Online Available at: https://www.sciplatform.com/index.php/wjb/article/view/1000

ISSN (Online) = 2522-6754 ISSN (Print) = 2522-6746

WORLD JOURNAL OF BIOLOGY AND BIOTECHNOLOGY

Review Manuscript www.sciplatform.com

The human microbiome: A critical player in health and disease

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Authors' Contribution | **Ali, Z., A. Athar & H. S. Muzaffar** designing methodology. **M. Abdullah, A. Rasool, A. Mahmood & Y. Majeed** collaborated on the visualization aspect of the article.

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Review Proccess: Peer review

ABSTRACT

The human microbiome is a remarkable and sophisticated ecology made up of billions of bacteria that live in various regions of the human body, and its importance in supporting human health cannot be understated. The gut microbiome, in particular, has been widely studied and determined to have an important role in immune system regulation, digestion and absorption of nutrients, and the creation of numerous metabolites. Gut microbiome dysbiosis has been related to a variety of conditions and diseases, including metabolic disorders and inflammatory bowel disease. However, the encouraging outcomes of microbiome-based therapeutics like fecal microbiota transplantation and probiotics have given fresh hope for the treatment and prevention of many disorders. Similarly, the skin microbiome and oral microbiome have been discovered to play significant roles in pathogen protection, inflammatory regulation, and general health. Skin and mouth microbiome dysbiosis have been linked to a variety of dermatological and dental illnesses, respectively. Microbiome-based treatments, such as topical probiotics, oral probiotics, and prebiotics, have shown success in the treatment and prevention of various disorders. The human microbiome is an intriguing and promising field of research that might lead to new ways of preserving and improving human health. We can create novel ways for preventing and treating a variety of illnesses and diseases by better understanding the intricate connections between the microbiome and the host. It is imperative to continue exploring the microbiome to discover novel and effective therapeutics to battle the increase in chronic illnesses and enhance the general health of our communities.

Keywords: The human microbiome, ecosystem, gut microbiome, skin microbiome, oral microbiome, dysbiosis.

INTRODUCTION: The human microbiome is a complicated ecology made up of billions of bacteria that live in different regions of the human body, such as the stomach, skin, and oral cavity. These microorganisms, including bacteria, fungi, viruses, and other microbes, are critical to human health because they perform various tasks. Understanding the human microbiome is a fast-growing area of research, and technological developments have allowed for unprecedented depth in the exploration of these microbial communities (Dekaboruah *et al.*, 2020). The gut microbiome is one of the human body's most intensively researched microbial ecosystems. It starts developing at birth and is impacted by several variables such as food, genetics, and exposure to the environment (Sbihi *et al.*, 2019). The gut microbiota is essential for nutritional digestion and absorption, immune system control, and the creation of different metabolites. Dysbiosis, or a malfunction of the gut microbiome, has been linked to a variety of illnesses and diseases, including metabolic problems like obesity and diabetes, as well as inflammatory bowel diseases like Crohn's syndrome and ulcerated colitis (De Paula *et al.*, 2018). Microbiome-based treatments, such as fecal microbiota transplantation and probiotics, have demonstrated promising outcomes in the treatment and prevention of several disorders (Gulliver *et al.*, 2022). The skin microbiome is another significant microbial community that performs an important function in human health. It begins to form soon after birth and is regulated by several elements, such as skin pH, temperature, and moisture. The skin microbiome is essential for protecting the skin from infections, controlling inflammation, and sustaining skin barrier integrity (Sanford and Gallo, 2013). Skin microbiome dysbiosis has been linked to a variety of dermatological illnesses, including acne, eczema, and psoriasis. Topical probiotics and bacteriotherapy, two microbiome-based therapeutics, have demonstrated promising outcomes in the treatment and prevention of several disorders (Pistone *et al.*, 2021). The oral microbiome is another important microbial community that offers an important function in human health. It begins to form shortly after birth and is impacted by several variables, such as food, cleanliness, and environmental exposure. The oral microbiota is essential for defending the oral cavity against infections, controlling inflammation, and sustaining oral health (Kilian *et al.*, 2016). Oral microbiome dysbiosis has been linked to a variety of dental disorders, including caries, periodontitis, and halitosis. Oral probiotics and prebiotics, which are microbiome-based medicines, have demonstrated encouraging outcomes in the treatment and prevention of various disorders (Bacali *et al.*, 2022). So, the human microbiome is an extensive and varied ecology that is vital to human health. Technological advancements have enabled a greater knowledge of the microbiome and its functioning, as well as the impact of dysbiosis on human health (Malla *et al.*, 2019). Microbiome-based therapeutics have great potential for the treatment and prevention of a variety of diseases, but more study is needed to create novel ways for preserving and improving human health (Li *et al.*, 2021).

