte, G. Falony, S. Vieira-Silva et al., "Prebiotic inulin-type fructans induce specific changes in the human gut microbiota," *Gut*, vol. 66, no. 11, pp. 1968–1974, 2017.

[30] C. Ramirez-Farias, K. Slezak, Z. Fuller, A. Duncan, G. Holtrop, and P. Louis, "Effect of inulin on the human gut microbiota: stimulation of Bifidobacterium adolescentis and Faecalibacterium prausnitzii," *British Journal of Nutrition*, vol. 101, no. 4, pp. 541–550, 2009.

[31] J. Kaulpiboon, P. Rudeekulthamrong, S. Watanasatitarpa, K. Ito, and P. Pongsawasdi, "Synthesis of long-chain isomaltooligosaccharides from tapioca starch and an _in vitro_ investigation of their prebiotic properties," *Journal of Molecular Catalysis B: Enzymatic*, vol. 120, pp. 127–135, 2015.

[32] L. A. Bosnea, T. Moschakis, P. S. Nigam, and C. G. Biliaderis, "Growth adaptation of probiotics in biopolymer-based coacervate structures to enhance cell viability," *LWT*, vol. 77, no. 77, pp. 282–289, 2017.

[33] A. Terpou, P. S. Nigam, L. Bosnea, and M. Kanellaki, "Evaluation of Chios mastic gum as antimicrobial agent and matrix forming material targeting probiotic cell encapsulation for functional fermented milk production," *LWT*, vol. 97, pp. 109–116, 2018.

[34] V. Schoina, A. Terpou, L. Bosnea, M. Kanellaki, and P. S. Nigam, "Entrapment of _Lactobacillus casei_ ATCC393 in the viscus matrix of _Pistacia terebinthus_ resin for

functional myzithra cheese manufacture," *LWT*, vol. 89, pp. 441–448, 2018.

[35] A. Terpou, A. Bekatorou, M. Kanellaki, A. A. Koutinas, and P. Nigam, "Enhanced probiotic viability and aromatic profile of yogurts produced using wheat bran (Triticum aestivum)_ as cell immobilization carrier," *Process Biochemistry*, vol. 55, pp. 1–10, 2017.

[36] E. C. Gritz and V. Bhandari, "The human neonatal gut microbiome: a brief review," *Frontiers In Pediatrics*, vol. 3, p. 17, 2015.

[37] O. Goulet, "Potential role of the intestinal microbiota in programming health and disease: figure 1," *Nutrition Reviews*, vol. 73, supplement 1, pp. 32–40, 2015.

[38] T. L. Gur, L. Shay, A. V. Palkar et al., "Prenatal stress affects placental cytokines and neurotrophins, commensal microbes, and anxiety-like behavior in adult female offspring," *Brain, Behavior, And Immunity*, vol. 64, pp. 50–58, 2017.

[39] K. Patel, K. Konduru, A. K. Patra, D. S. Chandel, and P. Panigrahi, "Trends and determinants of gastric bacterial colonization of preterm neonates in a NICU setting," *PLoS One*, vol. 10, no. 7, article e0114664, 2015.

[40] V. Mai, Q. M. McCrary, R. Sinha, and M. Glei, "Associations between dietary habits and body mass index with gut microbiota composition and fecal water genotoxicity: an observational study in African American and Caucasian American volunteers," *Nutrition Journal*, vol. 8, no. 1, 2009.

[41] E. Barrett, C. Kerr, K. Murphy et al., "The individual-specific and diverse nature of the preterm infant microbiota," *Archives of Disease in Childhood-Fetal and Neonatal Edition*, vol. 98, no. 4, pp. F334–F340, 2013.

[42] R. Oozeer, K. Van Limpt, T. Ludwig et al., "Intestinal microbiology in early life: specific prebiotics can have similar functionalities as human-milk oligosaccharides," *The American Journal Of Clinical Nutrition.*, vol. 98, no. 2, pp. 561S–571S, 2013.

[43] M. L. Wright and A. R. Starkweather, "Antenatal microbiome," *Nursing Research*, vol. 64, no. 4, pp. 306–319, 2015.

[44] F. Bäckhed, J. Roswall, Y. Peng et al., "Dynamics and stabilization of the human gut microbiome during the first year of life," *Cell Host & Microbe*, vol. 17, no. 5, pp. 690–703, 2015.

