Wellness academy
FOR MIND, BODY & SOUL

Human Microbiome:
The key to optimal health

By Silvi Siddhu,
Global Scientific and Technical Manager,
Nutraceuticals, Univar Solutions

UnivarSolutions

TABLE OF CONTENTS

ABSTRACT 3

INTRODUCTION 3

MICROBIOTA VARIATIONS AND INTERACTIONS 4

- EARLY LIFE IMPLICATIONS 4
- DIET 5
- EXERCISE 5
- ANTIBIOTICS 6

MICROBIAL METABOLITES 6

THE ROLE OF GUT MICROBIOTA BEYOND THE GUT 7

- MICROBIOME IN DISEASES 7
- GUT-LUNG AXIS 7
- GUT-IMMUNE CONNECTION 7
- GUT-BRAIN AXIS 8
- GUT MICROBIOME, SLEEP, MOOD, STRESS, AND ANXIETY 9
- MICROBIOME AND WEIGHT MANAGEMENT 10
- GUT-SKIN AXIS 10

MODULATING GUT MICROBIOTA WITH PROBIOTICS AND PREBIOTICS 11

CONCLUSION 12

REFERENCES 13

ABSTRACT

Our understanding of the link between the gut microbiome, its metabolites, and overall health is constantly expanding. Advances in metagenomics have helped us understand the composition and function of the microbiome in both diseased and healthy states. Variability in the gut microbiota is largely dependent on the host's diet, lifestyle, and environment. It rapidly establishes in early life and continues to determine health and wellbeing in adult life. A lot of evidence highlights the role of the microbiota in various metabolic, immunological, and neurological diseases. Both gut microbiota and its metabolites can be significantly modulated by diet, including their diversity and composition. Continuous exploration of the human microbiome and affecting factors will provide opportunities for personalized nutrition and preventative treatments.

INTRODUCTION

The term microbiome (microbe + biome) is relatively new to our vocabulary; however, the concept of microbiome isn't. It dates to the first discovery of microbes by Antonie van Leeuwenhoek, the father of microbiology, in late 1600s. Marchesi and Ravel (2015) define microbiome as the entire habitat, including the microorganisms, their genomes (i.e., genes), and the surrounding environmental conditions. These microorganisms, also referred to as the microbiota, include bacteria, archaea, viruses, and eukaryotes (such as fungi). The majority of microbiota reside in the gut (Bengmark, 1998) and greatly influence human physiology and nutrition—and they are fundamental to human life.

It has been estimated that 100 trillion microbes inhabit the human gut, belonging to almost 1,000 species. Over 99% of the identified genes are bacterial (Qin et al., 2010). The number of bacteria alone significantly outnumbers the human cells within an individual (HMP Consortium, 2012a). The microbes differ in different body sites and even different areas along the gut likely because of different conditions (HMP Consortium 2012a). Each nutrient that enters the digestive system affects the type, the amount, the diversity, and the function of gut microbiota (Mills et al. 2019).

The human microbiome is a complex ecosystem. Large scale government funded projects were initiated a few years ago to better understand the microbiome colonization in humans. In 2008, the International Human Microbiome Consortium (IHMC) was established to enable researchers globally to understand and depict the relationship of the human microbiome in the maintenance of health and diseases. Two major multi-year, multi-institutional, multi-nation projects—the Human Microbiome Project (funded by National Instituted of Health, USA) and the Metagenomics of the Human Intestinal Tract (MetaHIT) project (funded by European Commission)—gathered extensive data on microbes in and on the human body as a basis for further in-depth studies. The aim is to put together a complete picture of microbiota, their genes, their role, their potential, and their overall impact on human life.

Recent studies have revealed some fascinating details about the human microbiome. Gut microbiota is believed to have coevolved with us. It complements human biology in ways that are mutually beneficial (Bäckhed et al., 2005). Due to its critical role in human biology, researchers have suggested that the gut microbiome could be a virtual organ. However, the human-to-human variation and fluctuating diversity make the microbiota a very complex 'system' (Mills et al., 2019). There is increasing evidence that the human microbiome plays an important role in overall health. Although we have only begun to scratch the surface in our understanding of its scope, the prospects seem endless.

MICROBIOTA VARIATIONS AND INTERACTIONS

The composition of gut microbiota is largely affected by geography, food culture, and lifestyle influences in addition to other factors listed below. It has also been speculated that the gut microbiome differs between advanced and developing countries (Tanaka and Nakayama, 2017). Yatsunenko et al. (2012) compared the microbiota composition of over 500 individual people ranging from 0-70 years from Venezuela, Malawi, and the United States and concluded that microbiota composition clustered according to country, irrespective of age. This is corroborated by other researchers where they found significant correlations between the composition of gut microbiomes among individuals sharing the same household (Rothschild et al., 2017).

