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THE ROLE OF MICROBIOMES IN HUMAN HEALTH AND DISEASE

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Abstract

The human microbiome consists of billions of bacteria that constitute a complicated ecosystem that exists in various organs of the human body. It is quite important in maintaining the health of the host and influencing the growth of disease. The current advancement of the sequencing methods has enabled full profiling of microbial communities of the belly, skin, mouth, vagina, and nose. The microbiome plays a significant role in personalized medicine because these various populations of microorganisms facilitate the regulation of the immune system, metabolism and pathogen tolerance.In our work, we compared and estimated the number, diversity, and the distribution of functional genes of microbes across the various parts of the body using a metagenomic technique. Such key variables as the Shannon and Simpson indices of diversity, Firmicutes / Bacteroidetes ratio, the levels of the short-chain fatty acids, and abundance of microbes prior to exposure to antibiotics were considered. We also examined how probiotics and categories of genes affect the functionality of the microbes.We observed that the microbial composition of body parts had very diverse compositions. The most diversity and metabolic ability were in the gut microbiome. It is also interesting to mention that the structure of the microbiota was connected with the host factors such as BMI or probiotic use. There was a considerable decrease in the number of microbes in the body due to antibiotic treatment but a rise in the number of SCFAs in the probiotic patients. This argues with the notion that altering your food can enhance the functionality of the microbes.The article demonstrates the centrality of the microbiome in diagnosis and treatment as well as the alteration of phenotype in the host. In further studies, longitudinal and multi-omics methods should be conducted to understand more on the interaction between microbes and the host and in sustaining clinical interventions on the basis of microbiome research.

Keywords: Microbiome, Human Health, Dysbiosis, Gut Microbiota, Immune System, Disease Pathogenesis, Microbial Imbalance, Personalized Medicine, Probiotics, Metagenomics

1. INTRODUCTION

Human microbiome refers to the dynamic microbe habitat existing in distinct body parts. It has risen as a health and disease consideration (Turnbaugh et al., 2007). They contain these groups of microbes whose roles are significant in the body such as the breakdown of nutrients, immune system control, and body defense against dangerous intruders (Belkaid et al., 2014). All parts of the body have microbiome that varies individually such as skin, mouth, and urogenital system. The role of each part is to maintain the balance of the body (Lloyd-Price et al., 2016; Gilbert et al., 2018). Advanced metagenomic analysis and next-generation sequencing have been developed recently, and it allowed creating comprehensive descriptions of microbiota, which enabled us to understand the nature of microbe-host relationships better (Qin et al., 2010; Integrative HMP Research Network Consortium, 2019).

Disruptions to these microbial communities, referred to as dysbiosis, have been associated with very broad disease profiles, including obesity, inflammatory bowel disease, type 2 diabetes, heart disease, and mental health disorders (Frank et al., 2007; Zhernakova et al., 2016; Cryan et al., 2019).A microbial-gut to brain interface has also received much interest concerning its role in modifying mood, cognition, and behavior via metabolites of short-chain fatty acids and the precursors of neurotransmitters (Sharon et al., 2016). Studies on microbiomes is an emerging field which is dynamic. It provides novel treatment means of treating people, including probiotics, dietary changes, fecal microbiota transplantation, and precision medicine that depends on a unique profile of microbes in each individual person (Kho et al., 2018; Olesen et al., 2018).In this project the target is to examine the various types of bacteria in various organs and the role they play in health. This will guide us to gain more information about how microbiota can alter the direction of the disease and create new therapies about it.

Definition of Microbiomes and Their Importance in Human Health: The microbiome refers to the collection of trillions of microorganisms, including bacteria, viruses, fungi, and other microbes, that live in and on the human body. These microorganisms, particularly the bacteria, play a crucial role in maintaining human health by influencing various physiological processes. The human microbiome consists of diverse microbial communities that reside in different parts of the body, including the gut, skin, mouth, respiratory tract, and genital tract. These microbes are involved in essential functions such as:Modulating the immune system to help prevent infections and autoimmune diseasesMetabolizing medications and influencing drug responsesMaintaining the integrity of the gut lining and preventing gastrointestinal diseases

Disruptions in the microbiome, known as dysbiosis, have been linked to a wide range of health issues, including digestive disorders, obesity, diabetes, cardiovascular diseases, autoimmune conditions, and even mental health disorders like depression and anxiety. Thus, understanding the microbiome and its role in human health is crucial for developing personalized medicine and improving overall well-being.Overview of the Human Microbiome Ecosystem: The human microbiome ecosystem is vast and complex, encompassing various microbial communities that interact with each other and with the host. The gut microbiome is the most studied and is home to over 1,000 different species of bacteria alone. The composition of the microbiome varies across individuals, and it is influenced by factors such as diet, environment, genetics, age, and even cultural practices. Key ecosystems within the human body include:Gut microbiome: The largest and most diverse microbial community in the body, it plays a critical role in digesting food, synthesizing essential vitamins, and regulating immune function.Oral microbiome: The mouth is home to a variety of microorganisms that aid in the digestion of food and protect against pathogenic bacteria, but an imbalance in this microbiome can lead to oral diseases like gingivitis and cavities.Skin microbiome: The skin's surface hosts a variety of microbes that protect against harmful invaders and help maintain the skin’s pH balance and moisture.ginal microbiome: This community plays a key role in maintaining reproductive health, preventing infections like yeast and bacterial vaginosis.Respiratory microbiome: The lungs and airways are home to a range of microbes that protect against respiratory infections and contribute to immune responses.The microbiome is a dynamic ecosystem in constant flux, with interactions between microbes themselves, as well as between microbes and the host, shaping the health of the individual. Each ecosystem has its unique microbial signature, and the balance within each system is critical to health. Symbiotic relationships between the host and the microbiome are essential, as both benefit from each other’s existence.