The human microbiome: An ecosystem: The human microbiome refers to the enormous variety of microorganisms that live inside the human body. A key role in human health and illness is played by this diverse and dynamic population of microbes. The microbiome interacts with the human body in a variety of ways, from digestion and intake of nutrients to immune system control and even emotions and behaviors. It is made up of billions of microorganisms, including bacteria, fungi, viruses, and other microbes (Gebrayel *et al.*, 2022). The makeup, development, and function of the human microbiome are still largely unknown, even though they are of utmost importance (Conlon and Bird, 2014). This article will go into the intriguing world of the human microbiome and examine both its potential as a therapeutic target for various illnesses and disorders as well as its function in sustaining health.

Gut microbiome: The eukaryotic microorganisms, bacteria, archaea, and viruses that live inside and at the surface of the human body make up the microbiome. These bacteria have a significant ability to affect our physiological state of health and illness. They play a role in metabolic processes, offer defense against infections, develop the immune system, and through these basic functions, have a direct and indirect impact on the majority of our physiological activities (Shreiner *et al.*, 2015). About 100 trillion microorganisms living in the digestive tract make up the gut microbiome, which is their collective genome. The gene repertoire of our gut bacteria includes 150 times more unique genes than the individual's genome (Ghaisas *et al.*, 2016).

Gut microbiome development: The microbial population in a baby's gut begins to grow from birth. Even though newborns are exposed to microbes from various environmental sources and in the postpartum period that follows, the maternal gut is the primary source of stably colonizing taxa. The resemblance of the bacterial strains present in the mother and newborn dyad has also been demonstrated using culture-independent approaches, such as strain-level metagenomics analysis. In addition to its microbial components, breast milk also contains a complex mixture of macronutrients and bioactive molecules such as lactoferrin and secretory immunoglobulin IgA, which protect the new-born against pathogens, as well as a variety of cytokines, growth factors, and microRNAs that influence the infant's immunologic and metabolic development. A similar conclusion has been reached using feature selection approaches, bacterial composition enumeration, and fecal collection from birth cohorts in low and middle incomes countries. These results highlight a small subset of "age discriminatory" bacterial taxa whose changing patterns of representation define a programmed gut microbial community assembly shared by healthy children across cohorts. By the end of the second phase, this process

seems to be nearly complete. Analysis of waste samples has dominated much of the work done so far in the field of gut microbiome research because they are relatively simple to acquire. Due to the difficulty of collecting samples, the small intestine microbiota has remained an understudied "wilderness". A minor intestinal enteropathy with an uncertain etiology is term as environmental enteric dysfunction (EED). Undernutrition in children is a symptom of the generational effects of social injustice and poverty. Among the various causes, evidence is mounting for the importance of microbial communities passed down from mothers to their children as well as the disturbed growth of this microbial "organ" during the crucial first two years of life. Although how the various microbial communities in the gut contribute to the growth and metabolism of the host are still unknown (Barratt *et al.*, 2022).

Functions of the gut microbiome: The extensive groups of microbes that live in the human gastrointestinal system are becoming important regulators of human health and illness. The important function of the microbiome in the gut is attested to by the fact that a person receives a variety of essential services from it.

These include converting indigestible food components into absorbable metabolites, synthesizing essential vitamins, removing harmful substances, competing with pathogens, and fortifying the intestinal wall (Heintz-Buschart and Wilmes, 2018).

Dysbiosis and gut microbiome-based therapies: There is mounting evidence that the development of both intestinal and extra-intestinal illnesses is influenced by gut microbiota dysbiosis, but environmental factors like nutrition (high sugar low fiber), xenobiotics (antibiotics, medications, food additives), and cleanliness play a more significant role (Hrncir, 2022). Coeliac disease, irritable bowel syndrome (IBS), and inflammatory bowel disease are intestinal disorders. In this respect, intestinal microbiota transplantation (IMT) is one alternative treatment for inflammatory bowel disease (IBD), particularly for individuals with recurrent pseudo-membrane colitis caused by *Clostridium difficile* (Carding *et al.*, 2015). On several levels, the gut microbiota could be therapeutically useful. First, fecal microbiota transplantation (FMT) could be used to re-establish the complete microbiota population. Second, to fill in for missing functions, the gut microbiota may be supplemented with specific helpful strains or groups of such strains (probiotics), whilst undesired or hazardous strains may be eliminated using antibiotics, antifungals, or bacteriophages. The production of toxic metabolites may be decreased or blocked while the generation of advantageous metabolites is stimulated by targeting certain microbial metabolic pathways. FMT has a cure rate of more than 90% and is a very powerful and lifesaving treatment for recurrent *C. difficile* infection (rCDI). Since the majority of CDI patients recover following a single FMT treatment, it is frequently suggested as the first line of treatment. To achieve market exclusively, the pharmaceutical industry is attempting to categorize FMT as a medicine. Other gastrointestinal conditions that have been treated with FMT include ulcerative colitis, constipation, irritable bowel syndrome, liver conditions like cirrhosis with encephalopathy and alcoholic hepatitis, as well as neurological conditions like multiple sclerosis and Parkinson's disease. New diagnostic and treatment methods may be created with a better understanding of gut microbiota, its metabolites, and its interactions with hosts. To make a diagnosis, identify the disease subtype, and track illness progression and treatment effectiveness, invasive diagnostic techniques like tissue biopsy are frequently needed. Therefore, the need for trustworthy and non-invasive markers exists. Some components of the gut microbiota and certain metabolites, according to recent research, may serve as helpful diagnostic and prognostic markets. Promising therapeutic strategies include those that try to influence the microbiome to boost the synthesis of protective metabolites or inhibit or reduce the production of harmful metabolites. For instance, the microbial conversion of dietary choline to TMA has been successfully stopped using 3,3- dimethyl-1-butanol, a structural counterpart of choline. Atherosclerosis and serious cardiovascular disease have been linked to trimethylamine N- oxide (TMAO), an oxidation product of TMA. It's interesting to note that a recent study contends that TMA, not TMAO, may be the primary offender because of its nephrotoxicity and cardiotoxicity. Preclinical results demonstrate that SCFA (Short-chain fatty acids) supplementation improves hepatic steatosis, suggesting that manipulating the microbiome to boost SCFA production may potentially be advantageous (Hrncir, 2022).

