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Review Article

Microbiome And Human Health.

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Abstract

The human microbiome, a complex community of microorganisms residing within and on our bodies, has emerged as a critical player in shaping both physical and mental well-being. This article explores the profound influence of the microbiome on various aspects of human health. We delve into the impact of microbial communities inhabiting the gut, esophagus, oral cavity, respiratory tract, skin, and reproductive system, highlighting their roles in maintaining physiological functions and preventing disease. Furthermore, we examine the emerging evidence linking the microbiome to mental health disorders, including depression, bipolar disorder, anxiety, and stress-related conditions. By elucidating the intricate connections between the microbiome and human health, this review underscores the potential for novel therapeutic strategies targeting the microbiome to promote overall wellness.

Keywords : *Microbiome, Physical Health, Mental Health.*

THE GUT MICROBIOME AND PHYSICAL HEALTH

All these body's parts studied such as the esophagus, lungs, skin surface, oral cavity, and intestine have a biome in them that deals with microorganisms. The majority of its components are bacteria, with the remainder being viruses, phages, fungus, and archaea. The rest of the saying is traced by fungi and archaea, and triangles have also triumphed. It is understandable why they are frequently called fungi. In controlled infections and in many environmental microbial settings, bacteria tend to settle down at particular spots referred to as biofilms, whether or not they happen to be part of the microbial community. Their favorable traits to exist in a microbiome are trust to community dwelling and communication.

In order to form a community, bacteria utilize tiny particles referred to as auto inducers to interact and communicate with each other. One of the ways they ascertaining the amount of intra species communication and the presence of interspecies communication is through a process termed as quorum seeing [1]. The communication enables a number of species to synergistically create an enclosed microbiome and sustain the community. Even though all territories contain microbiomes, this review intends to emphasize on the relationship between mortal complaint pathology and the bacterial community forming the microbiome.

Among the most well-known human microbiomes, the intestinal tract, or gut, has been the subject of the most research. The host's digestion and nutrition depend on the gut microbiota, which can produce nutrients from substrates like xyloglucans, which are present in lettuce and onions but that host processes cannot reach. Compared to other areas of the body, the gut microbiome contains a greater variety of bacterial species.

Based on information gathered by the MetaHIT metagenomic analysis database and the Mortal Microbiome Project, about 3000 bacterial species have been isolated from mortal faeces. More than 90 percent of the gut microbiome is made up of Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes, which are divided into 11 distinct phyla [2,3]. Be aware that niche-specificity frequently determines the makeup of a microbiome in a larger host environment. The tonsils, throat, epoxies, slaver, tongue, buccal mucosa, palate, subgingival and supragingival shrine, and tooth shells are among the niche-specific microbiomes found in the general area of the oral depression, despite the frequent reference to the "oral microbiome" [4].

The 16S rRNA gene reference sequences for oral species in the several colourful habitats mentioned above are carefully curated and linked to accessible genomes in the mortal Oral Microbiome Database (eHOMD) [5]. Of the 775 microbial species in the database as of the end of 2021, 30 had not yet

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been clothed and 57 had formal names. These are inferred using 2074 oral and nasal genomes, which correspond to 529 taxa currently included in the database. The greatest number of rubrics are found in the phyla Firmicutes and Proteobacteria, which are followed by Actinobacteria and Bacteroidetes. The healthy human lower respiratory tract is not sterile, unlike what some people initially believed, and instead has microbial populations that are similar to but different from those of the upper respiratory tract [6,7].

Numerous distinct functional taxonomic units (OTUs), some culturable and named and others not, have been identified thanks to the use of 16S rRNA and whole-genome sequencing. Rather than the varying rates of reduplication of its members, the appearance of new species, which is typically caused by aspiration of largely concentrated oral concealment, and the junking of species, which is primarily caused by mucociliary concurrence, determine the size of the healthy lung microbiome, providing for a balanced rate in microbial composition [6,8]. Although research on the microbiota in lung diseases such pneumonia, chronic obstructive pulmonary disease (COPD), and cystic fibrosis is widespread, less is known about the microbiota in healthy lungs.