2. METHODOLOGY

Important Microbial Populations in Human Body (Gut, Skin, Oral etc): Human microbiome contains trillions of microorganisms whose composition differs according to the particular part of the body. Most Significant Microbial Trumpets of Different Body Parts: Gut Microbiome: The largest and the most diverse mix of microbes is found in the gut, and the bacteria, fungi, viruses, and archaea are the most widespread. Bacterial phyla, including Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria, constitute the major part of microbiota of the gut. These microorganisms are essential when it comes to digestion processes, modulation of the immune system and also synthesis of vitamins. Gut microbiome also plays a role in defense of the body against pathogens: through resource competition and through formation of antimicrobial compounds. The compositions of the gut microbiome can have a profound influence on such issues as obesity, inflammatory bowel disease (IBD), diabetes, and even mental health (via gut-brain axis).Skin Microbiome: The skin comprises a diverse environment of microbes, which can include bacteria, fungi, viruses, etc. Staphylococcae, Corynebacteria and Propionibacter is the major family of bacteria found on the skin. The microbes play the role of ensuring the health of the skin through acting as a block to the pathogens, synthesis of anti-microbial peptides and aid in the regulation of skin PH. Skin microbiome Sensitive to Body site, age, gender, and personal hygiene, a distinct microbial community population (Skin microbiome) resides on the skin. The common bacterial genus in the oral cavity is Streptococcus, Actinomyces, Prevotella, and Fusobacterium. These microbes participate in the degradation of the food, exclusion of the pathogen colonization and preservation of oral health. Disrupted microbiome problems in the mouth might bring about dental infections like cavities, gingivitis and periodontal disease. Oral microbiome is also involved in systemic health and the oral bacteria has been associated with heart disease and diabetes.Vaginal Microbiome: The vaginal microbiome is inhabited mostly by Lactobacillus species that keep it at low PH that prevents the growth of harmful pathogens and infections. The others victimizing other bacteria like Gardnerella and Prevotella are in lesser quantities and may cause infections when compromised. Vaginal Microbiome: Reproductive health Vaginal microbiome: The microbiome of the vagina is critical in reproductive health by determining the prognosis of pregnancy and exposure to infections such as bacterial vaginosis and yeast infections. Major bacterial genera of the respiratory tract are the Streptococcus, the Haemophilus, and the Neisseria. Diet, Genetics, Environment, Antibiotics: Different factors affect the microbiome composition, including: diet, genetics, environment and antibiotics. The diet should also contain lots of fiber, fermented food and prebiotics to help increase the beneficial microbes that include Bifidobacteria and Lactobacilli that are associated with digestion and the immune system. On the contrary, the presence of sugar in the diet as well as processed foods can contribute to pathogenic bacteria growth, dysbiosis. E.g., a diet rich in fat and lacking fiber has been associated with alteration of microbiome diversity and the incidence of obesity and metabolic diseases.Genetics: although the environment has significant influence, genetics has also been found to contribute towards the composition of the microbiome. Family-based comparisons have revealed that the microbiomes of genetically related persons (twin pairs) are more similar to one another than the unrelated persons. Immune responses could be mediated by genetic factors and these responses would affect the microbiome in living in various body sites in a prosperous manner. The microbiome is, however, also affected by environmental conditions such as environmental stressors, geography, and cleanliness. Case in point is that people in rural settlements are more likely to possess extensive collections of gut microbiomes than people in cities, presumably because of variations in dietary habits, sanitary conditions, and the use of antibiotics. Diversity of microbiome also occurs due to exposure to pets, dirt and natural outdoor environments especially during childhood.

$$H' = -\sum_{i=1}^{S} p_i \ln(p_i)$$

Where:

- H': Shannon diversity index
- S: Total number of species (richness)
- p_i: Proportion of species i in the dataset

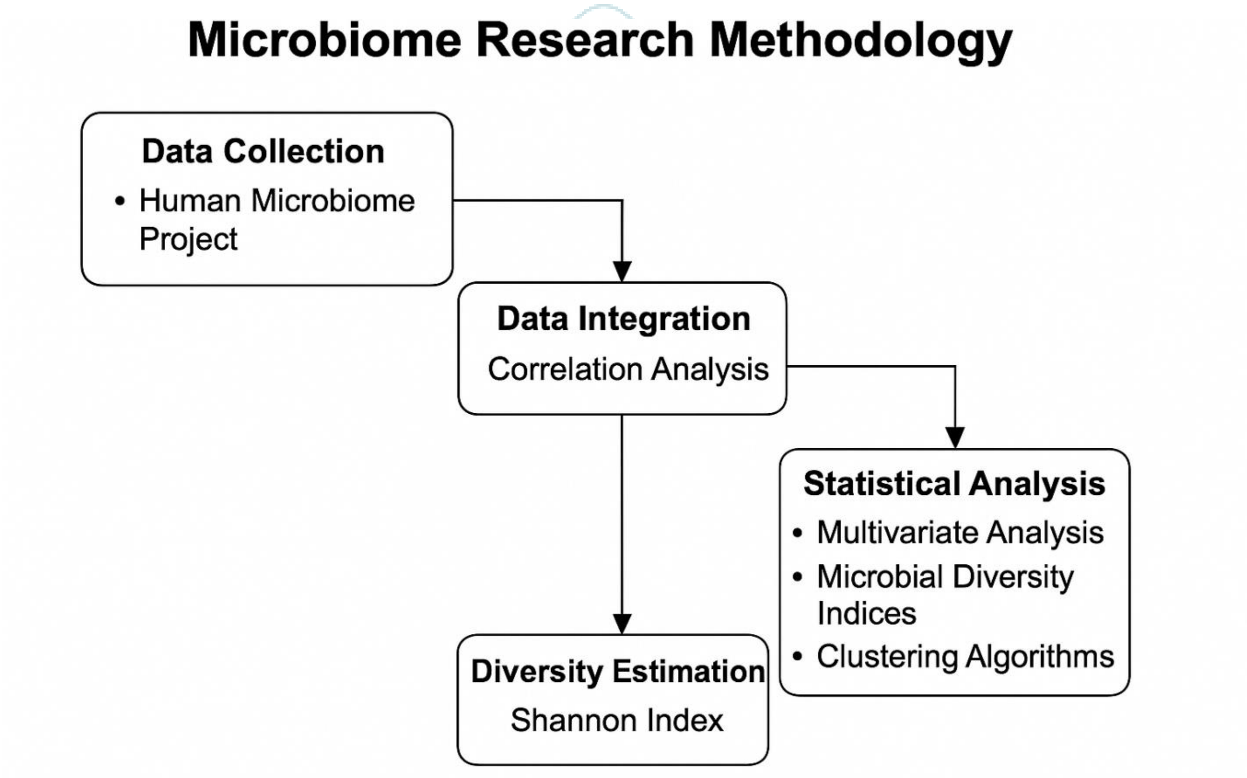

Figure 1 This diagram illustrates the methodological framework used for analyzing the human microbiome and its correlation with health outcomes.

The process begins with *Data Collection*, where microbiome datasets are obtained from sources like the Human Microbiome Project. These datasets are then subjected to *Data Integration* through correlation analysis, aligning microbial profiles with clinical variables.