In an interesting study, Caporaso et al. (2011) found that while microbiota is distinguishable between different body sites and individuals, there is a distinct variability in an individual's microbiota over time from the same sites. Only a small fraction of the total taxa is always present at the same time. This suggests that no core temporal microbiome exists at high abundance, at least for the ones that were detected (Caporaso et al., 2011). *Bacteroidetes* and *Firmicutes* phyla make up the majority of bacteria in a healthy gut (Falony et al., 2016; Eckberg et al., 2005). These two dominant phyla can vary from 10% to 90% between healthy individuals (HMP consortium, 2012b). Microbial diversity is linked to several human diseases. The diversity of microbes can be defined as the number and distribution of distinct types of organisms within their body habitat. A higher microbial diversity in the gut is associated with a healthier microbiota (Yu et al., 2015) and low diversity is linked to obesity and inflammatory bowel disease (Turnbaugh et al., 2009). There are, however, certain exceptions where higher diversity isn't necessarily better. For example, bacterial vaginosis is a result of high diversity in the vagina (Fredricks et al., 2005). *Proteobacteria (Escherichia coli), Verrucomicrobia, Actinobacteria, or Fusobacteria* are found in large percentages in an 'unhealthy' gut (Allaband et al., 2019).

EARLY LIFE IMPLICATIONS

The interaction between human microbiota and the environment is dynamic. The major factors that modulate gut microbiota are maternal microbiota, factors during birth (delivery mode, infant diet, immediate environment), adulthood dietary habits, aging, exercise, stress and drugs (e.g. antibiotics) (Kumar et al., 2019; Mackie et al., 1990). Intestinal microbial colonization is believed to begin when a fetus is in the uterus. However, an infant's gut microbiota is established after birth (Tanaka and Nakayama, 2017). These microbes originate mainly from the mother's gut, vaginal tract, skin, and the surrounding environment (Mackie et al., 1990). There are several factors that affect the microbial profile that early on, including genetics, maternal weight during pregnancy, mode of delivery, newborn diet (breastfeeding or/and formula), and immediate environment (Collado et al., 2010). One study found that infants living with pets had a richer and diverse microbiota (Azad et al., 2013).

It is evident that a healthy intestinal microbiota profile in early life is directly associated with health later in life (Isolauri, 2012; Dalby and Hall, 2020). Infants that are delivered naturally and breastfed show a *Bifidobacterium* rich microbiota (Turroni et al., 2018), while infants delivered via a C-section show a disrupted transfer of *Bifidobacterium* (Shao et al.,2019). The microbiota continues to evolve and change through infancy and childhood due to various factors including changing nutritional environment and other external factors such as antibiotics that significantly impact the composition of microbiota (Dalby and Hall, 2020). This change continues until three years of age, after which a typical adult like gut microbiota is established (Yatsunenko et al., 2012).

It is critical to explore the role of gut microbiota in early life as evidence mounts up that its imbalance (dysbiosis) is also associated with certain childhood or adult diseases such as asthma, atopic dermatitis, allergies, obesity, cardiovascular diseases, and neurological disorders (Sarkar et al., 2021).

DIET

Diet is a known modulator of gut microbiota, its composition, diversity, function, and metabolism activity (Sonnenburg et al., 2016; Zmora et al., 2019). One study analyzed bacterial 16S rRNA gene sequences from the fecal microbiota of 60 mammalian species: humans and 59 other species living in the zoo and in the wild. The results indicate that both the host diet and phylogeny influenced their bacterial diversity. Herbivores, compared to omnivores and carnivores, had the most diverse microbiota (Ley et al., 2008). This finding is further supported by evidence that vegan diets positively affect both bacterial composition and metabolic pathways of gut microbiota by increasing beneficial microorganisms (Sakkas et al., 2020). The gut microbiota of humans living a modern lifestyle bear a resemblance to that of omnivorous primates (Ley et al., 2008).

One human study hypothesized that long-term diets effect distinct enterotypes seen between those who follow an omnivorous diet and those who eat none or little animal products (Wu et al., 2011). Another study, however, postulates that the gut microbiome rapidly responds to an altered diet. The animal-based diet can lead to an increase in the number of bile-tolerant microorganisms *(Alistipes, Bilophila and Bacteroides)* and decrease the ones that metabolize dietary plant polysaccharides *(Roseburia, Eubacterium rectale and Ruminococcus bromii)* (David et al., 2014). Both are promising scenarios when looking to alter gut microbiota via diet to improve the risk factors of metabolic diseases.

Two dietary components that have been heavily studied in directly influencing the gut microbiota are prebiotics and probiotics, which are later documented in this article.