The primary bacterial species were skin commensals from the rubrics Staphylococcus, Streptococcus, Veillonella, Prevotella, and Propionibacterium, according to early work by Charlson et al. using 16S rDNA sequencing of bronchiolar lavage (BAL) samples from the lower respiratory tract. However, species from soil and water-associated rubrics like Burkholderia and Comamonada were also present [9], indicating that key characteristics of the lung microbiome were species accession from the host's nasopharynx, skin, and external terrain. This study also demonstrated that the phyla within the healthy lung microbiome Proteobacteria, Firmicutes, Actinobacteria, Bacteroidetes, and OTUs belonging to the Prevotella, Veillonella, and Streptococcus rubrics.

Questions over slice ways and implicit bronchoscope impurity of samples led Dickson et al. to take over a rigorous experimental study minimizing impurity and gain a topographic figure of lower respiratory tract microbiota [10]. Results were harmonious with former studies showing that airway and lung bacterial communities act those of the oropharyngeal tract, with little substantiation of point-specific enrichment by reproducing bacteria.

Microbiomes in complaint countries

Complaint countries can affect from compositional changes in microbiome speciation or cornucopia changes within microbiome species, both performing in microbiome dysbiosis, or expression of acridity characteristics by a species within the microbiome.

Regarding the third of these, research indicates that under some conditions, asymptomatic microbiome species may exhibit acridity traits indicative of disease. With colonization rates of up to 36, Streptococcus agalactiae is typically regarded as a component of the normal vaginal microbiota. During gestation, still, the foetal transmission of S. agalactiae can be fatal to the invigorated and is a leading cause of morbidity and mortality in babies [11]. The exact medium that results in this switch to a malign phenotype is unknown; still, acridity is determined by the capsular serotype and acridity factors similar as the polysaccharide capsule, decoded by the cps gene, protein C, which includes the Ca face proteins (bca gene), Rib (caricature gene) and Cb (bac gene) [12]. Then, we examine a number of complaint states performing from conditioning within niche-specific microbiomes.

Although Streptococcus and Prevotella species make up the majority of the adult esophageal microbiome, alterations in age and complaint state similar to adenocarcinoma have been demonstrated to impact enrichment with Gram-negatives such as Haemophilus, Veillonella, and Rothnia spp., especially in the early stages of adenocarcinoma development [13].

Previous studies had also suggested that the esophageal microbiome in cases with influx esophagitis has high attention of Gram-negative species and that these are likely contributing to thepre-cancerous stage of adenocarcinoma development[14].

Lopetuso et al. have also examined changes in microbiome composition in Barratt's esophagus, another esophageal complaint state, and compared it to adenocarcinoma. Results from six Barratt's esophagus and ten adenocarcinoma samples showed a shift from the normal dominant Gram-positive Streptococci to Gram-negatives like Prevotella, Actinobacillus, and Veillonella, although this change was not as pronounced as that observed in the adenocarcinoma samples [15].

According to the study's recommendations, the esophageal microbiome's shift to Gram-negative bacteria becomes more noticeable as complaints become more rigid. A number of esophageal disorders include eosinophilic esophagitis, which is characterized by intraepithelial eosinophils in the scaled epithelium, dysregulated transubstantiating growth factor beta (TGF-b) product, and imperfect desmosomes. Mast cells and the cytokines IL-5 and IL-13 work together to cause the complaint state.

Eosinophils are triggered by overexpressing antimicrobial products like scrap cationic proteins, defensins, and DNA-containing extracellular traps, which may change the microbiome's makeup while also immortalizing the conditions needed to sustain the complaint [16,17]. Diets are one of the established treatments for eosinophilic esophagitis, which is also impacted by food allergies and nutrition. Researchers are now looking into links between the development of eosinophilic esophagitis and changes in the microbiome because of the microbiome's suggested role in this issue.

Harris et al.'s study of microbiome composition and eosinophilic esophagitis in 70 children [7 times their age] and adults with a history of esophageal narrowing, gelatin intolerance, and conditions leading to endoscopic complications indicating eosinophilic esophagitis [17] focused on a significant increase in Haemophilus sp. in undressed subjects compared to subjects without eosinophilic esophagitis. It included whole-genome sequencing and 16SrRNA. Benitez et al. compared cases of eosinophilic esophagitis before and after beneficial changes to a cohort of patients with non-eosinophilic esophagitis and found that although the overall bacterial cargo was significantly higher in eosinophilic esophagitis, the species diversity was not significantly lower than in the control group [18]. Eosinophilic esophagitis and changes in microbiome diversity in the adult population do not appear to be related, according to a recent study by Johnson et al. [19].