[45] H. Plovier, A. Everard, C. Druart et al., "A purified membrane protein from _Akkermansia muciniphila_ or the pasteurized bacterium improves metabolism in obese and diabetic mice," *Nature Medicine*, vol. 23, no. 1, pp. 107–113, 2017.

[46] H. Velly, R. A. Britton, and G. A. Preidis, "Mechanisms of cross-talk between the diet, the intestinal microbiome, and the undernourished host," *Gut Microbes*, vol. 8, no. 2, pp. 98–112, 2017.

[47] S. Subramanian, S. Huq, T. Yatsunenko et al., "Persistent gut microbiota immaturity in malnourished Bangladeshi children," *Nature*, vol. 510, no. 7505, pp. 417–421, 2014.

[48] L. V. Blanton, M. R. Charbonneau, T. Salih et al., "Gut bacteria that prevent growth impairments transmitted by microbiota from malnourished children," *Science*, vol. 351, no. 6275, 2016.

[49] L. E. Zambrana, S. McKeen, H. Ibrahim et al., "Rice bran supplementation modulates growth, microbiota and metabolome in weaning infants: a clinical trial in Nicaragua and Mali," *Scientific Reports*, vol. 9, no. 1, pp. 1–8, 2019.

[50] C. M. Stark, A. Susi, J. Emerick, and C. M. Nylund, "Antibiotic and acid-suppression medications during early childhood are associated with obesity," *Gut*, vol. 68, no. 1, pp. 62–69, 2019.

[51] J. F. Cryan, K. J. O'Riordan, C. S. Cowan et al., "The microbiota-gut-brain axis," *Physiological Reviews*, vol. 99, 2019.

[52] B. P. Chumpitazi and R. J. Shulman, "Underlying molecular and cellular mechanisms in childhood irritable bowel syndrome," *Molecular And Cellular Pediatrics*, vol. 3, no. 1, pp. 1–9, 2016.

[53] K. Chen, X. Luan, Q. Liu et al., "Drosophila histone demethylase KDM5 regulates social behavior through immune control and gut microbiota maintenance," *Cell Host & Microbe*, vol. 25, no. 4, pp. 537–552, 2019.

[54] K. Lau, V. Srivatsav, A. Rizwan et al., "Bridging the gap between gut microbial dysbiosis and cardiovascular diseases," *Nutrients*, vol. 9, no. 8, p. 859, 2017.

[55] E. Sanchez-Rodriguez, A. Egea-Zorrilla, J. Plaza-Díaz et al., "The gut microbiota and its implication in the development of atherosclerosis and related cardiovascular diseases," *Nutrients*, vol. 12, no. 3, p. 605, 2020.

[56] H. A. Schenkein, P. N. Papapanou, R. Genco, and M. Sanz, "Mechanisms underlying the association between periodontitis and atherosclerotic disease," *Periodontology*, vol. 83, no. 1, pp. 90–106, 2000.

[57] F. D'Aiuto, M. Parkar, L. Nibali, J. Suvan, J. Lessem, and M. S. Tonetti, "Periodontal infections cause changes in traditional and novel cardiovascular risk factors: results from a randomized controlled clinical trial," *American Heart Journal*, vol. 151, no. 5, pp. 977–984, 2006.

[58] J. H. Ramírez, B. Parra, S. Gutierrez et al., "Biomarkers of cardiovascular disease are increased in untreated chronic periodontitis: a case control study," *Australian Dental Journal*, vol. 59, no. 1, pp. 29–36, 2014.

[59] C. Roncal, E. Martínez-Aguilar, J. Orbe et al., "Trimethylamine-N-oxide (TMAO) predicts cardiovascular mortality in peripheral artery disease," *Scientific Reports*, vol. 9, no. 1, pp. 1–8, 2019.

[60] S. H. Zeisel and M. Warrier, "Trimethylamine N-oxide, the microbiome, and heart and kidney disease," *Annual Review Of Nutrition*, vol. 21, no. 37, pp. 157–181, 2017.

[61] M. Arbyn, E. Weiderpass, L. Bruni et al., "Estimates of incidence and mortality of cervical cancer in 2018: a worldwide analysis," *The Lancet Global Health*, vol. 8, no. 2, pp. e191–e203, 2020.