Gut Microbiome and metabolic disorders: Trillions of microbes residing in the human gut make up the gut microbiota or gut microbiome. Recent research has shown that the gut microbiome plays a crucial part in maintaining overall well-being and good health. Various factors influence the makeup of the gut microbiome. Diet, environment, genetics, etc. are some of these factors. Gut microbiome disruptions can cause various metabolic disorders, which may include obesity, type two diabetes, and bowel inflammation. Additionally, the importance of the gut microbiome in metabolic disorders has become increasingly clear in recent years. For example, studies have shown that gut microbiome changes can cause the body to process food differently, which can lead to obesity. Additionally, type two diabetes has been linked to imbalances in the gut microbiota, which has an impact on over 400 million people globally. Similarly, bowel inflammation, which encompasses ailments like Crohn's disease and ulcerative colitis is also strongly influenced by disruptions to the gut microbiome (Zhao *et al.*, 2022) (figure 1).

Figure 1: Representative description of the metabolic diseases, gastrointestinal disorders, neuromusculoskeletal conditions, endocrine pathologies, neurodegenerative, and cardiovascular diseases associated with gut dysbiosis (Baptista et al., 2020).

The statistics and facts surrounding gut microbiome and metabolic disorders highlight the significant impact that these conditions have on individuals and communities around the world. For example, according to WHO, approximately 2 billion people living on earth are overweight or obese, with obesity rates tripling since 1975. In addition, the global prevalence of type two diabetes has also drastically increased in recent years, with over 90% of cases being attributed to lifestyle and environmental factors. Finally, inflammatory bowel disease affects over 10 million people worldwide, with significant impacts on quality of life and healthcare costs (Zawada *et al.*, 2020). Moreover, the impact of gut microbiome and metabolic disorders on communities is significant, with implications for healthcare systems, public policy, and individual well-being. The growing body of research on the gut microbiome highlights the need for greater attention to be paid to this critical aspect of human health, including developing new treatments and interventions targeting the gut microbiome. By addressing these conditions and promoting overall gut health, communities can improve the well-being of individuals and promote a healthier, more sustainable future (Zawada *et al.*, 2020).

Gut Microbiome and inflammatory bowel disease: The gut microbiome, which comprises trillions of microorganisms that reside in the human digestive system, plays a crucial role in maintaining human health. The gut microbiome is involved in digestion and nutrition absorption, the regulation of the immune system, moreover intestinal barrier maintenance. However, disturbances to the gut microbiome can lead to various gastrointestinal disorders, including bowel inflammation. Bowel inflammation, which includes Crohn's disease and ulcerative colitis, is a chronic inflammatory illness of the gastrointestinal tract [20]. In this condition, there is inflammation in the intestinal lining, which might bring on signs like tummy pain, diarrhea, and bleeding from the rectum. The exact causes of inflammatory bowel disease (IBD) are not fully understood, but research suggests that disruptions to the gut microbiome can have an impact on the onset and spread of the disease (Candelli *et al.*, 2021). Furthermore, the statistics and facts surrounding IBD highlight the significant impact that this condition has on individuals and communities worldwide. According to the World prevalence of approximately 0.3% in North America and Europe. The condition may have a major effect on life quality, with studies showing that individuals with IBD experience lower levels of employment, education, and social participation compared to the general population. Additionally, the healthcare

 Digital Object Identifier: https://doi.org/10.33865/wjb.008.01.1000

costs associated with IBD are substantial, with estimates suggesting that the annual cost of IBD in the United States alone is over $6 billion (Sýkora *et al.*, 2018). Finally, the impact of IBD on communities is multifaceted, affecting individuals, families, and healthcare systems. The chronic nature of the disease requires ongoing medical care, including medications and regular monitoring, which can be burdensome for individuals and families. Additionally, IBD can lead to long-term complications, such as intestinal strictures and cancer, which can further impact the well-being of individuals and place additional strain on healthcare systems. The gut microbiome's evolving role in IBD highlights the need for further research and development of new treatments that target the gut microbiome, with the potential to improve outcomes and reduce the burden of this condition on individuals and communities (Candelli *et al.*, 2021).