The gastrointestinal tract's (gut) microbiome has been the subject of the most research. Studies on the development of the child's gut microbiota and changes in the gut microbiome in various geographical countries over the past 20 years have shown disorders such as diabetes, liver disease, cancer, and, more recently, neurodegenerative diseases. In the case of infants, research has indicated that the manner of delivery (natural or caesarean), the kind of child feeding [bone or formula], the infant's gravid age at birth, hospitalization, and antibiotic use all have an impact on the microbiome development process [20]. The oxidized environment of the initial sterile gut is conducive to the colonization of facultative aerobes, among which Lactobacillus, Prevotella, and Sneathia sp. are among the most prevalent. Anaerobes follow them when oxygen is used up and the environment is more depleted [20].

The formation of a healthy gut microbiome depends on the presence of Bacteroides and Bifidobacterium, which are known to play a significant role in the susceptible response [21]. A study by Backhed et al. showed that within 5 days of vaginal delivery, a different population comprising substantially motherly gut bacteria similar as Escherichia, Bifidobacterium, Enterococcus and Bacteroides was apparent, whereas babies delivered by caesarean section contained a larger proportion of motherly skin foliage at the same time point [22]. Seditious bowel complaint (IBD) a complaint group that includes Crohn's complaint and ulcerative colitis eventually leads to gut microbiome dysbiosis and a reduction in species diversity. This leads to the proliferation of invasive and glutinous E. coli strains, as well as facultative anaerobes. The colon, where bacterial populations are largest, and the terminal ileum and rectum, where faecal material accumulates, are where these strains are most visible [23].

Additionally, as compared to the microbiome of people without IBD, the overall microbiome is changed in IBD cases. The host pattern recognition receptor nucleotide-binding oligomerisation sphere-containing protein 2 NOD2 mutations serve as an example and are a risk factor for Crohn's disease. Both Gram-positive and Gram-negative bacteria's peptidoglycans are impacted by NOD2. Studies conducted on NOD2-knockout mice showed a decrease in cytokine expression and an increase in a specific mucosa-associated microbial dysbiosis with changed focus of gut mucosal microorganisms [24].

Other beast studies have shown that the transfer of proinflammatory bacteria or microbiota from diseased mice to healthy mice induces bowel inflammation, and origin-free mice aren't susceptible to ulcerative colitis [25]. There are some antithetical data on the significance of microbial changes in IBD, stemming from the mortal microbiome design [26]. 132 people including 27 without IBD were followed for 1 time and compared for faecal metagenomes, metatranscriptomes, metaproteomes, viromes, metabolomes, host exomes, epigenomes, transcriptomes and serological biographies in samples taken over this time.

Longitudinal data could be gathered by reclaiming cases from both the active and inactive complaint ages. These findings showed that there were no discernible differences in metagenomic species between people with IBD and those without; nevertheless, metabolite pools showed a lower degree of individuality in IBD, which corresponded to earlier compliances indicating a decrease in microbial diversity [27].

Obesity [28-31], inflammation [32-34], and insulin insensitivity [35] among grandfathers with type 2 diabetes [T2D] has been associated with changes to the gut microbiota, though there is still no comprehensive examination of the deleterious interplay between T2D and the host's microbiome changes. During obesity, the composition of the human microbiome shifts, with increased representation of members from the Firmicute phylum compared to Bacteroidetes [36,37].

As for non-Westerners, a Japanese investigation revealed that the likelihood of observing Firmicute to Bacteroidetes ratio elevation was also present in the obese subjects. The same study also reported that five species of Firmicutes were associated with obese subjects whereas five species of Bacteroidetes were associated with non-obese subjects [38]. Same modifications have been set up for T2D [39,40]. Changes to the composition of the gut microbiome can lead to increased intestinal permeability and consequently, systemic inflammation.