[62] E. A. Golemis, P. Scheet, T. N. Beck et al., "Molecular mechanisms of the preventable causes of cancer in the United States," *Genes & Development*, vol. 32, no. 13-14, pp. 868–902, 2018.

[63] S. Ono, O. Dohi, N. Yagi et al., "Accuracies of endoscopic diagnosis of Helicobacter pylori-gastritis: multicenter prospective study using white light imaging and linked color imaging," *Digestion*, vol. 101, no. 5, pp. 624–630, 2020.

[64] T. Vyhnalova, Z. Danek, D. Gachova, and P. B. Linhartova, "The role of the oral microbiota in the etiopathogenesis of oral squamous cell carcinoma," *Microorganisms*, vol. 9, no. 8, p. 1549, 2021.

[65] K. Atarashi, W. Suda, C. Luo et al., "Ectopic colonization of oral bacteria in the intestine drives TH1 cell induction and inflammation," *Science*, vol. 358, no. 6361, pp. 359–365, 2017.

[66] S. Gomes, B. Cavadas, J. C. Ferreira et al., "Profiling of lung microbiota discloses differences in adenocarcinoma and

squamous cell carcinoma," *Scientific Reports*, vol. 9, no. 1, pp. 1–1, 2019.

[67] B. A. Peters, R. B. Hayes, C. Goparaju, C. Reid, H. I. Pass, and J. Ahn, "The microbiome in lung cancer tissue and recurrence-free survival," *Cancer Epidemiology, Biomarkers & Prevention*, vol. 28, no. 4, pp. 731–740, 2019.

[68] S. I. Grivennikov, K. Wang, D. Mucida et al., "Adenoma-linked barrier defects and microbial products drive IL-23/IL-17-mediated tumour growth," *Nature*, vol. 491, no. 7423, pp. 254–258, 2012.

[69] Z. Dai, J. Zhang, Q. Wu et al., "The role of microbiota in the development of colorectal cancer," *International journal of cancer*, vol. 145, no. 8, pp. 2032–2041, 2019.

[70] A. D. Kostic, D. Gevers, C. S. Pedamallu et al., "Genomic analysis identifies association of Fusobacterium with colorectal carcinoma," *Genome Research*, vol. 22, no. 2, pp. 292–298, 2012.

[71] P. F. De Groot, C. Belzer, Ö. Aydin et al., "Distinct fecal and oral microbiota composition in human type 1 diabetes, an observational study," *Plo S One*, vol. 12, no. 12, article e0188475, 2017.

[72] E. Mariño, J. L. Richards, K. H. McLeod et al., "Gut microbial metabolites limit the frequency of autoimmune T cells and protect against type 1 diabetes," *Nature Immunology*, vol. 18, no. 5, pp. 552–562, 2017.

[73] H. Zhou, X. Zhao, L. Sun et al., "Gut microbiota profile in patients with type 1 diabetes based on 16S rRNA gene sequencing: a systematic review," *Disease Markers*, vol. 2020, Article ID 3936247, 11 pages, 2020.

[74] K. Hou, S. Zhang, Z. Wu et al., "Reconstruction of intestinal microecology of type 2 diabetes by fecal microbiota transplantation: why and how," *Bosnian Journal of Basic Medical Sciences*, vol. 22, no. 3, 2022.

[75] E. Xiao, M. Mattos, G. H. Vieira et al., "Diabetes enhances IL-17 expression and alters the oral microbiome to increase its pathogenicity," *Cell Host & Microbe*, vol. 22, no. 1, pp. 120–128.e4, 2017.

[76] S. Radzicka, M. Pietryga, R. Iciek, and J. Brązert, "The role of visfatin in pathogenesis of gestational diabetes (GDM)," *Ginekologia Polska*, vol. 89, no. 9, pp. 518–521, 2018.

[77] J. Romano-Keeler and J. H. Weitkamp, "Maternal influences on fetal microbial colonization and immune development," *Pediatric Research.*, vol. 77, no. 1, pp. 189–195, 2015.

[78] V. Ponzo, I. Ferrocino, A. Zarovska et al., "The microbiota composition of the offspring of patients with gestational diabetes mellitus (GDM)," *Plo S One*, vol. 14, article e0226545, 2019.