Gut microbiome and cancer: It was confirmed disruptions to the gut microbiome with an increased risk of developing certain types of cancer. Understanding the relationship between the gut microbiome and cancer is essential for developing new strategies to prevent and treat this disease. The gut microbiome can influence various aspects of cancer development, including tumor growth, immune response, and response to therapy. For example, certain bacteria in the gut have been shown to produce metabolites that can promote tumor growth, while other bacteria can stimulate the immune system to attack cancer cells. Additionally, disruptions to the gut microbiome caused by factors such as diet, antibiotics, and chemotherapy can impact the effectiveness of cancer therapies (Louis *et al.*, 2014). The statistics and facts surrounding gut microbiomes and cancer highlight the significant impact of this disease on individuals and communities globally. The World Health Organization reports that cancer is the second most common cause of mortality worldwide, estimated to have caused 9.6 million deaths in 2018. Furthermore, disruptions to the gut microbiota have been linked to several cancers, including colorectal cancer, the third most prevalent cancer diagnosed worldwide. Concluding, the impact of cancer on communities is profound, affecting individuals, families, and healthcare systems. The financial burden of cancer is substantial, with estimates suggesting that the global cost of cancer is approximately $1.16 trillion annually. Additionally, cancer may have a major effect on life quality, with physical and emotional symptoms that can impact individuals and their families. The expanding knowledge of connection between cancer and gut microbiome emphasizes the need for additional study to better comprehend the factors underlying this connection and to develop new strategies to prevent and treat cancer by targeting the gut microbiome (Akbar *et al.*, 2022).

Human skin microbiome: The human skin is an important element of pathogen protection. Throughout the organism changes in its characteristics affect the microbial makeup. The skin microbiome comprises fewer taxa in comparison to the most varied body regions because of its textural properties, including oil, wetness, sebaceous glands, and an acidic pH (Chaudhari *et al.*, 2020). In a network that differs in terms of density and content, there are bacteria as well as fungi, viruses, archaea, and mites. The microbiome of the skin is made up of all of these different species (Grice *et al.*, 2009). The significance of skin homeostasis is highlighted by the consequences for wound healing and defense against possible pathogens or environmental factors (Boxberger *et al.*, 2021).

Skin microbiome development: The skin microbiome is made up of bacteria, fungi, archaea, viruses, and mites (Demodex) (Boxberger *et al.*, 2021). The physiology of the skin site was revealed to be the primary determinant of the makeup of microbial communities, with variations in the relative numbers of bacterial taxa that are associated with moist, dry, and sebaceous microenvironments (Byrd *et al.*, 2018). *Staphylococcus, Propionibacterium, Corynebacterium*, and *Streptococcus* are the four most prevalent genera in the skin. Additionally, *Propionibacterium* species dominate oilier environments (lipophilic), whereas *Staphylococcus* and *Corynebacterium* species flourish in humid niches. The microbiome includes fungi as a significant component. *Malassezia*, for instance, is a common lipophilic yeast found all over the body. Whereas some fungi such as *Aspergillus* species, *Cryptococcus* species, and *Rotorua* species are site-specific and only inhabit certain foot regions (Bay *et al.*, 2020).

Functions of skin microbiome: Human skin microbiomes are assumed to be distinct based on lifestyle and genetic susceptibility (Bay *et al.*, 2020). Comparable to those found in the gut, the skin microbiome plays important functions in the breakdown of natural products, immune system development, and defense against pathogen invasion. The skin microbiome can promote both innate and adaptive immune responses (Shen *et al.*, 2014). Skin's microbiome helps in maintaining skin homeostasis and its ability to act as a barrier. The desquamation process as well as stratum corneum renewal are aided by the production of protease enzymes by the skin microbiome. The production of sebum and free fatty acids also plays a role in pH regulation (Meisel *et al.*, 2018). Lipase enzyme secretion is involved in the breakdown of the lipidic film surface. In addition to these functions, the microbiome also makes biofilm, produces bacteriocins, and senses quorums (Baldwin *et al.*, 2017).

Skin microbiome and dermatological disorders: Different disease states can develop as a result of genetic or environmental changes in the normal microbiome (Ellis *et al.*, 2019). However, there is a chance that human skin's microbiome could be pathogenic, which closely corresponds to host homeostasis (Chen *et al.*, 2018). Pathogens are associated with some skin conditions including chronic wounds, psoriasis, atopic dermatitis, and acne vulgaris (Yang *et al.*, 2022) (figure 2).

