Mohsin Khurshid ·
Muhammad Sajid Hamid Akash *Editors*

Human Microbiome

Techniques, Strategies, and Therapeutic Potential

Springer

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This book is dedicated to
my boys,
Muhammad Saad Khurshid
and Muhammad Anas Khurshid

(Mohsin Khurshid)

This book is dedicated to
my beloved and adorable little twinkles,
Muhammad Aqdas Akash and Zainab Akash

(Muhammad Sajid Hamid Akash)

Foreword

In the realm of human health exploration, human microbiome has emerged as the crucial regulator, providing profound insights into the intricate relationship between microbial communities and their human hosts as well as the interactions between food and human body. We do recognize that human microbiome and gut microbiota can change our mind and health status, leading to a wide range of diseases like cancer, cardio-metabolic diseases, allergies, autoimmune disorders, and obesity. Within the pages of *Human Microbiome: Techniques, Strategies, and Therapeutic Potential*, readers embark on a transformative journey, guided by the expertise of distinguished scholars and researchers dedicated to unraveling the mysteries of this dynamic ecosystem.

This book goes beyond traditional disciplinary boundaries, offering a comprehensive view of the human microbiome from various perspectives. It serves as a beacon of knowledge, shedding light on fundamental principles, cutting-edge methodologies, and innovative strategies propelling microbiome research forward. From the complexities of host–microbiome interactions to the epigenetic influences of the microbiota on human cells, each chapter delves deeply into this symbiotic relationship, revealing its profound implications for human health and disease.

As the narrative unfolds, readers are invited to explore the therapeutic potential of the microbiome, ranging from its role in gastrointestinal disorders and metabolic diseases to its impact on cancer, mental health, and beyond. Through meticulous exploration and rigorous scientific inquiry, the contributors to this volume showcase the transformative power of microbiome-based interventions, heralding a new era in medical treatment and personalized healthcare. However, the scope of this book extends far beyond therapeutics. It examines the nuances of microbiome modulation, the influence of xenobiotics, the promise of microbiome engineering, and the regulatory considerations shaping the landscape of microbiome-based therapeutics. Moreover, given the unprecedented challenges posed by the COVID-19 pandemic, this volume offers invaluable insights into the potential of microbiota-based interventions in combating infectious diseases and their aftermath.

Human Microbiome: Techniques, Strategies, and Therapeutic Potential is a testament to the collaborative spirit of the scientific community. It demonstrates the tireless dedication of researchers and scholars who have devoted their careers to advancing our understanding of the microbiome. This book will not only help academicians in developing course curriculum but will also contribute to the vast

potential of interdisciplinary collaboration to drive innovation and transform the education and healthcare landscape.

It is poised to ignite curiosity and propel the next wave of groundbreaking discoveries in microbiome research and therapeutics. The goal in health education and research is to modulate states of health and disease. This becomes particularly crucial when the balanced interaction between the microbiome, food, and the human body is disrupted, leading to imbalances and diseases. Emerging microbial therapeutic approaches may entail the use of drug- or food-incorporating microbes aimed at curing diseases.

Together, let us continue to unravel the mysteries of the human microbiome and harness its potential to improve the lives of individuals worldwide.

Warm regards,

Shahana Urooj Kazmi

Center for Non Communicable Diseases
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Pakistan Society for Microbiology
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Swabi, Pakistan
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Preface

In the intricate tapestry of human health, the microbiome stands as a frontier of exploration, offering profound insights into the symbiotic relationship between microbial communities and their human hosts. This book entitled *Human Microbiome: Techniques, Strategies, and Therapeutic Potential* embarks on a comprehensive journey into this dynamic landscape, weaving together diverse perspectives and cutting-edge research to illuminate the multifaceted role of the microbiome in shaping our well-being.

This book transcends disciplinary boundaries to provide a holistic exploration of the human microbiome. It navigates through the fundamental principles, methodologies, and computational tools driving microbiome research, offering readers a comprehensive understanding of the intricate interplay between microbes and human biology.

The narrative unfolds, revealing the complex relationship between the microbiome and its human host, exploring the far-reaching implications of this symbiotic relationship on various physiological systems ranging from overall well-being to systemic diseases. This book delves into the diverse dimensions of microbiome–host interactions. Some of the chapters focus on the therapeutic potential of the microbiome and explore innovative approaches for microbiome-based interventions in conditions ranging from gastrointestinal tract disorders and metabolic diseases to cancers and mental health conditions. This book also underscores the transformative power of microbiome-based therapies in reshaping the landscape of medical treatment.