[79] J. Wang, J. Zheng, W. Shi et al., "Dysbiosis of maternal and neonatal microbiota associated with gestational diabetes mellitus," *Gut*, vol. 67, no. 9, pp. 1614–1625, 2018.

[80] H. C. van Woerden, C. Gregory, R. Brown, J. R. Marchesi, B. Hoogendoorn, and I. P. Matthews, "Differences in fungi present in induced sputum samples from asthma patients and non-atopic controls: a community based case control study," *Bmc Infectious Diseases*, vol. 13, no. 1, pp. 1–6, 2013.

[81] L. Millares, R. Ferrari, M. Gallego et al., "Bronchial microbiome of severe COPD patients colonised by Pseudomonas aeruginosa," *European Journal Of Clinical Microbiology & Infectious Diseases*, vol. 33, no. 7, pp. 1101–1111, 2014.

[82] S. Alnahas, S. Hagner, H. Raifer et al., "IL-17 and TNF-α are key mediators of Moraxella catarrhalis triggered exacerbation of allergic airway inflammation," *Frontiers In Immunology*, vol. 14, no. 8, p. 1562, 2017.

[83] M. Garcia-Nuñez, L. Millares, X. Pomares et al., "Severity-related changes of bronchial microbiome in chronic obstructive pulmonary disease," *Journal Of Clinical Microbiology*, vol. 52, no. 12, pp. 4217–4223, 2014.

[84] M. Sokolowska, R. Frei, N. Lunjani, C. A. Akdis, and L. O'Mahony, "Microbiome and asthma," *Asthma Research And Practice.*, vol. 4, no. 1, pp. 1–9, 2018.

[85] A. Roussos, P. Koursarakos, D. Patsopoulos, I. Gerogianni, and N. Philippou, "Increased prevalence of irritable bowel syndrome in patients with bronchial asthma," *Respiratory Medicine*, vol. 97, no. 1, pp. 75–79, 2003.

[86] E. P. Rutten, K. Lenaerts, W. A. Buurman, and E. F. Wouters, "Disturbed intestinal integrity in patients with COPD: effects of activities of daily living," *Chest*, vol. 145, no. 2, pp. 245–252, 2014.

[87] R. T. Sprooten, K. Lenaerts, D. C. Braeken et al., "Increased small intestinal permeability during severe acute exacerbations of COPD," *Respiration*, vol. 95, no. 5, pp. 334–342, 2018.

[88] M. Ottiger, M. Nickler, C. Steuer et al., "Gut, microbiota-dependent trimethylamine-N-oxide is associated with long-term all-cause mortality in patients with exacerbated chronic obstructive pulmonary disease," *Nutrition*, vol. 1, no. 45, pp. 135–141, 2018.

[89] M. C. Arrieta, L. T. Stiemsma, P. A. Dimitriu et al., "Early infancy microbial and metabolic alterations affect risk of childhood asthma," *Science Translational Medicine*, vol. 7, no. 307, article 307ra152-, 2015.

[90] C. Roduit, R. Frei, R. Ferstl et al., "High levels of butyrate and propionate in early life are associated with protection against atopy," *Allergy*, vol. 74, no. 4, pp. 799–809, 2019.

[91] N. Arpaia, C. Campbell, X. Fan et al., "Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation," *Nature*, vol. 504, no. 7480, pp. 451–455, 2013.

[92] A. Cait, M. R. Hughes, F. Antignano et al., "Microbiome-driven allergic lung inflammation is ameliorated by short-chain fatty acids," *Mucosal Immunology*, vol. 11, no. 3, pp. 785–795, 2018.

[93] M. K. Tulic, T. Piche, and V. Verhasselt, "Lung–gut cross-talk: evidence, mechanisms and implications for the mucosal inflammatory diseases," *Clinical & Experimental Allergy*, vol. 46, no. 4, pp. 519–528, 2016.

[94] Y. Huang, K. Mao, X. Chen et al., "S1P-dependent interorgan trafficking of group 2 innate lymphoid cells supports host defense," *Science*, vol. 359, no. 6371, pp. 114–119, 2018.

[95] E. E. Perrone, E. Jung, E. Breed et al., "Mechanisms of methicillin-resistant Staphylococcus aureus pneumonia-induced intestinal epithelial apoptosis," *Shock (Augusta, Ga.)*, vol. 38, no. 1, p. 68, 2012.