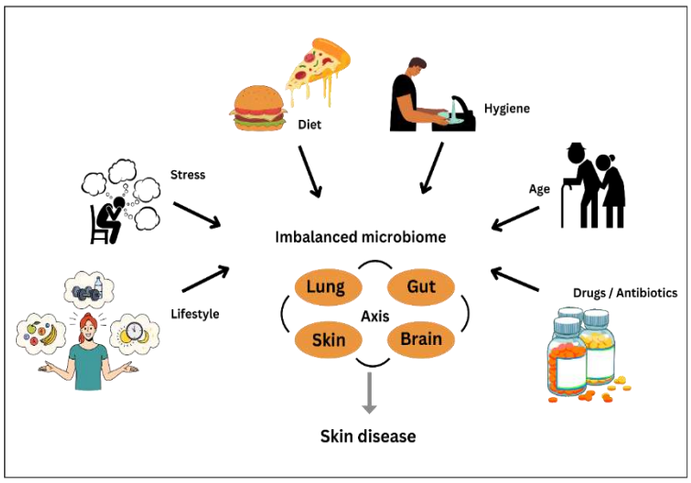

Figure 2: Factors linked to skin disorders, including lifestyle, stress, nutrition, hygiene, age, and medication (antibiotic) use, are all linked to skin illnesses via the gut, lungs, skin, and brain axis (Yang et al., 2022).

Role of the skin microbiome in acne: Teenagers frequently suffer from the chronic inflammatory skin condition acne vulgaris (Bhate and Williams, 2013). Acne is characterized by symptoms including nodular cystic lesions, pimples, and pustules that are brought on by bacteria that penetrate hair follicles (Kurokawa *et al.*, 2009). *P. acnes,* follicular keratinocytes, and the sebaceous glands are thought to be the three main contributors to the formation of acne (Tom and Barrio, 2008). Antibiotics are being used to prevent the growth of *P. acnes*. It is crucial to comprehend the skin microbiome related to acne and find alternative acne treatment methods because antibiotic resistance is an increasing issue in clinical practices (Xu and Li, 2019).

Psoriasis: The relationships between innate and adaptive immune cells and keratinocytes which are facilitated by cytokines in addition to signaling molecules are hypothesized to be the pathophysiology of psoriasis (Martins *et al.*, 2020). The psoriasis-affected skin and skin adjacent to it had similar microbiomes. Particularly, it was found that skin with psoriasis lesions had higher levels of firmicutes, Bacteroidetes, and streptococcus and lower levels of actinobacteria and Propionibacterium (Yan *et al.*, 2017; Langan *et al.*, 2019). *Xanthomonadacea*, a proteobacterium known to be keratolytic, was linked to clinical improvement following to 3-week balneotherapy treatment. Probiotics taken orally have a favorable effect on the course of psoriasis (Olejniczak-Staruch *et al.*, 2021).

Atopic dermatitis (AD): Atopic dermatitis often known as eczema, is a persistent allergic skin disease characterized by an erythematous, dry, and severely pruritic rash with a characteristic distribution (Avena-Woods, 2017). Atopic dermatitis is recognized as multifactorial, with both hereditary and epigenetic factors playing a role (Avena-Woods, 2017). Generally, the skin microbiome of AD patients is low in diversity, with *S. aureus* predominating (Tom and Barrio, 2008). In certain cases, *S. aureus* overgrowth precedes the formation of AD (Grice *et al.*, 2009). However, studies investigating the effect of systemic antibiotics alone did not show lasting improvements in AD skin lesions and only revealed a short-

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term decrease in the cutaneous *S. aureus* burdens (Boguniewicz *et al.*, 2001).

Rosacea: Rosacea is a severe inflammatory disorder of the facial skin (Tan and Berg, 2013). *Demodex folliculorum*, a mite that exists within the sebaceous glands of normal skin, is a pathogen that is frequently linked with rosacea (Jarmuda *et al.*, 2012). *Bacillus Oleronius* a pro-inflammatory, gram-negative bacterium is thought to be carried by *Demodex* mites. This bacterium is susceptible to many antibiotics typically prescribed for treating rosacea, including doxycycline (Lacey *et al.*, 2007) (table 1).

Disease	Disease-Associated Skin Microbiota	Further Insight	Reference
Acne vulgaris	Particular strains of *Propionibacterium acnes*	Probiotic bacteria administration may provide a protective benefit.	(Lomholt & Kilian, 2010)
Atopic Dermatitis	Decreased bacterial diversity. Increased abundance of *S. aureus.*	AD skin is susceptible to viral infections, including *Herpes simplex* and *coxsackie* viruses.	(Callewaert et al., 2020; Chng et al., 2016; Kong et al., 2012; Shi et al., 2016)
Psoriasis	Higher abundance of *Staphylococcus* and *Streptococcus.*	Skin microbiota changes can occur as a result of anti-psoriasis therapy.	(Alekseyenko et al., 2013; Chang et al., 2018; Statnikov et al., 2013; Takemoto et al., 2015)
Rosacea	*Demodex folliculorum* (mites)	Rosacea is associated with alterations in skin microbiota composition, including decreased *C. acnes* and increased levels of *Snodgrassella Alvi, Geobacillus*, and *Gordonia.*	(Forton & Seys, 1993; Woo et al., 2016)

Table 1: Skin disorders and their associated microbiota.