Dietary polyphenols have shown the ability to modulate the microbiota composition and exert prebiotic effects (Kumar et al., 2019; Alves-Santos, 2020). They can stimulate both the growth of microorganisms identified as prebiotic targets and an increase in the production of key metabolites of short chain fatty acids (SCFA). A systemic review of preclinical and clinical studies showed that dietary supplementation with polyphenols increased *Lactobacillus acidophilus, Bifidobacterium and Faecalibacterium spp.* in the gut, in addition to increasing butyrate, a SCFA (Alves-Santos, 2020). Omega 3 fatty acids have also been found to significantly impact the intestinal environment and gut microbiota composition. These polyunsaturated fatty acids are also shown to positively influence the gut-brain axis, acting through gut microbiota composition (Costantini et al., 2017).

The microbiome diet developed by Dr. Raphael Kellman centers around the concept of a balanced gut bacteria for optimal body function.

EXERCISE

There is a linear relation between physical activity and health state of an individual. It is widely known that regular exercise is beneficial to health in several ways, including managing stress, strengthening the immune system, and of course preventing weight related disorders that are usually associated with other metabolic diseases. Exercise can also adaptively alter the gut microbiota. In reverse, a healthy gut microbiota is also crucial for exercise performance (Hsu et al., 2015). The gut and its microbiota help facilitate the delivery of water, nutrients, and hormones during exercise. They also aid in the production, storage, and expenditure of energy obtained from the diet. All these resulting factors, including inflammation and redox reactions might be able to influence an individual's adaptation to exercise (Clark and Mach, 2016; Mach and Fuster-Botella, 2017). Recent studies have demonstrated benefits of certain microorganisms in fighting pathogens and reducing inflammation (McFadzean, 2014).

Physical exercise in early life is also associated with varying microbial diversity. During this time, the microbiota composition is still evolving and may positively influence this evolution that could create lasting adaptations in lean mass and psychological wellbeing (Mika and Fleshner, 2016). A surge in beneficial *Lactobacillus and Bifidobacterium* is associated with exercising, in addition to several health benefits (Queipo-Ortuño et al., 2013). Individuals who exercise more often show a significant elevation in their microbial diversity, as well as a significant elevation of certain members of the *Firmicutes* phylum (McFadzean, 2014). One study compared the fecal bacterial profile of athletes with non-athletes and found that athletes had a higher diversity of gut micro-organisms, representing 22 distinct phyla. This diversity also positively correlated with protein consumption and creatine kinase, a marker of extreme exercise, and other inflammatory and metabolic markers (Clarke et al., 2014).

ANTIBIOTICS

Numerous studies have demonstrated that external forces can alter the community of microbes in the gut and antibiotics are one such example. Antibiotics are prescribed to combat pathogenic bacteria that has caused adverse symptoms within the host. The antibiotics available today are broad spectrum and target the host's normal or 'good' microbiota as well. One such antibiotic, Ciprofloxacin, influenced the abundance of about a third of the bacterial taxa in the gut, and within three days, it decreased the richness, diversity, and evenness of the community. The extent of this effect varied among individuals. In some individuals, the taxonomic composition of the community began to closely resemble its pretreatment state four weeks after the end of treatment, but several taxa didn't recover even at six months (Dethlefsen et al., 2008). When studied the long-term effect of clindamycin, another antibiotic, highly significant disturbances in the bacterial community were observed and some persisted up to two years post-treatment (Jerbnerg et al., 2007). Similar effect was seen from antibiotics such as fluoroquinolones and β-lactam where they significantly reduced the host's microbial diversity by 25% and diminished the core phylogenetic microbiota by more than 50% (Panda et al., 2014).

MICROBIAL METABOLITES

Gut microbiome and its metabolites play a key role in human metabolism. The critical microbial metabolites include SCFAs, neuroactive molecules, vitamins, epigenetic factors, hormones, and probably hundreds of other still unidentified factors (Sarkar et al., 2016). The overall output of these metabolites is significantly dependent on the intake of dietary components (Flint et al., 2014). SCFAs are one of the main end products of microbial fermentation of non-digestible carbohydrates. Humans lack the enzyme to digest the bulk of dietary fibers. These non-digestible carbohydrates or fibers pass the upper gastrointestinal tract unaffected and are fermented by gut microbiota in the large intestine. SCFAs are saturated organic acids that consist of one to six carbon units and the most abundant one produced by the microbes are acetate (C2), propionate (C3), and butyrate (C4). The amount and type of fiber consumed has dramatic effects on the composition of the intestinal microbiota and consequently on the type and amount of SCFAs produced (Walker et al., 2011; den Beston et al., 2013; Campbell et al., 1997). In addition to supplying energy to multiple organs, SCFAs directly modulate host health via several identified mechanisms.