Beyond the therapeutic applications, this book explores strategies for modulating the gut microbiome, the impact of xenobiotics, microbiome engineering, and regulatory considerations for microbiome-based therapeutics. It also addresses the unprecedented challenges posed by COVID-19, examining the role of microbiota-based therapeutics in navigating the complexities of this global health crisis.

This book is a collaborative endeavor, bringing together the expertise of researchers and scholars dedicated to unraveling the mysteries of the human microbiome. It is our collective aspiration that the insights encapsulated within these pages will serve as a catalyst for further exploration, foster interdisciplinary collaborations, and inspire the next wave of transformative advancements in microbiome research and therapeutics.

Faisalabad, Pakistan — Mohsin Khurshid
Faisalabad, Pakistan — Muhammad Sajid Hamid Akash

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In crafting this comprehensive exploration of the ever-evolving human microbiome and its profound implications for public health, we extend our heartfelt gratitude to the Springer Nature group. We sincerely appreciate their recognition of the importance of our title and its timely contribution to literature.

Understanding that an edited book is the collaborative result of diverse authors sharing their knowledge, experiences, and expertise through contributed chapters, we wish to express our sincere thanks to all contributors. Their collective efforts have played a pivotal role in bringing this book to completion, and without their dedication, this project would not have come to fruition.

Our gratitude also extends to our families and our organization, Government College University Faisalabad, for their unwavering and selfless support throughout the preparation of this book.

Last but not least, special thanks are due to the members of the publishing team at Springer Nature, with a particular mention of Swati Sharma, Machi Sugimoto, Soumya Basu, Ashok Kumar, and Vijayalakshmi Dayalan, as well as other editorial and publishing team members. Their consistent support has been invaluable to us and to all the contributing authors.

Faisalabad, Pakistan — Mohsin Khurshid
Faisalabad, Pakistan — Muhammad Sajid Hamid Akash

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About the Editors

Mohsin Khurshid is an associate professor of microbiology and infectious diseases at the Institute of Microbiology at Government College University Faisalabad, Pakistan. He has also served as a faculty member at King Saud University in Riyadh, Saudi Arabia, and as a visiting researcher at the Institute of Antibiotics at Fudan University, Shanghai, China. Dr. Khurshid's research focuses on microbial pathogenesis, antimicrobial resistance, and gut microbiota. He has dedicated his career to understanding the potential of microbiome and probiotics in combating AMR and other infectious and non communicable diseases. He has published more than 130 articles in top-tier scientific journals and 18 book chapters in various books. Dr. Khurshid has served as a referee for numerous international journals, including *Briefings in Bioinformatics*, *Frontiers in Microbiology*, *Cancer Letters*, *Expert Review of Anti-infective Therapy*, *Microbial Ecology*, and *Lancet*. He is a sought-after speaker at conferences and symposiums worldwide. His active involvement in various professional organizations and editorial boards of prestigious scientific journals has established him as a prominent figure in the field of microbiology and infectious diseases.

Muhammad Sajid Hamid Akash is currently an associate professor at the Department of Pharmaceutical Chemistry, Government College University Faisalabad (GCUF), Pakistan. He received his bachelor's and master's degrees in pharmacy from Bahauddin Zakariya University, Multan, Pakistan, and his Ph.D. in pharmaceutical analysis from Zhejiang University, China. His current research focuses on investigating the impact of environmental contaminants (ECs) on various molecular and metabolic pathways involved in cardiometabolic disorders and developing corresponding treatment strategies. His cutting-edge research work is of significant value to developing countries like Pakistan, where it can be most effective and cost-efficient, particularly for diabetic patients. He has published 180 research articles in peer-reviewed journals, 60 book chapters, and 6 books. Dr. Akash also serves as an associate editor/academic editor and review editor for several international journals. He has also served as a guest editor for three special issues in *Metabolites*, *Frontiers in Toxicology*, and *BIOCELL* journals. Based on his contributions to medical and health sciences, Dr. Akash has received several awards,

including the PAS Gold Medal in Health Sciences from the Pakistan Academy of Sciences, the PROF AR Shakoor Gold Medal in Biological Sciences from the Zoological Society of Pakistan, and the Productive Scientist of Pakistan Award from the Pakistan Council for Science and Technology.