Strategies for skin disease treatment: Skin illness can be brought on by an unbalanced microbiome or by specific strains of microbes. Skin health is correlated with lots of lifestyle choices. Maintaining healthy skin might benefit from exercise (Yeh *et al.*, 2022). Regular exercise can help to protect the skin from free radicals, but intense or prolonged training as well as inactivity may cause oxidative stress and contribute to the development of skin cancer (Kruk and Duchnik, 2014). Living in an environment that is polluted may decrease skin hydration speed up sebum production and exacerbate the signs of chronic inflammatory skin conditions (Frankel *et al.*, 2012). Vigorous exercise, especially calisthenics and aerobic exercise has been independently associated with a lower chance of developing psoriasis. Therefore, in addition to other commonly used skin disease treatment methods, a proper diet, cleaning, exercise, and moisturizing should be used (Yang *et al.*, 2022).

Dysbiosis and skin microbiome-based therapies: When healthy and harmful bacteria in the gut are out of balance it is called Dysbiosis. It can hurt our health. This might occur as a result of factors like taking excessive amounts of antibiotics, eating unhealthily, being very stressed, or having specific medical conditions. We can treat it by altering our food, taking probiotics, and using other treatments to balance the healthy bacteria in our gut (Petersen and Round, 2014). Clinically managing AD may benefit by reducing the number of harmful bacteria and re-establishing the skin's normal microbial balance (Huang *et al.*, 2009). The majority of antibiotics are also tended to encourage *S. aureus* strains that are resistant to antibiotics, as well as disrupting the normal microbiome because of their lack of specificity. However, a phase 3 trial (NCT02840955) examines the potential for the treatment of a bacteriophage endolysin (Staphefekt) in atopic dermatitis adult patients (Pastagia *et al.*, 2013). Prebiotics are substances that support the development of beneficial bacteria. To discover probiotic strains and prebiotic substrates that might improve skin microbial communities and skin health, further research is required. In addition to therapeutic approaches, diagnostic tests that are based on the microbiome can improve the treatment and management of skin problems. Additionally, microbiome-based therapeutics and diagnostics are very applicable to precision and personalized medicine and may in the future revolutionize the management and treatments of dermatological diseases (Grice, 2014).

Oral microbiome: The microbes found in the human oral cavity are often called the oral microbiome, oral microbiota, or oral microflora. Dutch scientist Antony van Leeuwenhoek was the one who initially recognized the oral microbiota. After the gut, it is the second biggest microbial population in humans. The human microbiome has a core microbiome and a variable microbiome. All people contribute the same core microbiome, yet have different variable microbiomes based on their way of living and physiological makeup. The hard and soft tissues of teeth and the oral mucosa, are two places in the mouth where microbiomes can colonize. The bacterial biofilm is a great layer of bacteria that shields the whole oral cavity (Deo and Deshmukh, 2019). Most varied microbiomes in the human body, comprising viruses, fungi, protozoa, archaea, and bacteria, are found in the mouth. With about 1000 species present, the bacterial communities in the mouth are extremely complex (Wade, 2013).

Oral microbiome development: Usually, the womb of the fetus is infertile. The amniotic fluid, in particular, may be colonized by oral bacteria in as much as 70% of pregnant women, according to new studies. The baby is exposed to the microbiome of the mother's womb and vagina during delivery, and after birth, the baby is exposed to the bacteria in the environment. A newborn's mouth cavity is frequently sterile despite the considerable risk of contamination. The mouth obtains regular microbe inoculations starting with the first meal, encouraging the growth of the natural oral microbiota. The cultivable bacteria *Fusobacterium nucleatum* has been identified to be the most prevalent. Any surface gains the residing microflora by frequently transferring microbes to the location suitable for colonization. Although passive transfer from a mother and microbes found in milk, water, and the environment is also a way of transmission, saliva is the main method. Colonization starts at or soon after birth. Settler species, like *Streptococcus salivarius*, are the first species to colonize following birth. Alongside the first year, aerobes, such as *Streptococcus*, *Lactobacillus*, *Actinomyces*, *Neisseria*, and *Veillonella*, are the main invaders of the oral cavity. These microorganisms can colonize nonshedding surfaces after tooth eruption starts. Following the emergence of all the teeth, more surfaces are created for colonization. To allow periodontal microorganisms to colonize, gingival fissures develop. For various microbial communities to be created, plaque deposition is visible at various places on the tooth, such as smooth edges and pits, and fissures. This process leads to the development of significant diversity of species and microbial subsequence. When all the teeth are lost with aging, the flora resembles that of a child just before tooth emergence (Deo and Deshmukh, 2019).