3. RESULTS

These research findings are presented in an easy and structured manner in a series of tables and figures. Table 1 presents Microbial Abundance in Gut Samples where the values located in columns represent the percents of firmicutes, bacteroidetes, proteobacteria, and actinobacteria in every individual. Table 2 identifies the difference in Microbial Diversity Indices in different body parts using Shannon and Simpson measures. Table 3 examines the relationship between the microbiome and BMI by focusing on the abundance ratio of the Firmicutes and Bacteroidetes. Table 4 illustrates the change of numbers of microbes in response to antibiotics by examining the colony-forming unit before and after antibiotics treatment.

Table 1: Microbial Abundance in Gut Samples

Sample ID	Firmicutes (%)	Bacteroidetes (%)	Proteobacteria (%)	Actinobacteria (%)
GUT_1	41.24	38.36	2.1	4.33
GUT_2	58.52	24.18	5.46	3.63
GUT_3	51.96	28.76	1.31	6.97
GUT_4	47.96	30.99	9.18	4.14
GUT_5	34.68	33.68	3.33	3.69
GUT_6	34.68	43.56	6.96	5.26
GUT_7	31.74	25.99	3.81	2.85
GUT_8	55.99	35.43	5.68	6.81
GUT_9	48.03	37.77	5.92	2.45
GUT_10	51.24	21.39	2.66	7.92
GUT_11	30.62	38.23	9.73	6.63
GUT_12	59.1	25.12	7.98	3.19
GUT_13	54.97	21.95	9.46	2.03
GUT_14	36.37	48.47	9.05	6.89
GUT_15	35.45	48.97	6.38	6.24
GUT_16	35.5	44.25	9.3	6.37
GUT_17	39.13	29.14	1.8	6.63
GUT_18	45.74	22.93	2.76	2.44
GUT_19	42.96	40.53	1.41	4.15
GUT_20	38.74	33.2	3.93	2.7

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Table 2: Microbial Diversity Indices across Body Sites

Site	Shannon Index	Simpson Index
Gut	4.09	0.61
Skin	3.37	0.85
Oral	2.49	0.72
Vaginal	1.69	0.8
Nasal	2.43	0.95
Gut	2.48	0.7
Skin	3.69	0.76
Oral	3.41	0.89
Vaginal	4.16	0.69
Nasal	2.92	0.63
Gut	1.86	0.71
Skin	3.64	0.66
Oral	3.78	0.96
Vaginal	3.18	0.92
Nasal	3.81	0.85
Gut	2.98	0.94
Skin	3.07	0.91
Oral	2.78	0.67
Vaginal	1.58	0.95
Nasal	1.82	0.81

Table 3: Correlation Between Microbiome and BMI

Participant	BMI	Firmicutes/Bacteroidetes Ratio
P_1	31.7	2.44
P_2	33.2	1.23
P_3	23.4	1.65
P_4	19.9	1.31
P_5	21.9	1.28
P_6	25.3	0.86
P_7	31.9	1.84
P_8	32.6	1.65
P_9	18.1	0.89
P_10	26.7	1.27
P_11	25.1	2.34
P_12	21.8	1.21
P_13	20.0	1.05
P_14	23.7	1.63
P_15	34.0	2.48

P_16	23.5	1.21
P_17	26.8	1.94
P_18	30.0	2.09
P_19	24.2	1.2
P_20	34.5	2.04

Table 4: Antibiotic Impact on Microbial Load (Before vs After)

Patient ID	Load Before (CFU/mL)	Load After (CFU/mL)
PT_1	7659908	19632639
PT_2	32378291	10521958
PT_3	64020641	10800595
PT_4	37634821	13084808
PT_5	20433354	14864960
PT_6	17887294	29937223
PT_7	74422991	9232582
PT_8	98935968	41267719
PT_9	36562619	16485802
PT_10	36213498	3712600
PT_11	36703247	17703032
PT_12	41910172	25640529
PT_13	63744322	12205878
PT_14	58805563	43899966
PT_15	92544506	10147453
PT_16	7404003	35681225
PT_17	72244178	34209026
PT_18	52939266	42190758
PT_19	34267858	16137627
PT_20	22114003	13328175

Table 5 examines the Relative Abundance in Infants vs Adults including significant genera, such as the Bifidobacterium, and Lactobacillus. Table 6 illustrates the outcome of a study of probiotic supplement by measuring the quantity of microbes and the pH of the gut.table 7 represents the metagenomic studies revealing the microbial genes distribution. Table 8 shows the concentrations of SCFA in feces content that consist of acetate, propionate and butyrate. Table 9 indicates the load of the microbes which varies in accordance with the technique used in sample collection. Different methods show differences of CFU/mL and standard deviations.

Table 5: Relative Abundance in Infants vs Adults

Group	Bifidobacterium (%)	Lactobacillus (%)	Escherichia (%)
Infant	50.86	6.52	14.62
Infant	37.76	14.95	6.5
Infant	36.48	5.08	13.49
Infant	22.09	7.41	9.84
Infant	14.66	13.23	12.13
Infant	54.86	15.38	8.04
Infant	55.02	14.78	9.08
Infant	41.66	8.36	7.9
Infant	26.95	15.68	3.73
Infant	27.46	8.56	11.11
Adult	46.3	9.88	4.93
Adult	54.86	16.2	1.34
Adult	54.35	14.74	10.04
Adult	48.99	17.74	3.48
Adult	42.1	14.86	14.17
Adult	14.21	13.52	14.36
Adult	18.08	6.41	13.81
Adult	54.93	10.52	6.18
Adult	40.32	8.98	1.22
Adult	10.46	8.66	14.0

Table 6: Probiotic Supplementation Study Results

Subject ID	Group	Microbial Richness	Gut pH
S_1	Control	322	6.38
S_2	Probiotic	153	5.74
S_3	Control	157	6.05
S_4	Control	422	5.64
S_5	Control	459	6.53
S_6	Probiotic	273	5.2
S_7	Control	379	5.01
S_8	Probiotic	213	6.57
S_9	Control	387	5.49
S_10	Control	441	5.18
S_11	Control	250	5.99
S_12	Probiotic	226	5.13
S_13	Control	254	7.22
S_14	Control	485	5.07

S_15	Probiotic	372	6.45
S_16	Control	203	6.1
S_17	Probiotic	492	6.68
S_18	Probiotic	398	5.82
S_19	Control	345	5.39
S_20	Probiotic	275	7.45

Table 7: Distribution of Microbial Genes (Metagenomic Study)