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An Introduction to the Human Microbiome

1

Prashanth Kotthapalli and Ann Catherine Archer

Abstract

The human microbiome represents a fascinating and rapidly evolving field of research that unveils the composition of a diverse array of microorganisms inhabiting various niches within the human body. Advances in tools and technology have facilitated a deeper understanding of the human microbiome, its diversity, and its intricate role in maintaining health and contributing to disease. Future in-depth analyses of specific microbiomes are poised to pave the way for the development of preventive and therapeutic strategies, potentially leading to the harnessing of microbiota for personalized medicine. This chapter provides an insight into the human microbiome, offering an overview of the diverse microbiomes across the human body and emphasizing the imperative for multi-omics approaches to propel research in this field.

Keywords

Human microbiome · Gut microbiome · Placental microbiome · Oral microbiome · Skin microbiome · Omics · Xenobiotics

1.1 Introduction

The human microbiome is a diverse community of microorganisms, encompassing bacteria, viruses, protozoa, and fungi, along with their functional properties, existing within a specific host or environment (Dekaboruah et al. 2020). The significance

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of the microbiome in translational science has spurred increased research focusing on its role. Considering its substantial impact on human physiology, the human microbiome can be viewed as a "superorganism" or an "additional organ." Although not a typical organ, it represents a complex bacterial system that interacts with the human body in various ways, including digestion, metabolism, immunological function, vitamin production, and brain function (Morar and Bohannan 2019).

Moreover, the microbiome has been implicated in a range of medical conditions such as gastrointestinal disorders, autoimmune diseases, and infectious diseases. Therefore, comprehending the microbiome's influence on human health is crucial for the development of effective therapies and interventions for medical problems. Studies on the human microbiome reveal significant variations in the microbes inhabiting the gut, skin, and vagina, even among individuals in good health. A substantial portion of this variability remains unknown, notwithstanding recognized factors such as host genetics, nutrition, environment, and early microbial exposure (Gilbert et al. 2018).

1.2 Evolutionary Dynamics and Diversity of the Human Microbiome

The history of microbiome research dates back to the seventeenth century with the development of germ theory, a revolutionary concept in medicine that marked the inception of our understanding and observation of the microbial world (Farré-Maduell and Casals-Pascual 2019). In the twentieth century, the discovery of the coincidental association between microbes and diseases laid the foundation for microbiological research. This era witnessed the identification of antibiotics and the experimental culture of microbes, offering insights into certain species while neglecting the majority that could not be cultivated (Davies and Davies 2010).

The advent of DNA sequencing has enabled researchers to directly investigate microbial communities, expanding our comprehension of the microbiome's complexity and diversity. The launch of the Human Microbiome Project (HMP) from 2007 to 2012 aimed to delineate microbial communities, providing a platform for future research exploring the role of the microbiome in health and illness (Turnbaugh et al. 2007). Advances in metagenomics and high-throughput sequencing now empower scientists to explore the substantial genetic diversity observed in microbial communities across various environments. To gain a comprehensive understanding of microbiomes in health, researchers are integrating genomics, transcriptomics, proteomics, and metabolomics (Martín et al. 2014). These advancements have enhanced microbiome research and led to the development of therapies such as fecal microbiota transplantation (FMT) and probiotics (Gupta et al. 2016).

The evolutionary dynamics of the human microbiome unfold as a captivating journey through time. Over millions of years, humans and their microbiota have coevolved in a symbiotic relationship. The ancestral microbiome was shaped by factors such as diet, environmental exposure, and interactions with other species (Gilbert et al. 2018). This diversity played a crucial role in supporting various bodily functions, including digestion, immune system regulation, and cognitive processes.

Our early hunter-gatherer ancestors maintained a diverse and dynamic microbiome through a varied diet rich in fibers, exposure to diverse environmental microorganisms, and limited use of antibiotics (Schnorr et al. 2014).

As humans transitioned to agriculture and settled communities, dietary changes and closer proximity to animals brought about shifts in the microbiome (Wells and Stock 2020). Fast forward to the modern era, where factors like processed diets, antibiotic use, and increased sanitation have significantly altered the composition and diversity of our microbial communities. The consequences of these changes are not confined to the gut; the microbiome influences various aspects of health, from metabolism and immune function to mental well-being. Understanding the evolutionary dynamics helps us appreciate the importance of maintaining a balanced and diverse microbiome for optimal health (Foster et al. 2017).