[96] C. M. Coopersmith, P. E. Stromberg, C. G. Davis et al., "Sepsis from Pseudomonas aeruginosa pneumonia decreases intestinal proliferation and induces gut epithelial cell cycle arrest," *Critical Care Medicine*, vol. 31, no. 6, pp. 1630–1637, 2003.

[97] K. Gleeson, S. L. Maxwell, and D. F. Eggli, "Quantitative aspiration during sleep in normal subjects," *Chest*, vol. 111, no. 5, pp. 1266–1272, 1997.

[98] C. M. Bassis, J. R. Erb-Downward, R. P. Dickson et al., "Analysis of the upper respiratory tract microbiotas as the source of

the lung and gastric microbiotas in healthy individuals," *MBio*, vol. 6, no. 2, 2015.

[99] L. N. Segal, A. V. Alekseyenko, J. C. Clemente et al., "Enrichment of lung microbiome with supraglottic taxa is associated with increased pulmonary inflammation," *Microbiome*, vol. 1, no. 1, pp. 1-2, 2013.

[100] J. Durack, S. V. Lynch, S. Nariya et al., "Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment," *Journal of Allergy and Clinical Immunology*, vol. 140, no. 1, pp. 63–75, 2017.

[101] S. D. Aaron, J. B. Angel, M. Lunau, K. Wright, C. Fex, and LE SAUX NI, Dales RE, "Granulocyte inflammatory markers and airway infection during acute exacerbation of chronic obstructive pulmonary disease," *American Journal Of Respiratory And Critical Care Medicine*, vol. 163, no. 2, pp. 349–355, 2001.

[102] P. S. Thomas, "Tumour necrosis factor-α: the role of this multifunctional cytokine in asthma," *Immunology And Cell Biology*, vol. 79, no. 2, pp. 132–140, 2001.

[103] P. Jousilahti, V. Salomaa, K. Hakala, V. Rasi, E. Vahtera, and T. Palosuo, "The association of sensitive systemic inflammation markers with bronchial asthma," *Annals of Allergy, Asthma & Immunology*, vol. 89, no. 4, pp. 381–385, 2002.

[104] W. A. de Steenhuijsen Piters, E. G. Huijskens, A. L. Wyllie et al., "Dysbiosis of upper respiratory tract microbiota in elderly pneumonia patients," *The ISME Journal*, vol. 10, no. 1, pp. 97–108, 2016.

[105] N. H. Vissing, B. L. Chawes, and H. Bisgaard, "Increased risk of pneumonia and bronchiolitis after bacterial colonization of the airways as neonates," *American Journal Of Respiratory And Critical Care Medicine*, vol. 188, no. 10, pp. 1246–1252, 2013.

[106] J. C. Gomez, M. Yamada, J. R. Martin et al., "Mechanisms of interferon-γ production by neutrophils and its function during Streptococcus pneumoniae pneumonia," *American Journal Of Respiratory Cell And Molecular Biology*, vol. 52, no. 3, pp. 349–364, 2015.

[107] H. M. Salk, W. L. Simon, N. D. Lambert et al., "Taxa of the nasal microbiome are associated with influenza-specific IgA response to live attenuated influenza vaccine," *PLoS One*, vol. 11, no. 9, article e0162803, 2016.

[108] J. Fan, X. Li, Y. Gao et al., "The lung tissue microbiota features of 20 deceased patients with COVID-19," *Journal of Infection*, vol. 81, no. 3, pp. e64–e67, 2020.

[109] Y. Han, Z. Jia, J. Shi, W. Wang, and K. He, "The active lung microbiota landscape of COVID-19 patients through the metatranscriptome data analysis," *Bio Impacts: BI*, vol. 12, no. 2, p. 139, 2022.

[110] T. J. Schuijt, J. M. Lankelma, B. P. Scicluna et al., "The gut microbiota plays a protective role in the host defence against pneumococcal pneumonia," *Gut*, vol. 65, no. 4, pp. 575–583, 2016.

[111] K. M. Felix, S. Tahsin, and H. J. Wu, "Host–microbiota interplay in mediating immune disorders," *Annals of the New York Academy of Sciences*, vol. 1417, no. 1, pp. 57–70, 2018.