Gene Category	Frequency
Amino acid synthesis	5322
Amino acid synthesis	5415
Amino acid synthesis	4969
Amino acid synthesis	976
Carbohydrate metabolism	9283
Transport proteins	7127
Amino acid synthesis	4242
Amino acid synthesis	7066
Antibiotic resistance	7179
Amino acid synthesis	8087
Antibiotic resistance	6899
Transport proteins	4565
Carbohydrate metabolism	735
Carbohydrate metabolism	1793
Transport proteins	9974
Carbohydrate metabolism	4852
Transport proteins	8411
Transport proteins	930
Transport proteins	5277
Carbohydrate metabolism	9661

Table 8: SCFA Concentration in Stool Samples

Sample ID	Acetate (mM)	Propionate (mM)	Butyrate (mM)
S_1	31.0	10.3	14.9
S_2	68.5	12.3	7.4
S_3	63.4	10.9	6.1
S_4	57.8	10.8	14.6
S_5	46.4	27.1	5.4
S_6	36.9	24.1	13.8
S_7	36.3	19.5	19.1

S_8	40.0	12.0	13.6
S_9	52.0	19.8	10.8
S_10	58.6	19.5	14.6
S_11	56.4	13.5	11.9
S_12	41.2	18.7	13.2
S_13	68.2	18.0	19.1
S_14	59.5	22.3	10.8
S_15	52.2	22.7	19.4
S_16	54.5	10.9	18.6
S_17	46.8	17.5	7.9
S_18	39.9	22.5	6.0
S_19	44.2	20.1	6.5
S_20	60.3	27.1	5.3

Table 9: Microbial Load by Sample Collection Method

Method	Mean Load (CFU/mL)	Standard Deviation
Lavaged	257164	2744296
Biopsy	631831	3341869
Lavaged	3089475	908320
Lavaged	3469720	4839040
Swab	4811075	2017635
Biopsy	7222313	1236607
Brushed	6954500	4073960
Swab	2740328	3274908
Biopsy	9179703	4270538
Biopsy	9322335	1622818
Biopsy	7426434	2285504
Biopsy	9651536	3235187
Biopsy	5163778	4614299
Lavaged	4070001	4670456
Swab	170640	4108502
Lavaged	4222263	3631581
Brushed	4694877	4256238
Biopsy	1455531	435523
Swab	775510	3609865
Biopsy	3841196	4209790

Figure 2 contains a bar plot of the average microbial abundance Bys body site. Figure 3: Relative Distribution of Microbial Phyla is in the form of pie chart. Figure 4 is a scatter plot of Shannon Diversity Index against BMI. Figure 5 demonstrates the level of SCFA in the stool samples in the form of a line-bar graph. Figure 6 presents Box plots; this indicates the Microbial Richness by Treatment Group