It is a complex and ongoing story, with researchers continuing to unravel the intricate web of interactions between humans and their microbial counterparts (Berg et al. 2020). Coevolutionary processes are the outcome of a host's and its associated microbiota's significant influence on their mutual strength, which remains poorly understood. Relative abundances may change due to evolutionary trends, and every stage of the microbiome's evolution may present challenges, such as those arising from speciation, migration, and mutations (Gevers et al. 2012).

The human microbiome is diverse and can be categorized into several types of microorganisms found within the human host. These include the mycobiome, protistome, virome, archaeome, and bacteriome (Matijašić et al. 2020). Rapid advancements in understanding the complex relationships and structure of these microbiomes have significant implications for both ecological research and human health. Bacteria were the sole living forms on Earth when it first emerged. Over the ages, multicellular organisms evolved to combat pathogens and coexist with others that colonized both internal and external surfaces (Ramanan et al. 2016). The microbial consortia, ranging in size from invertebrates to mammals, have not developed randomly. Specific microbial populations have been the focus of studies, including sequence analysis, indicating widespread sympatry between the human host and their microbial populations (Minich et al. 2022).

Considering the additional dimension of coevolution over time, the host and its microorganisms combine to generate a "holobiont," an emergent feature in which the whole is greater than the sum of its parts (Roughgarden et al. 2018). Considerable vertical transmission (from mother to child) between hosts and their microorganisms results from sympatry. Microbes are essential to human health and well-being, and humans and microbes have co-diversified due to their mutual dependence. Human lifestyle, being diet-dependent, has undergone changes from ancient times to the present (Moran et al. 2019). The diversity of microbes within a given body habitat can be defined as the number and abundant distribution of distinct types of organisms, which has been linked to several human diseases. Interindividual variation in the microbiome is specific, functionally relevant, and personalized. The human microbiome encompasses all microbiota residing on or within human tissues and biofluids, along with the corresponding anatomical sites, including the skin, mammary glands, seminal fluid, uterus, ovarian follicles,

lungs, saliva, oral mucosa, conjunctiva, biliary tract, and gastrointestinal tract (Ursell et al. 2012). The different types of the human microbiota include bacteria, archaea, fungi, protists, and viruses.

The two major microbial divisions, Firmicutes and Bacteroidetes, show different abundances depending on the phenotype. The microbiome is a living dynamic environment where the relative abundance of species may fluctuate daily, weekly, and monthly, depending on diet, medication, exercise, and a host of other environmental exposures. Different body niches have their own distinctive communities (Belizário and Napolitano 2015). For example, skin and vaginal sites exhibit smaller diversity than do the mouth and gut, with the latter showing the greatest richness. Additionally, different types of microbiota inhabit the colon, and a high-fiber diet affects the type and amount of microbiota in the intestines (Quigley 2013). The intricate behaviors of hosts can result in substantial variations in the composition of the microbiota within a species. The predominance of microbial species within a host-associated community is significantly influenced by external factors resulting from host-associated activities, including dietary habits, and the use of and exposure to antimicrobial medications (Jandhyala et al. 2015).

The gut microbiota is profoundly impacted by the transition from a traditional, high-fiber diet to a contemporary, Western diet. Diet plays a significant role in gut microbial diversity and composition (Leeming et al. 2019). Traditional diets, often rich in fruits, vegetables, and whole grains, provide a variety of fibers that support a diverse range of microbes in the gut. Serving as prebiotics, these fibers encourage the growth of beneficial microorganisms (Slavin 2013). In contrast, the Western diet, characterized by high consumption of processed foods, sweets, saturated fats, and low fibers, may result in a less diverse and potentially detrimental gut microbiota. This dietary shift has been associated with various medical conditions, including obesity, metabolic disorders, and inflammation (Clemente-Suárez et al. 2023). The gut microbiome of healthy individuals following an industrialized diet is dominated by Firmicutes and Bacteroidetes, whereas those adhering to traditional diets are more likely to harbor species like *Prevotella* and *Treponema*, which have been frequently associated with disease states (Fig. 1.1) (Rinninella et al. 2019). Importantly, during the industrialization of society, oscillating between two distinct diets can cause significant alterations in the microbiome; however, these dietary changes must be sustained over an extended period (Broussard and Devkota 2016). The taxonomic richness and diversity of the human gut microbiota have been linked to antibiotic use. Due to these effects, individuals with serious medical conditions may experience gut alterations, leading to dysbiosis, a slower rate of recuperation, and a reduction in the host's potential to maintain homeostatic balance (Francino 2015).