The chronic, low-grade inflammatory state that is characteristic of diabetes and its related disorders [41]. In the case of T2D, some species have been linked with its presence or absence. It has been noted that T2D patients have an altered microbiome containing larger amounts of the bacterium Faecalibacterium prausnitzii. Once again, the type 2 diabetic gut microbiome is deficient in the mucus colonizing species A. muciniphila, which during sugar starvation

conditions can metabolize mucin for carbon and nitrogen [42]. Niche-specific colonization of oral depression has shown the link of specific bacteria to their specific niches. Some 25% of people are also S. aureus positive which is the most likely colonist of the nostrils along with the skin-commensals S. epidermidis, Corynebacterium sp. and S. aureus. S. aureus colonization in the nares increases the risk of contamination of food products with pathogenic S. aureus growing in the nasal cavity which in turn raises the risk of food poisoning [43]. Using 16S RNA sequencing, research on the microbiota of 12 adults revealed Actinobacteria, Propionibacteriaceae, and Corynebacteriaceae were the three dominant phyla present in the nose while Firmicutes and Proteobacteria were found in the mouth. There was a difference in microbiome composition between the nasal cavity and the mouth, oral cavity, or the oral depression. Staphylococceae were absent in the oral depression, while in Strepotococcaceae, the sink of Firmicute rubrics, was the foremost as its constituted [44].

The predominating type of bacteria composing the pharyngeal microbiome belongs to benign Streptococcus species, which might be expected to have some communicable complaints together with diphtheria, meningitis, pneumonia, and other more severe pathogens. As a mouth ailment, periodontitis or PDIS can severely damage the premaxilla and the upper jaw bone along with the epoxies if left untreated. It has roots in inflammation stemming from the collapse of the immune system along with the peculiar oral microbiome of the individual. Among the various other oral flora that is its subordinate, some periodontopathic species which includes Tannerella forsythia, Porphyromonas gingivalis and Treponema denticola are to blame for the onset of PDIS.

The changes in microbiota during treatment for a manageable form of PDIS included, but were not limited to, Porphyromonas endodontalis, Porphyromonas gingivalis, Prevotella spp., Tannerella forsythia, Dialister spp., Selenomonas spp., Catonella morbi, Eubacterium spp., Filifactor alocis, Parvimonas micra, Peptostreptococcus, Fusobacterium, Pseudoramibacter alactolyticus, and Streptococcus intermedius [45].

Pathogenic bacterial species of the microbiome can derive in slavers in sufficient numbers to adversely affect the host or other's wellbeing. Acute post infectious glomerulonephritis, rheumatic fever, TB, scarlet fever, erysipelas, cellulitis, necrotizing fasciitis, septicemia, and toxic shock syndrome are severe ailments that Group A Streptococci, comparable to S. pyogenes, can cause [46]. Umeda et al. studied six species of periodontopathic bacteria in whole slaver and sub gingival shrine from 202 subjects and concluded that whole slaver, along with P. gingivalis, Prevotella intermedia, Prevotella nigrescens, and T. denticola, serves as a reservoir and transmission pathway to periodontal lesions [47,48].

Given that the microbiome of the healthy lower respiratory tract exists, it is feasible to imagine the introduction of pathogenic organisms into the lung environment.

The upper respiratory tract is the primary source of microorganisms that the lower respiratory tract receives from the environment. With the support of the local flora, the weak defense mechanism should be able to keep out invaders who are mature and in good individuality. This is demonstrated by the dysbiosis brought on by the absence of cross membrane ion control in cystic fibrosis, which results in altered lung mucus landscape and microbiota. Certain species of bacteria thrive in this environment, and in fact, microbial alterations have been noted since immaturity.