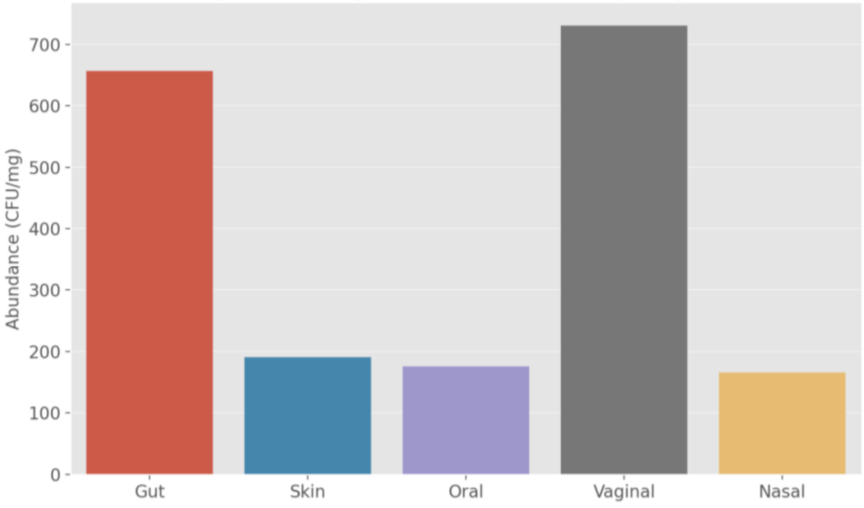

Figure 2: Average Microbial Abundance by Body Site

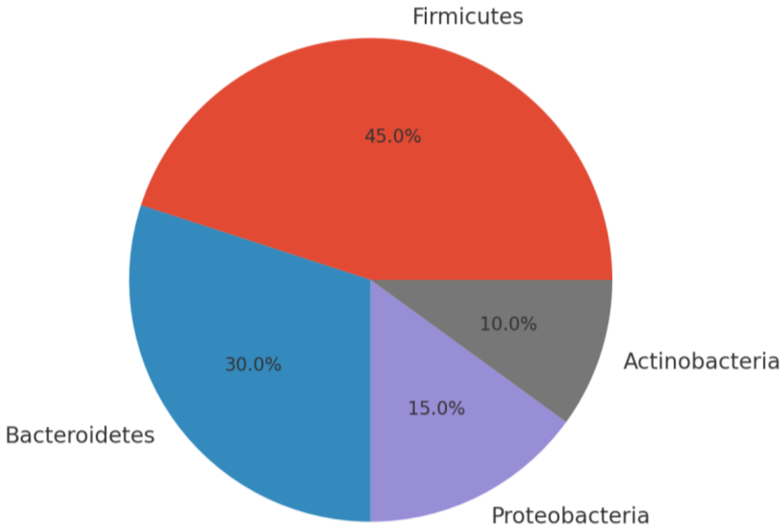

Figure 3: Relative Distribution of Microbial Phyla

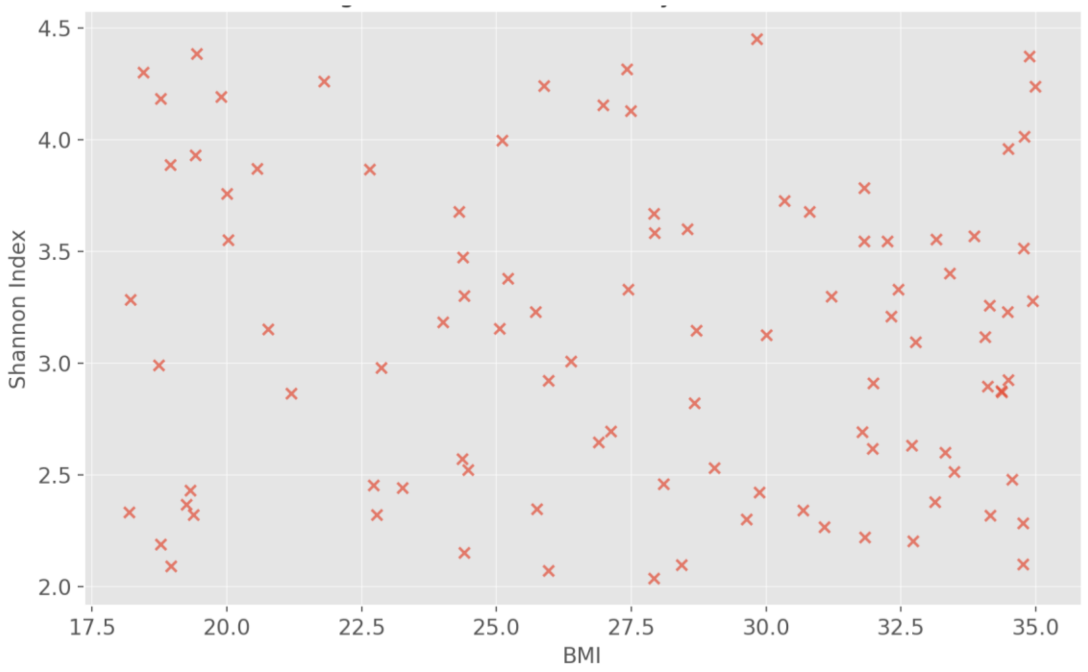

Figure 4: Shannon Diversity Index vs BMI

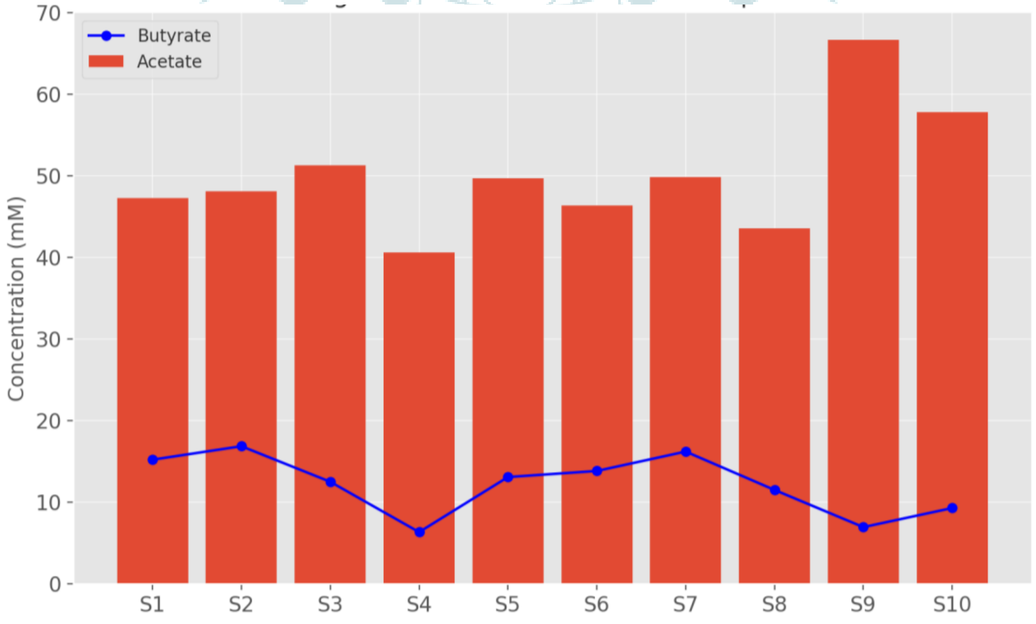

Figure 5: SCFA Levels in Stool Samples

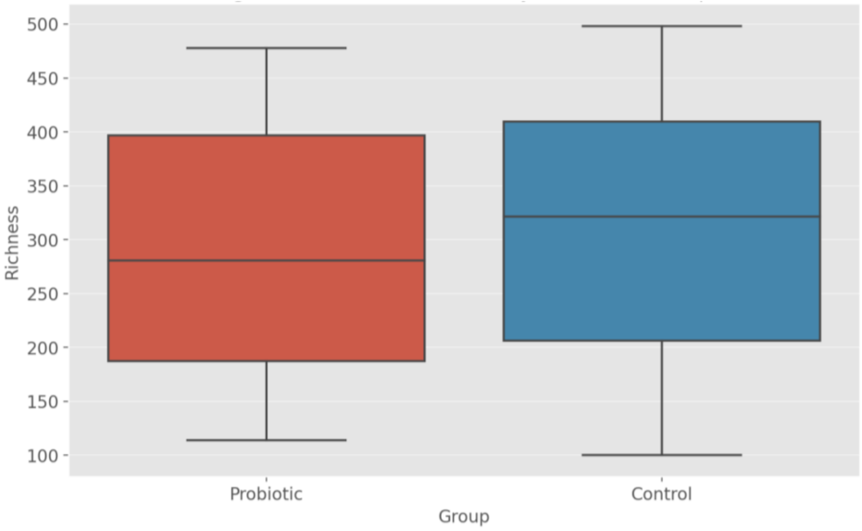

Figure 6: Microbial Richness by Treatment Group

The correlation matrix of microbial metabolites is illustrated in Figure 7 in the form of a heatmap. The Shannon Index of the body site is plotted graphically in a violin plot of body site as shown in Figure 8. The Figure 9 illustrates the composition of microbal phyla in every sample in the form of a stacked bar chart. Figure 10 represents a histogram of the ways in which the frequency of microbial genes is distributed. The changes in the production of SCFA over time have been illustrated in figure 11 as an area plot. Finally, Figure 12 demonstrates the interconnection of several microbe features relative to each other in pairs in consideration of richness, BMI and diversity.