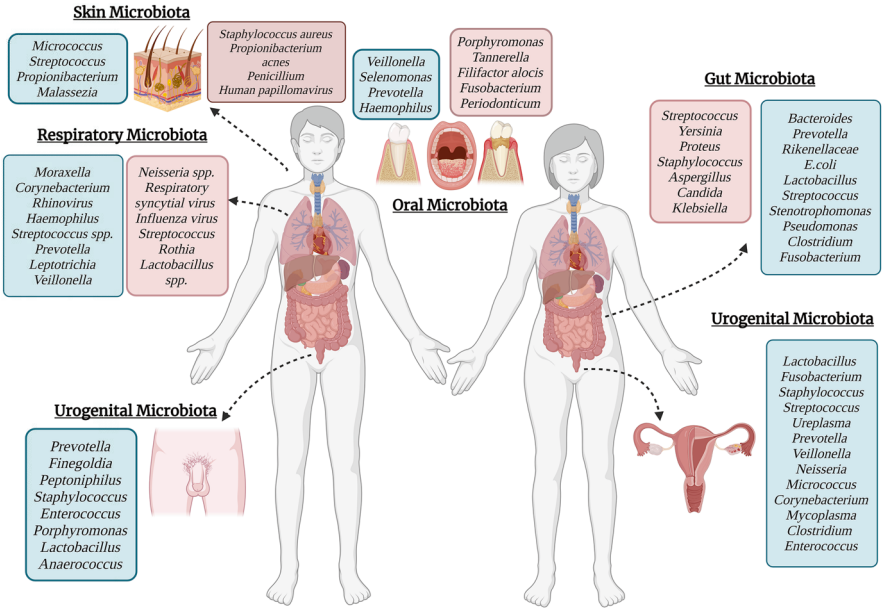

Fig. 1.1 Characteristics of various human microbiomes: normal (blue) and dysbiotic flora (red) at different anatomical sites. Image created with Biorender.com

1.3 Methods Involved in Human Microbiome Research

Microbiome research employs various approaches to investigate the intricate microbial communities in the human body, utilizing both traditional and emerging technologies (Arnold et al. 2016). Traditional methods encompass microscopy, biochemical assays, and cultivating microorganisms, whereas emerging technologies include high-throughput sequencing, metagenomics, and metabolomics. High-throughput sequencing, a popular technique for microbiome investigation, utilizes the 16S rRNA gene to identify the microbial speciation present in a sample (Janda and Abbott 2007).

Metagenomics is another technique that involves sequencing every genetic component of a sample, including the DNA of the microbe and the host. Meanwhile, metabolomics sheds light on the metabolic activities of the microbiome by identifying and measuring the small molecules it produces (Aguiar-Pulido et al. 2016). Molecular profiling technologies, statistical and machine learning methodologies, and single-cell analysis further contribute to the diverse approaches employed in microbiome research. Sample collection is equally crucial in microbiome research, and different body sites necessitate diverse methods of sample collection. Bioinformatics analysis is employed to process and analyze the vast amounts of data generated by these methods (Marcos-Zambrano et al. 2021).

1.4 The Human Microbiota in Health and Disease

The human microbiome plays a crucial and intricate role in both health and disease. The diverse communities of microbes that inhabit our bodies have a substantial impact on our physiology, influencing aspects such as digestion and metabolism, immune function, and psychological well-being (Bull and Plummer 2014). A diversified and well-balanced microbiome can aid in nutrient absorption and modulate immunological responses, contributing to the overall health (Hou et al. 2022). The gut microbiota, in particular, significantly contributes to human metabolism by producing enzymes not encoded by the human genome (Ogunrinola et al. 2020).