[112] Y. K. Yeoh, T. Zuo, G. C. Lui et al., "Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19," *Gut*, vol. 70, no. 4, pp. 698–706, 2021.

[113] B. Kochar, A. R. Orkaby, A. N. Ananthakrishnan, and C. S. Ritchie, "Frailty in inflammatory bowel diseases: an emerging concept," *Therapeutic Advances in Gastroenterology*, vol. 14, article 17562848211025474, 2021.

[114] L. Gao, T. Xu, G. Huang, S. Jiang, Y. Gu, and F. Chen, "Oral microbiomes: more and more importance in oral cavity and whole body," *Protein & Cell*, vol. 9, no. 5, pp. 488–500, 2018.

[115] V. Leone, E. B. Chang, and S. Devkota, "Diet, microbes, and host genetics: the perfect storm in inflammatory bowel diseases," *Journal Of Gastroenterology*, vol. 48, no. 3, pp. 315–321, 2013.

[116] E. R. Walker, R. E. McGee, and B. G. Druss, "Mortality in mental disorders and global disease burden implications: a systematic review and meta-analysis," *JAMA Psychiatry*, vol. 72, no. 4, pp. 334–341, 2015.

[117] F. P. Varghese and E. S. Brown, "The hypothalamic-pituitary-adrenal axis in major depressive disorder: a brief primer for primary care physicians," *Primary Care Companion To The Journal Of Clinical Psychiatry*, vol. 3, no. 4, p. 151, 2001.

[118] W. Z. Hao, X. J. Li, P. W. Zhang, and J. X. Chen, "A review of antibiotics, depression, and the gut microbiome," *Psychiatry Research*, vol. 1, no. 284, article 112691, 2020.

[119] H. Jiang, Z. Ling, Y. Zhang et al., "Altered fecal microbiota composition in patients with major depressive disorder," *Brain, Behavior, And Immunity*, vol. 48, no. 48, pp. 186–194, 2015.

[120] Y. Luo, B. Zeng, L. I. Zeng et al., "Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus," *Translational Psychiatry*, vol. 8, no. 1, p. 1, 2018.

[121] M. Crumeyrolle-Arias, M. Jaglin, A. Bruneau et al., "Absence of the gut microbiota enhances anxiety-like behavior and neuroendocrine response to acute stress in rats," *Psychoneuroendocrinology*, vol. 1, no. 42, pp. 207–217, 2014.

[122] E. Sherwin, K. Rea, T. G. Dinan, and J. F. Cryan, "A gut (microbiome) feeling about the brain," *Current Opinion In Gastroenterology*, vol. 32, no. 2, pp. 96–102, 2016.

[123] M. R. Minter, C. Zhang, V. Leone et al., "Antibiotic-induced perturbations in gut microbial diversity influences neuroinflammation and amyloidosis in a murine model of Alzheimer's disease," *Scientific Reports*, vol. 6, no. 1, pp. 1-2, 2016.

[124] I. Juárez, A. Gratton, and G. Flores, "Ontogeny of altered dendritic morphology in the rat prefrontal cortex, hippocampus, and nucleus accumbens following cesarean delivery and birth anoxia," *Journal of Comparative Neurology*, vol. 507, no. 5, pp. 1734–1747, 2008.

[125] C. C. Hung, C. C. Chang, C. W. Huang, R. Nouchi, and C. H. Cheng, "Gut microbiota in patients with Alzheimer's disease spectrum: a systematic review and meta-analysis," *Aging (Albany NY)*, vol. 14, no. 1, p. 477, 2022.

[126] V. Singh, S. Roth, G. Llovera et al., "Microbiota dysbiosis controls the neuroinflammatory response after stroke," *Journal of Neuroscience*, vol. 36, no. 28, pp. 7428–7440, 2016.

[127] S. D. Hicks, R. Uhlig, P. Afshari et al., "Oral microbiome activity in children with autism spectrum disorder," *Autism Research*, vol. 11, no. 9, pp. 1286–1299, 2018.

[128] J. Ball and I. Darby, "Mental health and periodontal and peri-implant diseases," *Periodontology 2000*, vol. 90, 2022.

[129] B. Bikbov, C. A. Purcell, A. S. Levey et al., "GBD chronic kidney disease collaboration. Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic

analysis for the global burden of disease study 2017," *The Lancet*, vol. 395, no. 10225, pp. 709–733, 2020.