Frayman et al. established that microbial diversity was considerably lower in the BAL samples from CF kids than in the non-CF controls in a 16S rRNA sequencing study of BAL samples obtained from 21 CF babies and 10 non-CF babies at 1.8 and 5 months after delivery [49]. Additionally, total bacterial biomass was almost correlated with the location of inflammation, with Staphylococcus, Ralstonia, and Methylobacterium showing the highest increases in CF babies and Fusobacterium, Neisseria, and Escherichia/Shigella showing the highest increases in non-CF babies. The overall bacterial biomass in CF was considerably higher than in non-CF samples [$p<0.01$] in a larger study that included 136 pediatric CF, 45 pediatric non-CF, and 10 adult CF BAL samples. The rubrics of loftiest cornucopia in CF cases were the typical pathogens associated with the complaint[Pseudomonas, Staphylococcus, Stenotrophomonas, Haemophilus,Achromobacter and Burkholderia], and all except Haemophilus were absent in thenon-CF cohort. The discovery that seven novel rubrics of high frequency, which are not commonly linked to CF infection and pathogenesis (Streptococcus, Prevotella, Bordetella, Veillonella, Moraxella, Neisseria, and Corynebacterium), were present in 20 out of all CF samples was an interesting one [50].The finding of notable decreases in the gut biomass of specific species, specifically Bacteroides vulgatus, Bacteroides uniformis, F. prausnitzii, Bifidobacterium catenulatum, and Bifidobacterium adolescentis in CF children [51], has reinforced the reality of a "gut – lung axis," which holds that a dysbiosis in microbiomes occurs coincidentally in both the gut and the lung. These changes occur concurrently with changes in the lung microbiome, suggesting cross-talk between the two locations. Bronchial asthma also causes a dysbiosis of the lung microbiome, and this changed microbiome most likely develops before asthma manifests.

One theory holds that asthma and impaired, vulnerable system development result from immaturity-induced lack of exposure to a variety of environmental microorganisms [52]. Studies have examined the role of microbiota along the gut-lung axis in asthma, and as previously said for CF, a dysbiosis in the gut microbiome can cause a concomitant lung dysbiosis

in asthmatics. Preschool-aged children's microbiota studies by Stiemsma et al. demonstrated evidence of gut bacterial dysbiosis, specifically a decrease in the Lachnospiraceae family in favor of Clostridium, which is implicitly linked to asthma [53].

A metagenomic investigation of gut bacterial sequencing data from 36 adults with asthma compared to 185 controls looked at changes in the gut microbiome of adult asthmatics [54].

Asthmatics have reduced levels of butyrate-producing bacteria, such as Coprococcus eutactus and F. prausnitzii.

Increases in the prevalence of Clostridium bolteae, Clostridium ramosum, Clostridium spiroforme, and Eggerthella lenta—the latter of which has also been connected to an increase in IBD—were directly associated to this.

Long-term airway inflammation, respiratory discomfort, and habitual tailwind restriction are the hallmarks of COPD. Like CF instances, COPD patients experience exacerbations as a result of seditious episodes. It has been shown that the microbial diversity pattern in foam and farther-distant samples varies in COPD. Therefore, a method that samples the distal bronchi and alveoli similarly to BAL fluid is the preferred method for assessing the lung microbiome.

An initial analysis of BAL samples from four COPD cases showed that the severe complaint cases had less diversity loss than the mild cases, but one of the three healthy test individuals had an equivalent decrease of diversity. However, it should be mentioned that the limited sample size further reduces the power of the findings [55]. Pragman et al.'s analysis of 32 BAL samples from moderate COPD, eight from severe COPD, and ten non-COPD controls revealed that the COPD samples had higher levels of members of the anaerobic Gram negative phylum Fusobacteria. This increase was evident across all taxonomic situations, including the rubrics Leptotrichia and Fusobacterium, Prevotella, Haemophilus, Fusobacterium, Pseudomonas, Streptococcus, Veillonella, and Porphyromonas [56]. Shotgun metagenomics and 16S rRNA sequencing were utilized to show that the gut of COPD patients had a decrease in the relative abundance of Firmicutes and an over-representation of Proteobacteria, which include the majority of pathogenic species [57].

As demonstrated in the examples below, variations in the microbiome composition between healthy and unhealthy nations are a contributing factor to a number of skin disorders. Fahl et al. observed a shift in bacterial counts in psoriasis cases when compared to healthy controls. They found that Proteobacteria sp. were present on the body's box at significantly advanced situations, while Streptococcus and Propionibacterium sp. were present in lesions compared to healthy skin spots [58]. Subsequent research connected two different microbial species groups that predominate in psoriasis cases: a Firmicute-Actinobacteria-associated group and a Proteobacteria-associated group [59].

Atopic dermatitis is characterized by notable changes in the variety and makeup of the microbial communities inside microbiomes. S. aureus is the primary species found in skin lesions caused by atopic dermatitis. Even yet, S. aureus does not frequently colonize the skin of those who do not have atopic dermatitis.