Advancements in understanding and manipulating the microbiome have been rapid. Novel technologies include metagenomics and next-generation sequencing (NGS), clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR-associated protein 9 (Cas9) for microbiome editing, synthetic biology and designer probiotics, microbiome modulators, microbiome biobanks, machine learning and predictive models, and single-cell sequencing (Mimee et al. 2016). Metagenomics and next-generation sequencing (NGS) have revolutionized the study of microbiomes, offering a comprehensive insight into the genetic makeup of microbial communities. Metagenomics involves direct genomic analysis of microbial communities in their natural environment without the need for culturing individual species (Oulas et al. 2015). This approach allows for the simultaneous study of thousands of different microbial species in a single sample, providing a holistic view of microbial diversity. It helps identify the functional capabilities of microbial communities, including genes responsible for various processes such as nutrient cycling or pathogen resistance (Pérez-Cobas et al. 2020).

Researchers are employing advanced techniques to engineer custom bacteria as probiotics with specific therapeutic functions (Belizário and Napolitano 2015). These designer probiotics can be tailored to produce therapeutic molecules, enhance nutrient absorption, or modulate the immune system (Tegegne and Kebede 2022). Microbiome biobanks are repositories that store and manage biological samples containing microbial DNA, RNA, or other relevant material. They play a crucial role in advancing microbiome research by providing a centralized resource for studying microbial communities in various environments (Caenazzo and Tozzo 2021).

Applying machine learning algorithms to microbiome data helps predict how changes in the microbiome may impact health outcomes, thus allowing for more personalized and targeted interventions. Globally, numerous biobanks, such as Helmholtz Zentrum München (HMGU) Biobank (Germany), The Netherlands Donor Feces Bank (NDFB) (The Netherlands), OpenBiome (USA), and MetaGenoPolis (France), offer unique services utilizing cutting-edge tools for microbiome research (Bolan et al. 2016).

1.4.1 The Gut Microbiome

The gut microbiome is recognized as the largest colonization site for microorganisms compared to any other location in the body and has been extensively studied in terms of health and disease, owing in part to the Human Microbiome Project (HMP). The HMP extensively catalogued the gut microbiota, highlighting the diverse loads of microorganisms, particularly bacteria, present along the length of the gut. Although the initial colonization of the gut was traditionally believed to occur at birth, recent evidence has suggested that the first colonization may take place in utero. Studies on bacteria reported in the placenta, amniotic fluid, and umbilical cord, as well as the presence of microorganisms in the first stool of newborns (meconium), indicate that gut colonization begins during fetal development. This early colonization contributes to the development of the immune system and other processes during gestation (DiGiulio 2012). The composition of the gut microbiota is dynamic during the first 3 years of life and is influenced by factors such as the mode of delivery (vaginal or cesarean), mode of feeding (breast milk or formula-fed), diet post 6 months of age, environmental exposure, and antibiotic use (Salazar et al. 2014). In infants, the initial microbiota is dominated by *Bifidobacterium*, gradually shifting to the colonization of Firmicutes and Bacteroidetes seen in adults, with a decreased diversity of bacterial genera in the elderly population (Reynoso-García et al. 2022). Changes in microbiotic diversity with age are largely dependent on an individual's diet. A diet rich in fiber and plant material supports a diverse microbial flora, whereas a diet dominated by meat or high in sugar and fat is associated with an increase in pathogenic flora, contributing to various conditions affecting microbial composition, metabolites, immune processes, and disease progression (Cronin et al. 2021).

Several studies have implicated the role of the gut microbiota and changes in its composition in the development of conditions such as obesity, diabetes, cancer, asthma, allergic disorders, neurological disorders, and inflammatory conditions, among others (Wang et al. 2017; Afzaal et al. 2022). Evidence also shows distinct gut microbiota signatures based on geographical locations and the influences of stress and physical exercise in maintaining a healthy composition (Karl et al. 2018).

1.4.1.1 Gut Microbiota–Xenobiotic Interactions

Microbiome research is continually advancing due to the ongoing efforts to gain insights into the intricate connections established between microorganisms and their host ecosystems. Alongside technological advancements, researchers have enhanced their understanding of the role that microbiomes play in human well-being (Cullen et al. 2020). Recent observations of the effects of xenobiotics on gut bacteria have sparked interest in research environments. Xenobiotics, foreign substances not typically expected in the human environment, encompass compounds like drugs, environmental pollutants, food additives, and other industrial chemicals (Palmer et al. 2012). The relationship between xenobiotics and the gut microbiome is complex and dynamic, with significant impacts on both microbial populations and host organisms (Abdelsalam et al. 2020).