Human beings lack the capacity to produce most vitamins, which need to be provided by a nutritionally balanced diet. Some gut microbiotas are capable of synthesizing several B vitamins including biotin, cobalamin, folate, niacin, pantothenate, pyridoxine, riboflavin, and thiamine (Magnúsdóttir, 2015; LeBlanc et al., 2012). B-vitamins are necessary for numerous aspects of human metabolism, including fat and carbohydrate metabolism and DNA synthesis. Initially it was speculated that the gut bacteria contribute to almost 50% of Vitamin K (menaquinone) requirement (Conly et al., 1992), however, recent work shows that dietary Vitamin K amount influences microbial composition (Ellis et al., 2021). The modulation of gut metabolic activity and metabolites could prove critical in health and disease.

THE ROLE OF GUT MICROBIOTA BEYOND THE GUT

MICROBIOME IN DISEASES

The gut microbiota has been extensively linked to multiple diseases, such as obesity (Delzenne et al., 2011) diabetes (Yang et al., 2018), IBD, IBS (Tomasello et al., 2016), cancers (Dart, 2018; Ma et al., 2018), inflammatory diseases (Hakansson and Molin, 2011) and cardiovascular diseases (Jie et al., 2017; Jin et al., 2019) to name a few.

GUT-LUNG AXIS

It is evident that early life exposures regulate microbial composition. Many studies support a role of the intestinal microbiome in the development of childhood asthma and atopic disease. There is also evidence that reduced diversity in the infant gut microbiota directly correlates with heightened risk of allergic disorders (Russell et al., 2012; Bisgaard et al., 2011). A study conducted on 298 infants under 11 months of age, suggested that dysbiosis in neonatal gut microbiome promotes $CD4^+$ T–cell dysfunction associated with childhood atopy and asthma (Arrieta et al., 2015). $CD4^+$ T–cells play an important role in immune system by triggering the body's response to infection. In an animal study, mice that were fed a high-fiber diet showed higher circulating levels of SCFAs and were protected against allergic inflammation in the lung, while the ones on a low-fiber diet had reduced levels of SCFAs and increased allergic airway disease. These results suggested that dietary fermentable fiber and SCFAs can regulate the immunological environment in the lung while influencing the severity of allergic inflammation (Trompette et al., 2014). Antibiotic exposure in neonatal mice also showed enhanced susceptibility to allergies and asthma due to reduced microbial diversity (Russell et al., 2012).

GUT-IMMUNE CONNECTION

The immune system is an intricate system of both innate and adaptive components and has an extraordinary capacity to acclimatize and retort to various challenges. Several studies have focused on the interactions between the immune system and the gut microbiota. It gets a kick-start right at birth. Early encounters between the immune system and the microbiota have significant long-term implications for humans. Colostrum and breast milk contain live microbes, their metabolites, immunoglobulins (IgA, IgG), immune cells as well as cytokines. These, among other factors, help shape the breast-fed infant microbiota and the response of the host to these microbes (Belkaid and Hand, 2014).

It is speculated that the development of immune functions and gut microbiota may be mutually dependent and influenced by each other (Belkaid and Hand, 2014). This also explains why the immune system in infants is highly susceptible, while the gut microbiota is still 'in development'. The immune system remains neutral to beneficial microbes and dietary antigens but activates pro-inflammatory responses against pathogens for host defense (Kayama and Takeda, 2015). It quickly responds to the gut microbiota in an antigen-nonspecific manner by activating pattern recognition receptors, and releases cytokines (such as interferon-a, interleukin-18 (IL-18) and IL-22) to promote epithelial antimicrobial responses such as the production of antimicrobial peptides. Innate immunity is finely regulated in the gut (Kayama and Takeda, 2015) and any abnormalities in the communication between the innate immune system and the gut microbiota might contribute to diseases (Thaiss et al., 2016).

Recent research has also uncovered a relationship between the microbiome and the adaptive immune system (Zheng et al., 2020). T-helper cells of the adaptive immune system, Th1 and Th17 in particular, promote autoimmunity. These proinflammatory cells help clear microbial invaders. Healthy microbes that stimulate T-helper cell development may also increase the inherent immune reactivity of the host, mediated by the adaptive immune system (Lee and Mazmanian, 2010).

The strong link between gut microbiome and immune system has already formed the basis of microbiome-mediated therapeutic strategies in immune-mediated diseases. As an example, fecal microbiome transplantation has been used as a potential treatment to restore a healthy microbiome in Clostridium difficile infections (Zheng et al., 2020).