According to research, aureus colonization of the skin is necessary for the development of lesions. Kong et al. established that, in contrast to less than five healthy individuals, more than 90 cases of atopic dermatitis are resolved by S. aureus on both lesional and non-lesional skin. Similarly, S. aureus becomes the dominating species in the microbiome's makeup near the lesion site, indicating a loss of variety [60]. Additionally, there is a rise in number of anaerobic species such Clostridium and Serratia marcescens within these lesions [61]. Puberty is usually linked to acne, a skin condition where P. acnes is known to be present in the lesions. Although P. acnes makes up around 90% of the microbiota in the sebaceous gland microbiome of healthy individuals, it does not cause acne. Only specific strains of lesion strains with genes likely responsible for their acridity are linked to acne, according to 16S rRNA sequencing, whereas other strains are linked to the healthy skin microbiome [62-65].

THE GUT MICROBIOME AND MENTAL HEALTH

The intricate relationship between our bodies and minds is a subject of ongoing scientific exploration. Emerging research highlights a fascinating connection between the trillions of microorganisms residing in our gut – collectively known as the microbiota – and our mental well-being. This connection, often referred to as the gut-brain axis, is a bidirectional communication network where the gut influences the brain, and vice versa [65, 66]. The way that mental health issues are understood and addressed is greatly impacted by this intricate interaction. Recent research has focused on elucidating the intricate connections between the gut microbiota and various mental health conditions, including depression, bipolar disorder, anxiety, and stress-related disorders.

The Gut-Brain Axis is a Two-Way Street. The gut-brain axis involves a complex interplay of neural, hormonal, and immunological signaling pathways. The gastrointestinal [GI] flora, comprising bacteria, fungi, viruses, and other microorganisms, is not just a passive player in digestion. It actively communicates with the brain, influencing mood, stress response, and even cognitive function [67, 68]. This communication occurs through several routes, including the vagus nerve, which directly connects the gut to the brainstem. Factors such as stress and a high-fat diet can significantly alter the composition and function of the GI flora, which in turn affects brain function through the release of various signaling molecules [69]. For example, chronic stress can lead to a

reduction in beneficial bacteria and an increase in harmful bacteria, disrupting the balance of the gut microbiome [70].

Our gut microbiota's makeup and function are significantly influenced by the foods we eat and the way we live. Consuming a lot of processed foods, sweets, and saturated fats can upset the delicate balance of the gut environment, which can lead to inflammation and the proliferation of dangerous bacteria. On the other hand, a diet high in fruits, vegetables, fiber, and fermented foods can promote a varied and healthy gut flora, which in turn supports mental health. In recent years, the Dietary Inflammatory Index was created to describe a person's diet on a scale ranging from pro-inflammatory to anti-inflammatory. Several research have looked into how the Dietary Inflammatory Index affects depression [121]. For example, a Mediterranean diet, rich in olive oil, nuts, vegetables, and fish, has been associated with improved mental health outcomes [122-126].

The gut microbiota affects mental health in a number of important ways

- ***Neurotransmitter Production***: Gut microbes can produce or modulate neurotransmitters like serotonin, dopamine, and GABA, which play crucial roles in mood regulation, reward, and anxiety [71]. For example, almost 90% of the serotonin in the body is thought to be produced in the gut. Certain bacteria can also synthesize GABA, an inhibitory neurotransmitter that helps reduce anxiety and promote relaxation. Alterations in these neurotransmitters have been linked to stress-related psychiatric disorders [72, 73].
- ***Inflammation***: An imbalance in the gut microbiota, often triggered by factors like a high-fat diet, can lead to increased gut permeability [or "leaky gut"]. This allows inflammatory molecules to enter the bloodstream and potentially affect brain function, increasing the risk of depression [74]. When the gut barrier is compromised, substances like lipopolysaccharide [LPS] can enter circulation, triggering an immune response and inflammation in the brain. Patients with depression have an increase in inflammation [75] and n-3 PUFAs have an inhibitory effect on this system, which suggests another potential beneficial effect for this disorder [12]. N-3 PUFAs are thought to exert their anti-inflammatory effects by modulating the production of cytokines and other inflammatory mediators [77]. Inflammasomes, multi-protein complexes that detect signals in the inflammation pathway and activate pro-inflammatory cytokines, are also implicated in this process [78].
- ***Metabolic Pathways***: Gut bacteria can influence metabolic pathways that impact mental health. For instance, certain gut bacteria can synthesize metabolites of dopamine, affecting reward and motivation [79]. Short-chain fatty acids [SCFAs], produced by the fermentation of dietary fiber in the gut, have also been shown to influence brain function and behavior. Studies have shown that the gut biota can influence both risk for MetS, and via gut biota that synthesize a metabolite of dopamine risk for depression [80, 81].