In many aspects of human life and health, xenobiotics are essential. The biotransformation of xenobiotics, including antibiotics and drugs targeting the host, by the human gut influences the overall wellness (Maurice et al. 2013). Host metabolism evolution has made many xenobiotics easier to excrete from the body. Microbial modifications continually promote bacterial growth by providing nutrients or energy (Koppel et al. 2017). Gut microbes can metabolize xenobiotics, modifying their toxicity and efficacy by either inactivating or activating them into more potent variants. Most interactions between the human microbiota and xenobiotics occur in the gastrointestinal tract, where diverse environments influence metabolic processes due to variations in epithelial cell physiology, pH, oxygen levels, and nutritional requirements (Rowland et al. 2018). Certain drugs are designed as inert prodrugs that require activation by gut metabolism. Variations in gut microbial systems among individuals can lead to differences in xenobiotic metabolism, resulting in adverse drug reactions. The development of gut microbial communities can be influenced by selection pressures imposed by xenobiotic exposure (Wilson and Nicholson 2017).

Recent studies have highlighted that integrating traditional and emerging technologies can advance our molecular understanding of gut microbial xenobiotic metabolism. This knowledge has implications for personalized medicine, nutrition, toxicology risk assessment, and drug discovery and development. The significance of microbial metabolism of xenobiotics and its impact on host hepatic enzyme systems is gaining traction, posing a challenge to drug discovery efforts with potential implications for improving treatment outcomes and counteracting adverse drug reactions (Cai et al. 2023).

1.4.2 The Oral Microbiome

The study of the oral microbiome has become a focal point within the fields of microbiology, dentistry, and medicine. Researchers delve into the intricate ecology of the oral cavity, aiming to decipher the dynamic interplay between various microbes and their impact on health and disease (Deo and Deshmukh 2019). Healthy oral microbiomes showcase a diverse array of bacteria, fungi, and viruses, forming a complex ecosystem crucial for maintaining oral homeostasis. This intricate balance is vital for preventing the proliferation of pathogenic species and safeguarding against conditions such as dental caries, periodontal diseases, and oral malodor (Lee et al. 2021).

Conversely, dysbiosis within the oral microbiome, often triggered by factors like poor oral hygiene, dietary habits, or systemic conditions, can lead to disruptions in microbial equilibrium. This dysregulation is associated with the onset and progression of numerous oral diseases, ranging from common issues like gingivitis to more severe conditions such as periodontitis (Negrini et al. 2021). Researchers investigate the links between oral dysbiosis and systemic diseases, including cardiovascular diseases, diabetes, and respiratory diseases. In the quest for therapeutic interventions, researchers explore avenues such as probiotics and prebiotics tailored to

positively modulate the oral microbiome (Ji et al. 2023). Personalized medicine approaches also hold promise in targeting specific microbial imbalances, thus paving the way for more precise and effective treatments (Kashyap et al. 2017). Advances in three-dimensional (3D) printing technology are revolutionizing dental implants with respect to oral bacteria. These implant materials and designs are optimized to better integrate with the oral microbiota, thus lowering the possibility of complications (Huang et al. 2023). The popularity of sensor-equipped mouthwash and toothbrushes has enabled patients to monitor and enhance their dental hygiene practices. Some even provide personalized recommendations based on individual oral health needs using artificial intelligence (AI) algorithms (Huang et al. 2023).

Researchers at the Forsyth Institute in Cambridge, Massachusetts, have added more than 80 species to the recently updated Human Oral Microbiome Database (eHOMD), an online database of microbiological species found in the throat, nasal passages, and mouth (Dhopte and Bagde 2023; Escapa et al. 2018). The Tohoku Medical Megabank, Japan's first significant population-based biobank, assessed the microbial composition and community structure between saliva and plaque in a community-based cohort study. There was an association between the severity of periodontal disease and species diversities in both saliva and plaque. Saliva exhibited a favorable relationship with the groups Actinobacteria and Bacilli, which include oral health-associated bacterial species (Saito et al. 2020).

In their investigation of necrotizing periodontal disease, Jia et al. found a higher abundance of microorganisms in skin lesions. Sequencing analysis revealed the presence of bacterial phyla such as the *Prevotella* spp., with Actinobacteria members including *Corynebacterium* and *Actinomyces* spp. linked to periodontitis (Jia et al. 2021).