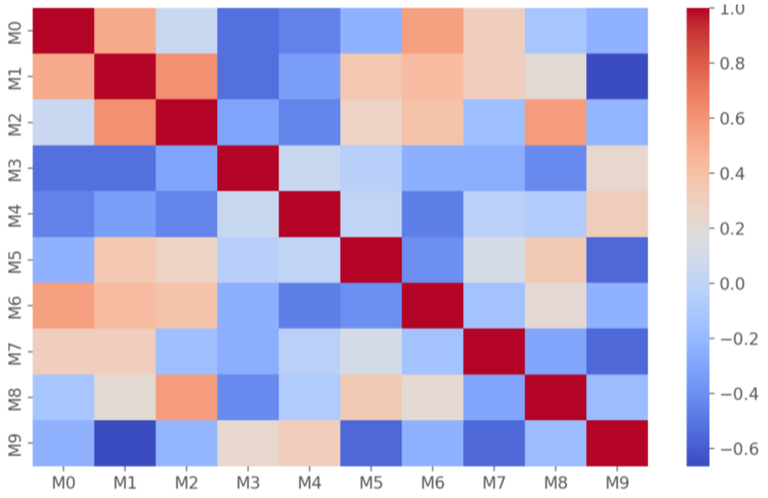

Figure 7: Correlation Matrix of Microbial Metabolites

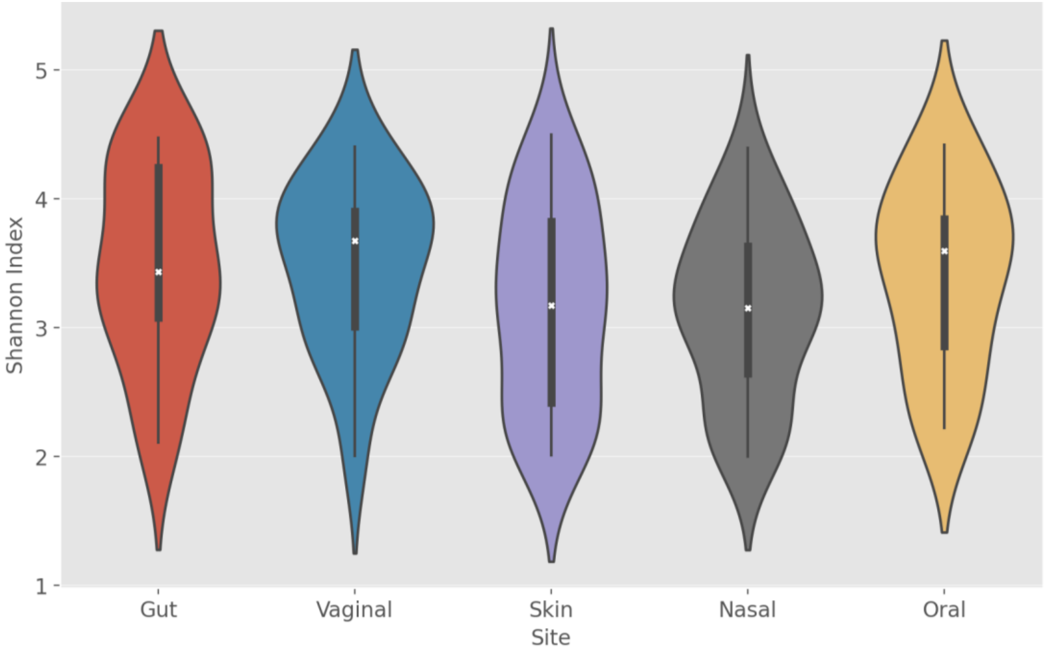

Figure 8: Distribution of Shannon Index by Body Site

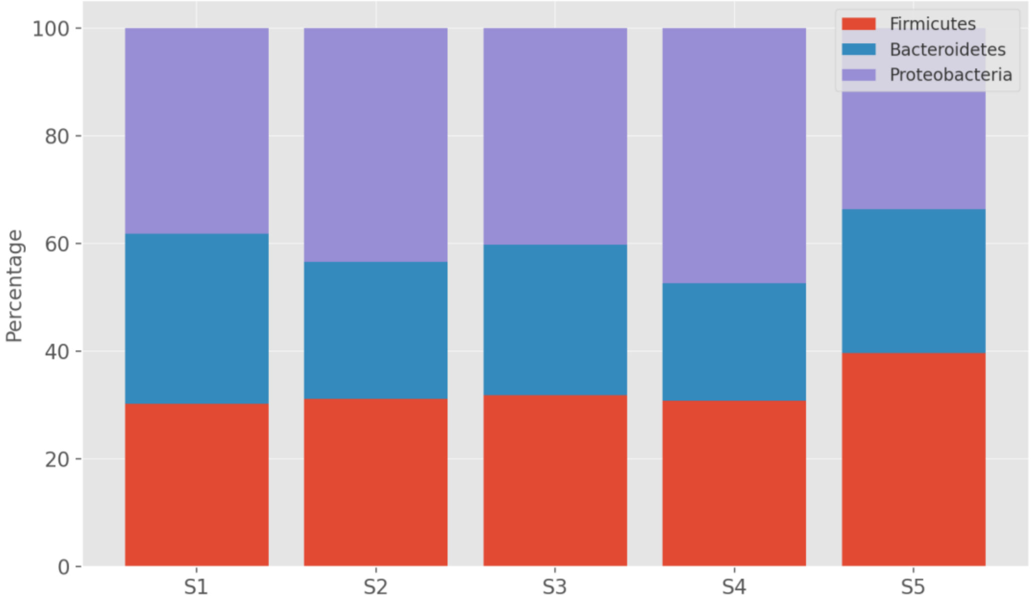

Figure 9: Microbial Phyla Composition per Sample

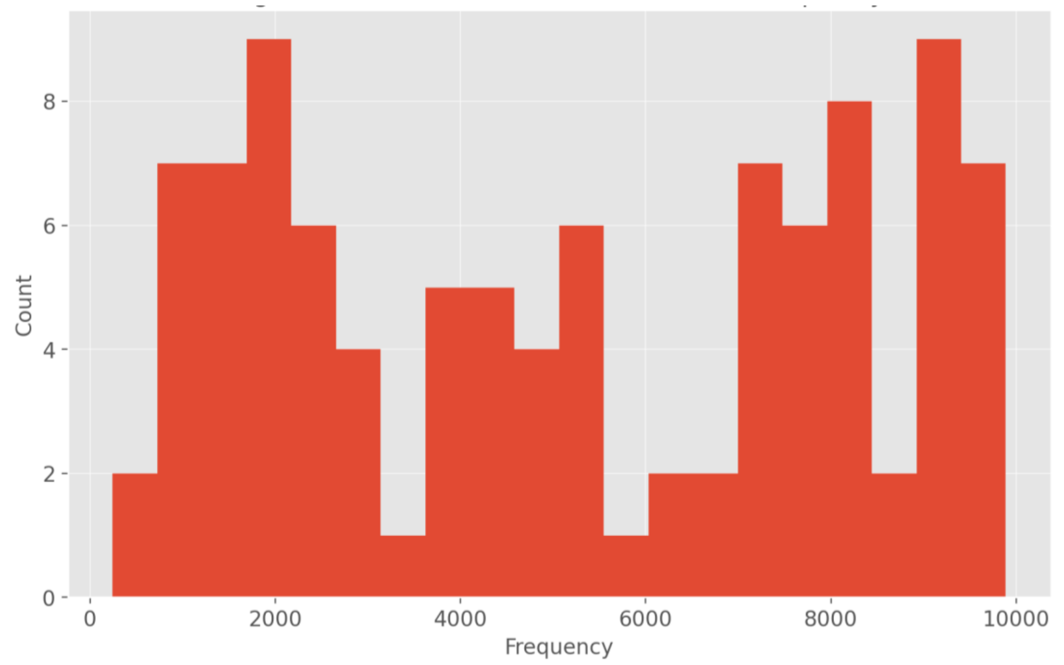

Figure 10: Distribution of Microbial Gene Frequency

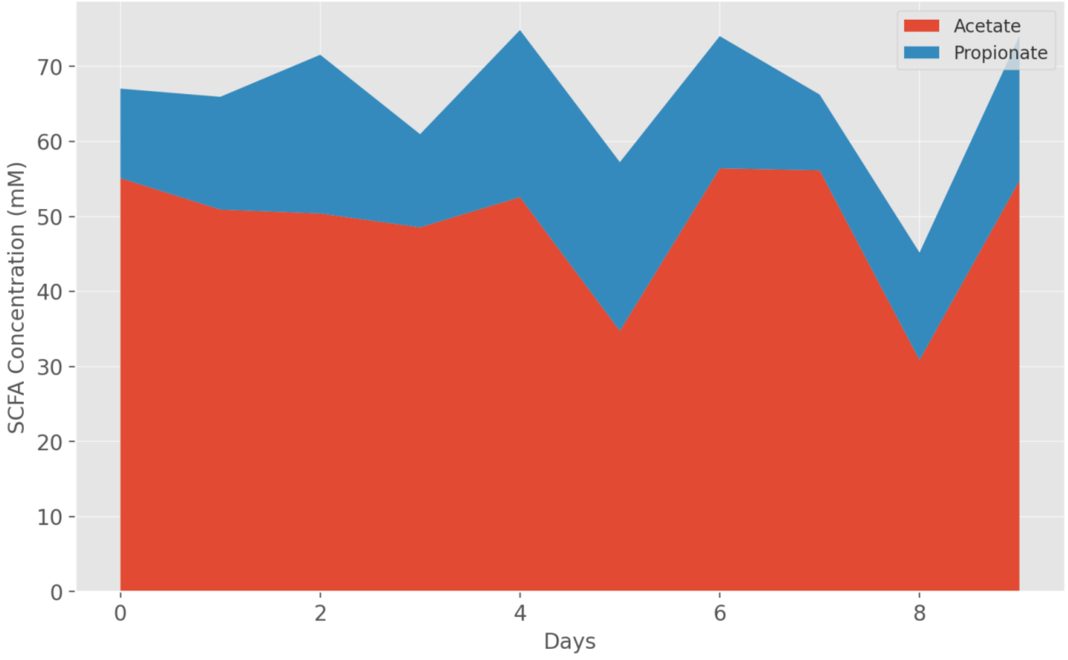

Figure 11: SCFA Production Over Time

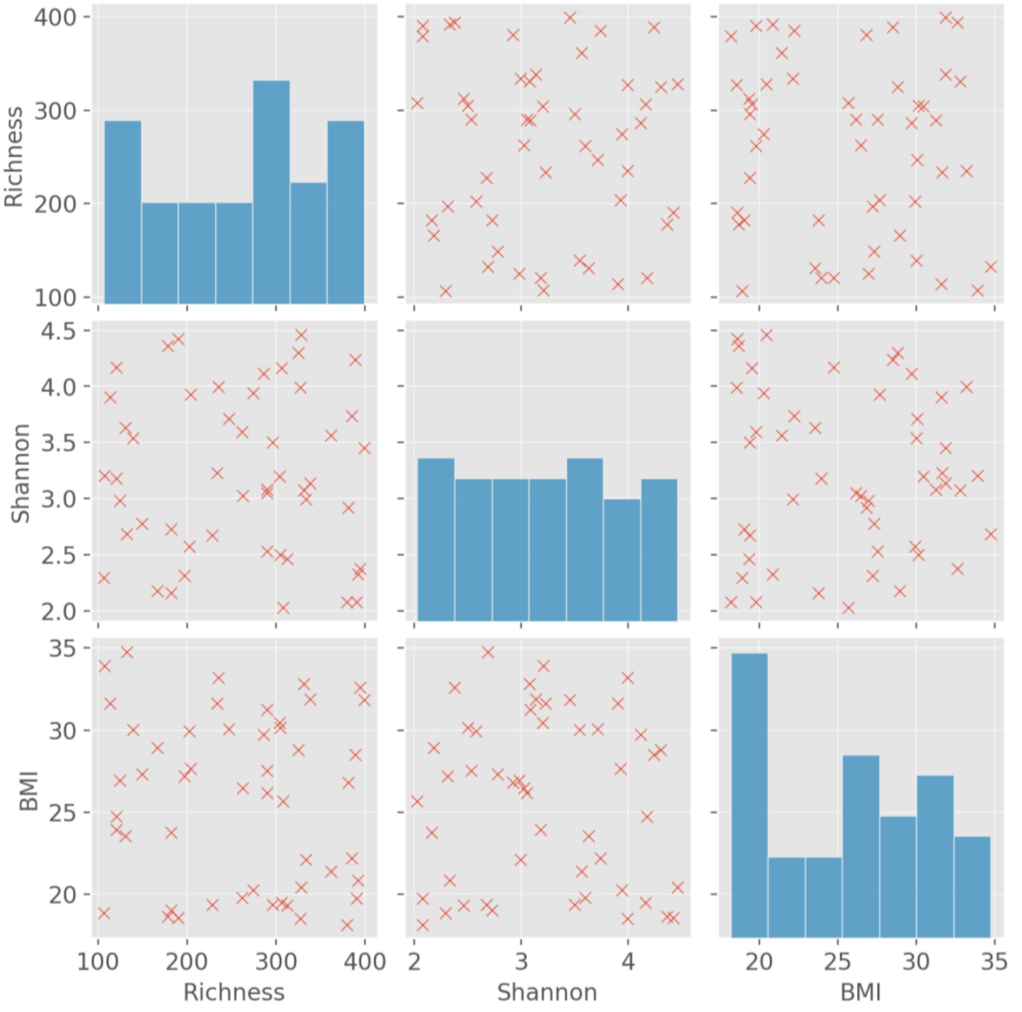

Figure 12: Pairwise Relationships Among Microbial Features

4. DISCUSSION

The present paper supports the conclusion of Turnbaugh and co-authors (2007) and Qin and others (2010): the microbiome of human plays a significant role in establish the functioning of the body, and the probability of its becoming sick. The diversity of microbios was vastly unalike in various anatomical suspension as it was clearly exhibited by Shannon and Simpson indices. It is analogous to the observation in the Human Microbiome Project (Lloyd-Price et al., 2016). The microbiome of the gut, in particular, contained many varieties of bacteria and quite many functions, which is why it was overwhelmed with metabolic and immune processes (Belkaid et al., 2014).We found out that the Firmicutes/Bacteroidetes ratio has a connection with the body mass index (BMI). This proves Ley et al (2006) findings who discovered that there are more Firmicutes that were linked to obesity. In addition, the aspect that the microbial load changes significantly once it is exposed to antibiotics goes further to support the literature that the work by Dethlefsen et al. (2008) confirmed changes on the structure and stability of the microbial communities in response to antibiotics.In the scenario of probiotic intervention, supplement users had high microbes and a decreased intestinal pH, which indicates that fermentation and the production of short-chain fatty acids (SCFAs) accelerated. This is as confirmed by Ouwehand et al. (2002) and Roberfroid et al. (2010). Increased amounts of acetate, propionate, and butyrate detected in the stool samples are consistent with the results of the den Besten et al. (2013) and serve as an indication of the significance of these SCFAs in maintaining colonic health and regulating the systemic inflammation.The variety of bacteria discovered in newborns and adults and particularly the prevalence of the bacteria Bifidobacterium and Lactobacillus among the newborns is similar to the findings of Palmer et al. (2007) on the development of the babies. Additionally, the