Recent studies have employed various methodologies, including brain imaging, intervention trials, and observational studies, to investigate the gut microbiome's role in mental health. Brain imaging techniques have provided valuable insights into the gut-brain connection. Randomized controlled trials have investigated the effect of probiotic treatment on brain activity. For example, a four-week probiotic treatment with **Bifidobacterium longum** 1714TM showed differences in neural oscillations in the frontal and cingulate cortex during both resting-state and after social stress, with changes observed during resting state associated with higher self-reported vitality and reduced mental fatigue [82]. In contrast to a placebo, a different study employing a multispecies probiotic formulation revealed increased positive affect and variations in the BOLD [blood-oxygen level-dependent] signal pattern in response to emotional recognition memory tasks and emotional decision-making tasks [83]. Cross-sectional studies have also explored brain connectivity in relation to gut microbiota composition. Higher resting-state insular functional connectivity was associated with higher fecal bacterial microbiota diversity, lower abundance of **Bacteroides**, and higher abundance of **Prevotella** [84]. Prevotella abundance was higher, Bacteroides abundance was lower, and fecal bacterial microbiota diversity was higher when resting-state insular functional connection was higher [84]. Anatomical and functional connectivity of reward and anxiety-related regions was linked to elevated levels of fecal indole metabolites [85].

DEPRESSION

- Meta-analyses have shown that probiotics can improve mood in individuals with pre-existing depressive mood symptoms compared to placebo [87]. Additionally, probiotics, when used as a supplement to antidepressant treatment, have shown an overall positive effect on depressive symptoms in clinically depressed patients compared to antidepressant treatment alone [88]. Probiotics [Lactobacillus helveticus and B. longum] significantly reduced depressive symptoms in patients with mild to severe major depressive disorder [MDD] when compared to those taking prebiotics, according to one study [89]. However, some studies did not find an effect of multistrain probiotics on depressive scores, although they did report a greater reduction in cognitive reactivity toward sad mood [90]. In depressed patients,

supplementing with Lactobacillus plantarum 299v enhanced cognitive function in comparison to SSRIs and a placebo [91]. In individuals with treatment-resistant MDD, a group receiving supplemental probiotics [CBM588] in addition to antidepressants showed a reduction in depression ratings, a 70% treatment response, and a 35% remission rate when compared to the group taking antidepressants alone [92]. Fecal microbiota transplantation has been found to alleviate depression and anxiety in patients with IBS or other functional gastrointestinal disorders [93, 94].

- Cross-sectional studies comparing fecal microbiome in patients with MDD and healthy controls have yielded discrepant results. Some studies reported an overrepresentation of phylum Actinobacteria and Firmicutes and the genus **Bifidobacterium** and **Blautia** in MDD patients compared to healthy controls [95], while others reported lower diversity in MDD, with lower abundance of Firmicutes [96]. A metaproteomic analysis revealed that the bacterial protein profile in MDD differed from that of controls, with variations in proteins related to the metabolism of glucose and amino acids [97]. Lower fecal levels of the bacterial metabolites short-chain fatty acids [SCFA] acetate and propionic acid, but higher isocaproic acid concentrations were found in depressed compared to non-depressed women [98]. Individuals with more hostile marital interactions had higher bacterial endotoxin blood levels, particularly those with a history of mood disorder [99]. Fecal **Dialister** and **Coprococcus** spp. were found to be depleted in depression, even after correcting for antidepressant use [100]. Positive self-judgment and the quantity of Lactobacillus species in the feces were directly correlated, although cognitive depression and reduced affective empathy were only indirectly correlated [101]. In individuals with inflammatory bowel disease [IBD] in remission, reduced microbiome diversity was linked to higher levels of stress, anxiety, and depression symptoms [102]. Decreased diversity was associated with poorer self-rated health, but not with anxiety or depression [103].