Functions of the oral microbiome: At both the Micron and host scales, the physiological and ecological processes of the microbiome become intricately entwined with the characteristics of the host. The microbiome has a great impact on whether health is encouraged or illness improvement is accelerated. Typically, the oral microbiome exists as a biofilm. It is significant for preserving oral homeostasis, safeguarding the cavity in the mouth, and halting the progression of the disease. Critical physiological, metabolic, and immunological operations are carried out by the communities of microbes found in humans including food and nutrition digestion, energy production, differences and development of the host mucosa and its immune system, ruling of fat depot and metabolism, processing, and elimination of environmental chemicals, conservation of the body's defenses, and the stability between pro and anti-inflammatory cytokines (Deo and Deshmukh, 2019).

Dysbiosis: The oral microbiome in disease: A healthy condition (in symbiotic), or a disease-related state (in dysbiosis) is maintained by the intricate balancing between species that live in the oral cavity. When the variety and average number of species or taxonomy within the microbial community are disrupted, the microbiome is said to be dysbiosis. While the diversity of microbial communities in the healthy mouth is extremely stable (after its microbiome developed in childhood), the interaction between the microbiome of the mouth and its host is dynamic, and biological alterations in an individual's life can affect the equilibrium of the species within those communities. These include changes in the body like aging or hormonal ones like those associated with puberty and pregnancy, which healthy people can typically adapt without harming their oral health. Other times, the delicate environment in the mouth can be upset, resulting in a dysbiotic shift, a loss of social balance or diversity within the biofilm, a predominance of one or a small number of species, and an elevated risk of disease. Salivary gland dysfunction, or modifications to saliva flow and composition, poor oral hygiene, gum inflammation, and lifestyle decisions including

 Digital Object Identifier: https://doi.org/10.33865/wjb.008.01.1000

smoking and eating habits are all modifiable causes of oral dysbiosis. Listed below is a summary of the dysbiosis-causing factors (Kilian *et al.*, 2016) (figure 3).

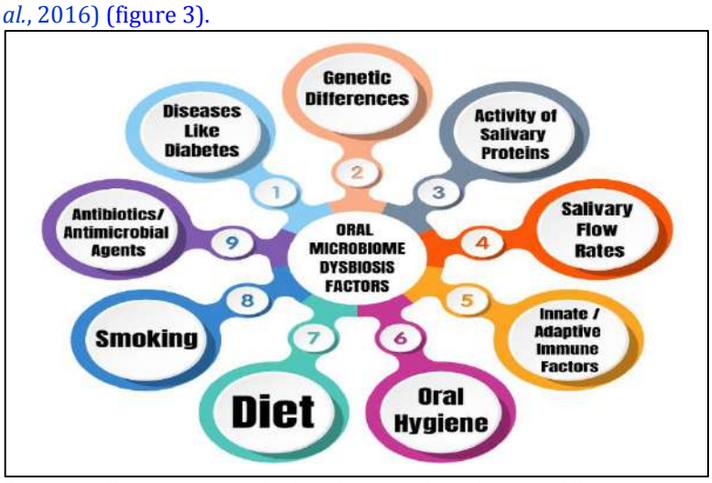

Figure 3: Causes of dysbiosis, diseases like diabetes (Graves et al., 2019), genetic differences (Rosier et al., 2018), activity of salivary proteins (Marsh et al., 2016), salivary flow rates (Lynge Pedersen & Belstrøm, 2019), innate/adaptive immune factors (Desai & Landay, 2018), oral hygiene (Kilian et al., 2016), diet (Gasmi Benahmed et al., 2021), smoking (Huang & Shi, 2019), and antibiotics/antimicrobial agents (Marsh, 2018).

It is now widely understood that the bacteria formerly thought of as oral pathogens can be found in small amounts in healthy areas and that oral disease results from a harmful alteration of the microbiota's natural equilibrium rather than from a foreign infection.

Oral microbiome-based therapies: Oral microbiome and periodontitis: Oral and systemic disorders may be brought on by disruptions in the symbiotic relationship between the human body and the oral microbiota. Through the breathing or circulatory systems, as well as the digestive tract, microorganisms from biofilm in the mouth can spread to other regions of the body. Periodontitis (PD) is a bacterially induced chronic periodontal inflammation that causes alveolar bone resorption, tooth loss, and progressive irreversible breakdown of the connective dental attachment. The most prevalent types of PD are linked to anaerobic, Gram-negative bacteria, including *Spirochetes* like *Treponema denticola* and bactericides like oral *Porphyromonas gingivalis* or *Prevotella intermedia* (Sela, 2001), (Jain and Darveau, 2010), (López, 2000) (figure 4).