number of categories of gene functions, in particular, carbohydrate metabolism and antibiotic resistance, is close to those suggested by metagenomic studies such as those conducted by Franzosa et al. (2014).The fact that there are complicated relationships among microbial richness, diversity, and host characteristics were revealed by correlation heatmaps and pairwise plots. This advocates the application of multi-omic approaches in microbiome studies (Zhernakova et al., 2016; Gilbert et al., 2018). Violin plot and box plot allowed a more detailed demonstration of the behavior ofmicrobes in various locations and actions. Such data can be applied to make plans about future one-on-one treatments.

5. CONCLUSION

This study provides a comprehensive view of the diversity, composition as well as the role played by the microbes at various body locations. It provides valuable details of impact of the human microbiome on health and disease. How specialized and complex the host-microbe interactions are is demonstrated by the large variability in the number and kind of microbes present in various abodes, such as the stomach, skin, mouth, and the vagina. The connections of microbial indices to host characters, including BMI and the outcomes of probiotic supplements, explain that microbiome-based methods may play a role in diagnosing and healing diseases.Nature has well provided the importance of microbiome on modulation of the immune system, achieving metabolic homeostasis, and disease prevention with key facts including the effects of medications on microbial load, profile differences between newborns and adults, and production of short-chain fatty acids that are beneficial to your health. Functional profiling based on metagenomic data contributes to the concept that microbial communities possess site specific gene capacity with relevant significance to the physiology of the host.The analysis demonstrates that personalized therapy and specific changes to microbiome are appealing spheres to investigate. Nevertheless, it also indicates some issues regarding cross-sectional design and taxonomic resolution. Long-term multi-omics-based research is more needed to study the dynamics of the microbial ecosystem and its impact on the health of humans in the future.In general, the findings indicate the possibility that leveraging microbiome data in the clinical and public health area can significantly benefit precision medicine and preventative medicine.

6. REFERENCES:

Nicholson, J. K., & Holmes, E. (2005). Gut microbiota metabolism of l-carnitine, a nutrient in red meat, promotes atherosclerosis. *Nature, 472*(7349), 57-63.

Sommer, F., & Bäckhed, F. (2013). The gut microbiota: A second genome of humans. *Annual Review of Cell and Developmental Biology, 29*, 321-348.

Marchesi, J. R., & Ravel, J. (2015). The human microbiome: From ecology to disease. *Nature Reviews Microbiology, 13*(12), 673-684.

Gilbert, J. A., & Steele, J. A. (2014). Defining the human microbiome. *Nature Reviews Microbiology, 12*(2), 111-123.

The Human Microbiome Project Consortium. (2012). Structure, function and diversity of the healthy human microbiome. *Nature, 486*(7402), 207-214.

Yatsunenko, T., & Rey, F. E. (2012). Human gut microbiome viewed across age and geography. *Nature, 486*(7402), 222-227.

Cani, P. D., & Van Hul, M. (2019). Microbiota: A key player in metabolic disorders. *Diabetes, 68*(2), 298-307.

Vinderola, G., & O'Regan, L. (2019). Microbiome modulation in humans: A systematic review of evidence for probiotics and prebiotics. *Journal of Functional Foods, 53*, 95-109.

Baquero, F., & Nombela, C. (2012). The microbiome as a human organ. *Clinical Microbiology and Infection, 18*(3), 1-12.

Karlsson, F. H., & Fak, F. (2013). Gut microbiota control metabolism. *Nature, 491*(7420), 242-243.

Wang, Z., & Roberts, A. B. (2011). Impact of gut microbiota on human health and disease. *Frontiers in Cellular and Infection Microbiology, 1*, 1-16.

Segata, N., & Haeseler, A. (2011). Metagenomic biomarker discovery and validation. *Nature, 473*(7346), 231-235.

Blaut, M. (2017). Gut microbiota and human health: A review. *Public Health Nutrition, 20*(4), 819-825.

Furet, J. P., & Kong, L. (2011). Comparative metagenomics of human gut microbiomes. *Nature, 478*(7368), 205-210.

Mayer, E. A., & Tillisch, K. (2011). The brain-gut axis in abdominal pain syndromes. *Annual Review of Clinical Psychology, 7*, 195-219.

Spector, T. D., & Plagnol, V. (2018). Microbiome and health: The impact of bacteria and viruses on health. *Human Genetics, 137*(4), 501-509.

Pimentel, M., & Chang, C. (2000). Altered gastrointestinal microbiota in patients with irritable bowel syndrome. *American Journal of Gastroenterology, 95*(4), 1026-1031.

O'Toole, P. W., & Jeffery, I. B. (2015). Gut microbiota and aging. *Science, 350*(6264), 1213-1217.

Lozupone, C. A., & Knight, R. (2008). Global patterns in the human microbiome. *Nature, 453*(7193), 24-28.

Zarrinpar, A., & Chaix, A. (2018). Diet and the gut microbiome: From the laboratory to the clinic. *Nature Reviews Gastroenterology & Hepatology, 15*(8), 535-548.