GUT-BRAIN AXIS

There is an increasing body of evidence that shows the ability of the gut microbiota in modulating the functions of central nervous system (CNS). The gut brain axis can be described as a bidirectional communication system between the brain and the gut, via multiple pathways, with the microbiome being at the center of this network. This network includes the CNS, the enteric nervous system (ENS), the sympathetic and parasympathetic parts of the autonomic nervous system (ANS) and the hypothalamic pituitary adrenal (HPA) axis (Carabotti et al., 2015; Baj et al., 2019). The ENS is also referred to as the gut brain (Knauf et al., 2020). It consists of approximately 200 million neurons that regulate the function of the entire digestive tract (Barbosa and Barbosa, 2020).

A variety of mechanisms are known to be involved in the modulation of gut-brain axis. Neuro mechanisms via the Vagus Nerve, endocrine via HPA axis, immune via pro-inflammatory cytokines involvement, and metabolic via the microbiota metabolites like SCFA, tryptophan, serotonin, other neurotransmitters, and more (Cryan and Dinan, 2012; Galland, 2014; Sarkar et al., 2016). The neuroactive elements that are released by the gut microbiota act locally on the ENS. These include γ-aminobutyric acid (GABA), serotonin, dopamine, acetylcholine (Sarkar et al., 2016) and some of these reach the CNS via the Vagus Nerve (Bonaz et al., 2018). The Vagus Nerve, which is the main component of the parasympathetic nervous system, and the longest nerve in the human body, connects numerous organs including the gut. It is thought to be at the interface of the gut-brain axis (Bonaz et al., 2016). It senses the microbial metabolites through its afferent nerve fibers and communicates the information to CNS, which generates the required response (Bonaz et al., 2018). Afferent fibers are also responsible for carrying signals from the brain and spinal cord. A strong association has been shown between balanced neurotransmitter levels and a healthy gut microbiome (Chen et al., 2021). Any glitch in the Vagus Nerve's function may also cause inflammatory bowel diseases and symptoms (Pellisier et al., 2014). The gut microbiota metabolites, SCFA, help release gut hormones like cholecystokinin (CCK), ghrelin, peptide tyrosine tyrosine (PYY), glucagon-like-peptide-1 (GLP-1), and glucose-dependent insulinotropic polypeptide (GIP) are involved in energy metabolism and important gut-brain communication as they can enter the CNS via Vagus Nerve (Sarkar et al., 2016; Sun et al., 2020).

The microbiota is also known to interact with the HPA (Galland, 2014; Foster and McVey Neufeld, 2013). Exposure to stress can activate the HPA axis (Carabotti et al., 2015; Misiak et al., 2020). Stress is described as a state of disharmony or threatened homeostasis and it has substantial impact on the immune system (Chrousos and Gold, 1992). Stress is also associated with inflammation, gastrointestinal dysfunction, increased intestinal permeability, altered bacterial-host interactions, epithelial abnormalities, and microbial translocation (Söderholm and Perdue, 2001; Gareau et al., 2008). Chronic stress can also impair glucose absorption (Boudry et al., 2007).

SCFAs and ENS neurotransmitters may improve cognitive functions by modulating gut microbial homeostasis and metabolism, and dietary prebiotics and probiotics could intensify this effect (Chen et al., 2021). Probiotics have been proven in various animal studies to be a potential targeted approach for stress management. In one study, probiotics *Lactobacillus helveticus and L rhamnosus* were able to prevent chronic stress induced intestinal abnormalities (Zareie et al., 2006), whereas *L. farciminis* helped minimize the HPA axis response to stress in another (Ait-Belgnaoui et al., 2012). Separating rat babies from their mothers during the first 14 days of life alters their GI microbiome (Barouie et al., 2012). A study conducted on adult rats that had undergone maternal separation as newborns, showed reduced depressive like symptoms when administered with probiotic *Bifidobacterium infantis* (Desbonnet et al., 2010).

Due to its important role in neuroinflammation, neurodevelopment, and neuroendocrine stress responses, the gut microbiome modulation could be crucial for psychobiological treatments (Liu, 2017).

GUT MICROBIOME, SLEEP, MOOD, STRESS, AND ANXIETY

It is increasingly becoming more evident that insufficient sleep causes hosts of adverse physiological and emotional dysfunctions. Insufficient sleep is prevalent across various age groups and is considered a public health epidemic (Chattu et al., 2018). Nutrients that support serotonin metabolism and stress reduction may benefit sleep related disturbances (Schaafsma et al., 2021). In a recent human clinical trial, adults between the ages of 30-50 years with mild-moderate sleep disturbances were given prebiotic galacto-oligosaccharides (GOS) and whey protein rich supplement enriched with amino acids tryptophan and cysteine, magnesium, zinc, niacin, vitamin B6, and vitamin D3 for a period of 3 weeks. The microbiota analysis of the treatment group showed an improvement in gut health by enhanced *Bifidobacterium* levels (Schaafsma et al., 2021).