Another study by Kistler et al., focusing on an experimental cohort of gingivitis patients, allowed gingivitis to progress. Pyrosequencing analysis showed a correlation between various potential periodontal bacteria and chronic periodontitis. *Rothia dentocariosa* was linked to periodontal health, whereas the taxa associated with gingivitis included *Fusobacterium nucleatum* subsp. *polymorphum*, *Lachnospiraceae* sp., *Lautropia* sp., and *Prevotella oulorum* (Kistler et al. 2013). In a study by Ghannoum et al. in 2010, which utilized a multi-tag pyrosequencing technique to describe the oral mycobiomes of 20 healthy individuals, the concept of a "core oral mycobiome" was established. Genera such as *Aspergillus*, *Fusarium*, *Aureobasidium*, *Candida*, *Cladosporium*, and *Cryptococcus* were identified. Subsequent research, citing the Ghannoum study, revealed a rather significant abundance of *Malassezia*, a common skin commensal isolated from the human respiratory tract, in the entire cohort study's oral cavity (Ghannoum et al. 2010).

Several viruses, including the herpes simplex virus (HSV), Epstein–Barr virus (EBV), Kaposi's sarcoma-associated herpesvirus (KSHV), human papillomavirus (HPV), human immunodeficiency virus (HIV), and coronaviruses, are often associated with oral health issues. The recent research on coronaviruses and HIV has revealed changes in the oral microbiota and various clinical symptoms, including cancer (Pinzone et al. 2015). HIV infection is characterized by immune-mediated hyperactivation triggered by microbial translocation of microbial products and

alterations of the intestinal immune barrier. Studies have indicated significant differences in the modifications of the oral microbiota between healthy HIV-negative controls and people living with HIV (PLWH). The potential mechanisms behind alterations in the oral microbiota associated with HIV infection remain uncertain (Zevin et al. 2016). Limited research has addressed how HIV affects immune cell distribution and function in the oral mucosa, thus increasing the risk of oral disease. Changes in the composition and physiological functions of saliva during HIV infection may contribute to oral microbiome dysbiosis. The significance of secretory components in microbial control and oral mucosal immunity, including immunoglobulin (Ig)A, lysozymes, and host defense peptides, has been demonstrated. Reduced IgA levels and elevated inflammatory cytokine levels have been associated with oral dysbiosis (Coker et al. 2021).

A study by Uehara et al. on the effect of COVID-19 immunization on the oral microbiome suggests that vaccination may alter the oral microbiota of healthy individuals, particularly with mRNA vaccines. The saliva microbiome was studied using next-generation sequencing (NGS). The results showed a significant variation in the flora's alpha- and beta-diversity, with no discernible impact on the percentage of periodontal and cariogenic bacteria, including *Streptococcus* spp. and *Porphyromonas* spp. These findings indicate that oral pathogenic microorganisms, dental caries, and periodontal disease are not affected by COVID-19 immunization at the initiation or progression (Uehara et al. 2022).

1.4.3 The Respiratory Tract Microbiome

The respiratory tract microbiome, comprising the upper respiratory tract and the lower respiratory tract, hosts a diversity of microorganisms, including bacteria, fungi, and viruses that colonize different locations of the respiratory system. The microbiome's composition varies based on the microenvironment, initial colonization exposures, and external environmental exposures. The lungs, constantly exposed to air carrying microorganisms, pollutants, aerosols, allergens, etc., can dynamically alter the lung microbiome's composition. Respiratory diseases can exacerbate microbiota dysbiosis, leading to increased susceptibility to pathogenic and opportunistic agents.

The upper respiratory tract, including the nostrils, rhinopharynx, and oropharynx connected to the larynx and middle ear by the Eustachian tube, is colonized by bacterial genera belonging to Bacteroidetes, Proteobacteria, Firmicutes, Actinobacteria, and Fusobacteria (Santacroce et al. 2020). Respiratory microbiome colonization occurs at birth and evolves based on factors such as the mode of delivery (vaginal or cesarean) and environmental exposures (diet, lifestyle, antibiotics, etc.). Dysbiotic microbiota in early life may contribute to disease susceptibility and allergies later on (Prescott and Logan 2016).

The gut–lung axis connects the microbiomes of the gut and lungs, critical for the maturation of the lung epithelium and immune system. The nostrils are generally enriched with *Propionibacterium*, *Corynebacterium*, *Staphylococcus*, and