[130] J. L. Pluznick, "The gut microbiota in kidney disease," *Science*, vol. 369, no. 6510, pp. 1426-1427, 2020.

[131] A. F. Barros, N. A. Borges, D. C. Ferreira et al., "Is there interaction between gut microbial profile and cardiovascular risk in chronic kidney disease patients?," *Future Microbiology*, vol. 10, no. 4, pp. 517–526, 2015.

[132] L. Li, Y. L. Zhang, X. Y. Liu et al., "Periodontitis exacerbates and promotes the progression of chronic kidney disease through oral flora, cytokines, and oxidative stress," *Frontiers in Microbiology*, vol. 11, no. 12, article 656372, 2021.

[133] J. A. Bastos, C. G. Diniz, M. G. Bastos et al., "Identification of periodontal pathogens and severity of periodontitis in patients with and without chronic kidney disease," *Archives Of Oral Biology*, vol. 56, no. 8, pp. 804–811, 2011.

[134] N. D. Vaziri, J. Wong, M. Pahl et al., "Chronic kidney disease alters intestinal microbial flora," *Kidney International*, vol. 83, no. 2, pp. 308–315, 2013.

[135] H. Lun, W. Yang, S. Zhao et al., "Altered gut microbiota and microbial biomarkers associated with chronic kidney disease," *Microbiology*, vol. 8, no. 4, article e00678, 2019.

[136] F. Li, M. Wang, J. Wang, R. Li, and Y. Zhang, "Alterations to the gut microbiota and their correlation with inflammatory factors in chronic kidney disease," *Frontiers in Cellular and Infection Microbiology*, vol. 12, no. 9, p. 206, 2019.

[137] N. A. Osna, T. M. Donohue Jr., and K. K. Kharbanda, "Alcoholic liver disease: pathogenesis and current management," *Alcohol Research: Current Reviews*, vol. 38, no. 2, p. 147, 2017.

[138] A. Tripathi, J. Debelius, D. A. Brenner et al., "The gut–liver axis and the intersection with the microbiome," *Nature Reviews Gastroenterology & Hepatology.*, vol. 15, no. 7, pp. 397–411, 2018.

[139] M. Arrese, D. Cabrera, A. M. Kalergis, and A. E. Feldstein, "Innate immunity and inflammation in NAFLD/NASH," *Digestive Diseases And Sciences.*, vol. 61, no. 5, pp. 1294–1303, 2016.

[140] H. Mohammed, E. M. Varoni, A. Cochis et al., "Oral dysbiosis in pancreatic cancer and liver cirrhosis: a review of the literature," *Biomedicine*, vol. 6, no. 4, p. 115, 2018.

[141] M. Yoneda, S. Naka, K. Nakano et al., "Involvement of a periodontal pathogen, Porphyromonas gingivalis on the pathogenesis of non-alcoholic fatty liver disease," *BMC Gastroenterology.*, vol. 12, no. 1, 2012.

[142] A. A. Akinkugbe, G. D. Slade, A. S. Barritt et al., "Periodontitis and non-alcoholic fatty liver disease, a population-based cohort investigation in the study of health in Pomerania," *Journal Of Clinical Periodontology*, vol. 44, no. 11, pp. 1077–1087, 2017.

[143] G. Hajishengallis, T. Maekawa, T. Abe, E. Hajishengallis, and J. D. Lambris, "Complement involvement in periodontitis: molecular mechanisms and rational therapeutic approaches," in *Immune Responses to Biosurfaces*, pp. 57–74, Springer, 2015.

[144] C. Acharya, S. E. Sahingur, and J. S. Bajaj, "Microbiota, cirrhosis, and the emerging oral-gut-liver axis," *JCI Insight*, vol. 2, no. 19, 2017.

[145] P. S. Santos, K. S. Fernandes, and M. H. Gallottini, "Assessment and management of oral health in liver transplant candidates," *Journal of Applied Oral Science*, vol. 20, pp. 241–245, 2012.

[146] Z. Ling, X. Liu, Y. Cheng et al., "Decreased diversity of the oral microbiota of patients with hepatitis B virus-induced chronic liver disease: a pilot project," *Scientific Reports*, vol. 5, no. 1, pp. 1–1, 2015.