Mounting evidence on the link between stress and gut microbiota is hard to ignore. A majority of the initial evidence on the crucial role for the microbiota in regulating stress-related physical and behavioral symptoms have come from animal studies. Stressors can induce differential responses in anxiety-like behavior and corticosterone outputs in mice. One study found that germ-free mice had exaggerated HPA reaction to stress with corticosterone elevation compared to SPF (specific pathogen free) and gnotobiotic mice, but it was reversed by *Bifidobacterium infantis* reconstitution (Sudo et al., 2004). Several subsequent studies have also supported a connection between gut microbiota and stress responsiveness, building up potential for possible microbe-based interventions for stress-related disorders (Bharwani et al., 2016; De Palma et al., 2015; Bailey et al., 2011; Jasarevic et al., 2015).

One study examined the impact of academic stress in undergraduate students on salivary cortisol concentrations and lactic acid bacteria activity. Significant findings indicated that fecal lactic acid bacterial levels were lower during the high-stress condition. This coincided with their perceived levels of stress as being greater during the exam period compared to the baseline condition (Knowles et al., 2008).

Loneliness may also possibly alter the gut microbiome, or alterations of the gut microbiome may predispose an individual to become lonely. When studying a possible connection between the gut microbiome and health affecting psychosocial factors in 184 adults, Nguyen et al. (2021) found that lower levels of loneliness and higher levels of wisdom, compassion, social support, and social engagement, were all associated with greater phylogenetic richness and diversity of the gut microbiome (Nguyen et al., 2021). They speculate the possibility that genetic and environmental effects on psychological well-being are via influence from the microbiome and vice versa.

Tryptophan, an essential amino acid, is the sole precursor of key neurotransmitter serotonin, which actively partakes in the modulation of central neurotransmission and enteric physiological function (Gao et al., 2020). While a majority of tryptophan from our diet is absorbed in the small intestine, a certain amount can still reach the large intestine, where it is metabolized by the gut microbiota (Kałużna-Czaplińska et al., 2017). Serotonin is produced in the brain through the tryptophan hydroxylase 2 enzyme (TpH2), where it plays an important role. However, almost 90% of the body's serotonin is produced in the gut. This process occurs through the tryptophan hydroxylase 1 enzyme (TpH1), which produces 5-hydroxytryptophan (5-HTP), which is further metabolized into serotonin, also known as 5-HT (Agus et al., 2018). In the gut, the three major Trp metabolism pathways leading to serotonin, kynurenine (Kyn), and indole derivatives are under the direct or indirect control of the microbiota (Agus et al., 2018). Serotonin dysmetabolism has been linked to various physiological disorders, including autism (Kałużna-Czaplińska et al., 2017), IBS (Clarke et al., 2012), obesity (Hodge et al., 2012), and possibly more, elucidating the importance of gut microbiome in tryptophan metabolism.

MICROBIOME AND WEIGHT MANAGEMENT

According to the World Health Organization (WHO), worldwide obesity nearly tripled between 1975 and 2016. An estimated 1.9 billion adults are overweight and of these, 650 million are obese (WHO fact sheet, 2021). It is one of the most chronic diseases and contributes to several comorbidities. Numerous animal and human clinical studies have shown that the gut microbiota is an integral component in the regulation of the host's physiology, energy, and metabolism, which makes it an attractive area of study for the treatment of obesity and other weight-related disorders. It affects energy balance by influencing how the calorie is harvested from the diet, used, and stored. It has been determined that obesity is linked to phylum-level changes in the gut microbiota, decreased bacterial diversity, and altered representation of bacterial genes and metabolic pathways (Ley et al., 2005; Turnbaugh et al., 2008; Turnbaugh et al., 2009). In an animal study, obesity rich genes showed an abundance of *Actinobacteria and Firmicutes* while most of the lean-enriched genes were from *Bacteroidetes*. The 'core' microbiome was different in both obese and lean mice, which influenced a number of important metabolic functions such as carbohydrate, fat and protein metabolism. The obese microbiome has a higher capacity to harvest energy from the diet (Turnbaugh et al., 2009; Turnbaugh et al., 2006). Interestingly, these traits are transferrable. When germ-free mice, devoid of any microbial inhabitants, were colonized with obese microbiota, an increase in total body and fat mass was observed (Turbnaugh et al., 2006). Gut microbiome is also a crucial factor in kwashiorkor, a severe form of acute malnutrition. In a similar study, transplantation of kwashiorkor microbiome into germ-free mice produced a rapid weight loss (Smith et al., 2013).