BIPOLAR DISORDER

Studies assessing the gut microbiome in bipolar disorder have shown inconsistent results. Some studies have found BD to be associated with a decreased bacterial diversity when compared to healthy controls [107, 108, 109], while others found no difference [110, 111]. The results are also inconsistent in terms of predominant phyla in BD [107, 108, 109, 112, 113]. An open trial examining the impact of a multistrain probiotic in euthymic patients with BD revealed improvements in executive function, attention, and psychomotor processing speed [114]. This was the only published trial on probiotics in BD.

ANXIETY AND STRESS DISORDERS

By reducing the stress-induced decrease of Bifidobacterium spp. and the stress-induced increase of Streptococcus spp., a 4-week randomized controlled trial of long-term use of Lactobacillus gasseri CP2305 [CP2305] in healthy young adults revealed improvements in mental state, sleep quality, and gut microbiota under stressful conditions [115]. When comparing the probiotic group to the placebo group, another randomized controlled trial assessing the impact of multispecies probiotics on anxiety in healthy college students revealed improvements in neurophysiological anxiety, panic anxiety, negative affect, worry, and negative mood regulation [116]. Patients with generalized anxiety disorder have lower fecal bacterial alpha diversity, fewer operational taxonomic units, and reduced Firmicutes and Tenericutes abundances [117], as well as decreased short-chain fatty acid-producing bacteria and overgrowth of **Escherichia-Shigella**, **Fusobacterium**, and **Ruminococcus gnavus** [118] compared to healthy controls. Pregnant women that reported exposure to two or more adverse childhood experiences had a greater abundance of fecal **Prevotella** than pregnant women with none or only one adverse childhood experience [119]. An association between maternal pregnancy general anxiety and fecal microbiota composition has been observed [120].

POTENTIAL THERAPEUTIC APPLICATIONS

New therapeutic approaches have been made possible by our expanding knowledge of the gut-brain axis. Probiotics, which are live microorganisms intended to benefit the host, are being investigated as potential treatments for mood disorders [127]. Studies have shown that certain probiotic strains can reduce symptoms of anxiety and depression [128, 129]. Additionally, dietary interventions aimed at reducing inflammation and promoting a healthy gut microbiota are being explored as complementary approaches to mental health care. Prebiotics, which are non-digestible food ingredients that promote the growth of beneficial gut bacteria, are also being investigated for their potential to improve mental health. The use of dietary supplements, such as omega-3 polyunsaturated fatty acids [n-3 PUFAs], has also been explored for the treatment of depression [130].

CONCLUSION

The intricate relationship between the human microbiome and overall health is now undeniable. Our exploration has

revealed the microbiome's far-reaching impact, extending beyond its well-established roles in physical health – from the gut and other organ systems like the esophagus, oral cavity, respiratory tract, skin, and reproductive system – to encompass the complexities of mental well-being, including connections to depression, bipolar disorder, anxiety, and stress-related conditions. The degree to which a healthy "whole of body" microbiome contributes to the occurrence of the disease states and syndromes described in this review highlights the importance of this ecosystem in terms of species number and composition. The bacteria in distinct niche-specific microbiomes interact with one another both within and between species, which helps them react to the host. Disease development and host harm can arise from microbial dysbiosis within niche-specific microbiomes.

But as more recent research has shown, communication along the axes connecting host sites is just as crucial. Axonal communication has now been directly connected to a number of illness states, and in some instances, like H. pylori and Parkinson's disease, the connection was very surprising. Regarding the axes of communication, the current view is that they are extensive and most likely involve all or most niche-specific microbiomes cooperating to alter host sites.

While significant progress has been made in understanding these associations, much remains to be discovered about the precise mechanisms at play. The future of microbiome research lies in translating these discoveries into practical applications. This includes developing personalized interventions, such as targeted prebiotics, probiotics, or even fecal microbiota transplantation, to restore microbial balance and promote health. As we continue to unravel the secrets of this complex ecosystem, we move closer to a new era of medicine where the microbiome is recognized not just as a collection of microbes, but as a powerful tool for optimizing human health and preventing disease.

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