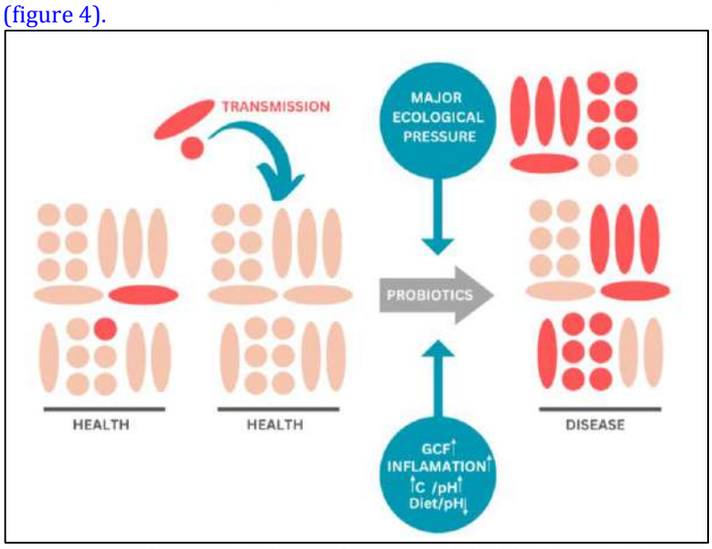

Figure 4: Insights into Oral Microbiome model of dysbiosis (Kilian et al., 2016).

In addition, PD or linked to systemic illnesses. These illnesses include cardiovascular, neurological, respiratory or autoimmune disorders, osteoporosis, diabetes, cancer, or premature birth. Improvements in systemic disorders may coincide with improvements in periodontal health, and vice versa; PD may be lessened by the therapy of these illnesses. Early detection and management of PD may be crucial in the treatment of systemic diseases.

Oral microbiome and Diabetes mellitus: Diabetes mellitus and oral flora change both influences the development and course of the disease, whereas high glycaemic levels change the composition of the microbiome. Treatments for periodontal disease may enhance metabolic regulation and blood glucose levels. Alterations in neutrophil function and potential development of advanced products of glycation (AGE) and subsequent activation of AGE receptor (RAGE), which results in increased production of pro-inflammatory cytokines, are hypothesized to explain the propensity for PD in diabetes mellitus.

Oral microbiome and pulmonary diseases: Poor mouth health and PD may be related to ongoing lung disease and pneumonia, as mouth bacteria may affect the colonization of respiratory pathogens. Additionally, oral pathogens have been discovered in the bronchoalveolar fluid of cystic fibrosis patients. By enhancing the composition of the oral taxa in favor of the typical H2O2-producing *Streptococcal commensals, Pseudomonas aeruginosa* may be inhibited in this environment.

Oral microbiome and osteoporosis: Age, smoking, drinking, BMI, and menopause are all risk factors for osteoporosis. The vicious cycle of osteoclast activation, gingival bone loss, greater periodontal space, bacterial proliferation, and inflammation may be caused by excessive production of inflammatory cytokines (Bacali *et al.*, 2022). Oral Microbiome and dental diseases. Dental caries (tooth decay) is the most prevalent bacterial disease in humans (Wade, 2013).

Dental caries: Dental caries, often known as tooth decay, is a main factor in tooth loss and oral pain. It can start as a slight change in the surface of the teeth and progress to lesions in the dentin. Acid-producing bacterial colonies gather in dental plaque as supragingival biofilm develops on teeth, lowering the pH of the mouth and fostering an environment where they can flourish and produce more plaque. These opportunistic infections include the fermentation of dietary carbohydrates, resulting in acidic by-products that either erode the enamel of the tooth crown or the tooth root. The absorption of calcium, phosphate, and carbonate from teeth, which typically shield the tooth enamel from these pathogens, is made simpler by a low pH environment. *S. mutants, Strep sobrinus*, and *Lactobacillus acidophilus* are the most frequent bacteria implicated in dental caries, yet the particular microbiome that signifies dental caries has not been yet identified. The best oral hygiene practices, a healthy diet, and fluoride exposure can all help prevent dental caries, which is the most treatable and reversible childhood disease (Zarco *et al.*, 2012).

CONCLUSION: To summarize, the human microbiome is a complicated and varied ecology of microbes that live in many regions of the human body, such as the stomach, skin, and oral cavity. These microbiomes conduct critical tasks that benefit human health, including digestion, immune system modulation, and pathogen defense. Dysbiosis, or a microbiome imbalance, has been linked to a variety of ailments and diseases. Probiotics and fecal microbiota transplantation, for example, show promise in the treatment and prevention of various disorders. However, much remains to be discovered about the human microbiome, including the intricate interactions between the microbiome and the host as well as the impact of environmental variables on changing the microbiome. Future research on this subject will be critical for generating new products.

CONFLICT OF INTEREST: Authors have no conflict of interest

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