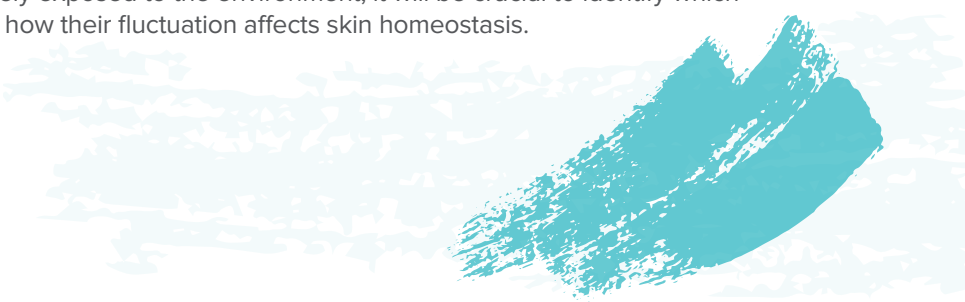
An inverse association between body mass index of obese individuals and detection of hydrogen gas and methane gas in breath tests has been reported (Jung et al., 2017; Wilder-Smith et al., 2018). One study suggests that differences in the microbiota precede overweightness and obesity. Children that had normal weight at 7 years of age, had higher Bifidobacterial and lower Staphylococcus aureus concentrations during infancy (ages 6 and 12 months) than did children who became overweight or obese (Kalliomäki et al., 2008).

Not all species of bacteria, however, work in the same manner. Even under the same genus, different species can have different interactions with the host and mechanisms and bring different outcomes. There is a lot of interspecies variation (Barrett et al., 2012). For example, different *Lactobacillus* species can affect both weight gain and weight loss. *Lactobacillus spp.* associated with weight- protection have developed defense mechanisms for enhanced glycolysis and defense against oxidative stress, while weight gain-associated *Lactobacillus spp.* have reduced ability to breakdown fructose or glucose monosaccharides and might reduce ileal brake effects (Drissi et al., 2014).

A clinical study comparing children with type 1 diabetes to their healthy counterparts found significant differences in their gut microbiota. Children in the diabetes group had a significant increase in the number of *Clostridium, Bacteroides* and Veillonella and a significant decrease in the number of *Lactobacillus, Bifidobacterium, Blautia coccoides/Eubacterium rectale group and Prevotella*. Moreover, the quantity of bacteria essential to maintain gut integrity was significantly lower in the children with diabetes than the healthy children (Murri et al., 2013).

GUT-SKIN AXIS

The skin is the human body's largest organ and is host to several microorganisms. These microorganisms, or skin microbiota, like gut microbiota, are important in maintaining homeostasis and any changes could contribute to several skin disorders (Ellis et al., 2019). Skin disorders not only alter the skin microbiome but also the gut microbiome (De Pessemier et al., 2021). The gut microbiome directly influences skin health through complex immune mechanisms (Salem et al., 2018). A strong link has been shown between inflammatory bowel disease and psoriasis, possibly because of the involvement of Th17 cells and their cytokines (Huang et al., 2019). Dietary supplementation with prebiotics and probiotics can also modulate the immune system to prevent various chronic inflammatory skin disorders such as acne, atopic dermatitis, sebhorric dermatitis, rosacea, and psoriasis (Salem et al., 2018; Krutmann, 2009). Gut microbiome modulation can also counteract UV damage and provide anti-aging benefits, as proven in human clinical trials by administration of probiotic *L. plantarum* HY7714 (Lee et al., 2015). A deeper understanding of the gut-skin axis and skin microbiota could be a significant tool in nutricosmetics and cosmetics applications. Since skin is largely exposed to the environment, it will be crucial to identify which microorganisms are resident or transient and how their fluctuation affects skin homeostasis.



MODULATING GUT MICROBIOTA WITH PROBIOTICS AND PREBIOTICS

Probiotics and prebiotics are some of the first microbiome therapies and have been extensively reviewed and researched. Probiotics are proposed to restore gut health and treat dysbiosis. Upon ingestion, they are believed to become transient residents of the gut microbiota and deliver numerous positive health benefits to the host. Largely used in functional foods and supplements, they have become a preferred targeted approach to impart microbial health benefits. *Lactobacillus and Bifidobacterium* are the most used probiotics. An important point to note is that not only is there an interspecies difference, but also variability between strains. These variations can dramatically change bacterial physiology and functionality (Barrett et al., 2012; Arnold et al., 2018).

There is no shortage of animal and human clinical studies in the field of probiotics. They have been evaluated for various health disorders ranging from gastrointestinal disorders, obesity, diabetes, skin health, immune health, and such. A recent meta-analysis that examined the effect of probiotics and synbiotics on inflammatory and oxidative stress markers in autoimmune disease concluded that their supplementation may have a promising role in the alleviation of some autoimmune disease-related inflammatory conditions (Askari et al., 2021). In a randomized double-blind placebo-controlled clinical trial, Peguet-Navarro et al. (2008) showed that oral supplementation with probiotic bacteria *Lactobacillus johnsonii* accelerates the recovery of skin immune homeostasis after UV-induced immunosuppression. The data showed promising results on the effect of probiotics on skin immune system. Supplementation with *B. longum* APC1472 in mice fed with a high fat diet was associated with decreased bodyweight and fat accumulation and increased glucose tolerance. However, when replicated in healthy overweight/obese human population, the supplementation of *B. longum* APC1472 strain did not affect weight markers. The authors, however, reported a positive effect on fasting blood glucose levels (Schellekens et al., 2020).

Prebiotics, on the other hand, are known to selectively influence the gut microbiota and their effect on health is mediated through the metabolites produced by the microbiota. The International Scientific Association for Probiotics and Prebiotics defines a prebiotic is “a substrate that is selectively utilized by host microorganisms conferring a health benefit”. To classify as a prebiotic, the product must be selectively utilized and have adequate evidence of health benefit for the target host and must not be degraded by the target host enzymes (Gibson et al., 2017). Fructooligosaccharides (FOS) and Galactooligosaccharides (GOS) are the most studied prebiotics, however the list continues to grow.

Prebiotics have mostly been assessed on *Bifidobacterium and Lactobacillus.* Upon fermentation, probiotics help produce SCFAs which confer a number of health benefits. They also help lower the pH in the intestines to prevent the growth of harmful pathogens. Prebiotics are believed to increase the number of beneficial microbiota and reduce the ones that are detrimental (Wang et al., 2020). In a human clinical trial, supplementation with FOS encouraged the production of higher levels of butyrate-producing microbes such as *Faecalibacterium, Ruminococcus and Oscillospira* (Tandon et al., 2019). In prebiotic (oligofructose) fed obese mice, researchers witnessed a decrease in *Firmicutes* and an increase in *Bacteroidetes* phyla. Prebiotics, in addition, reduced inflammation and oxidative stress. An improvement in glucose tolerance and reduction in fat-mass development was also observed (Everard et al., 2011). A study by Kubota et al. (2014) reported that an intake of 4 g of prebiotic FOS twice daily by pregnant and lactating women increased concentration of the immunoregulatory cytokine IL-27 in breast milk, which may have a role in preventing the onset of allergies in their children (Kubota et al., 2014). Prebiotics have a significant potential in preventing and managing gut dysbiosis and studying their effect on other genera will probably expand the magnitude of their impact in the gut.

CONCLUSION

Based on our current scientific understanding, there is an untapped potential in the human gut. A compromised intestinal barrier has a negative effect on nutrient absorption and pathogen defense, both of which can lead to an array of health disorders. The microbiome profile varies among individuals and the variance can be attributed to diet, lifestyle, and the immediate environment. The importance of early years in establishing the core microbiome is well studied and is known for being pivotal in lifelong health. The link between a rich microbial diversity and better health could be the basis of how diets evolve. The discovery of higher microbial diversity from a plant-based diet is one such example.

The human microbiome influences their host's susceptibility to chronic diseases ranging from gastrointestinal, cognitive, immunologic, respiratory, and other metabolic disorders. Modulation of the gut microbiota and its metabolites can open a myriad of opportunities in various health and wellness sectors. The next decade could very well witness personalized microbiome-targeted preventative and restorative treatments for a wide range of disorders. Fecal microbiota transplantation is becoming an accepted method for the restoration of a disrupted microbiota and increase microbial diversity in the recipient for health benefits (Smits et al., 2013). Taken from a healthy donor and introduced in the gastrointestinal tract of an unhealthy person, either by oral capsules or colonoscopy, this method is a forerunner in the field of microbiome therapeutics. There is an increasing evidence in the role of microbiome in life-saving surgical treatments. Recent research has highlighted the importance of gut microbiota in managing Graft-versus-host disease (GVHD), which contributes to a high mortality rate during stem cell or bone marrow transplantation (Kumari et al., 2019; Staffas et al., 2017). Loss of intestinal diversity is postulated to be a big factor in GVHD.

Research continues to evolve in several areas of human biology and each theory can change the way we understand life, health, and diseases. However, it is important to note that many discoveries in the field of gut microbiome and potential microbiome therapeutics have been demonstrated in animal models. For recognized therapeutical applications, similarities in human models will need to be evaluated and established. A lot of questions remain: What does the "core set" of microbiota in its healthiest form look like and can the microbiome be successfully modulated early on in life to maximize chances of a healthy and disease-free life? Could there be universal donors of healthy microbiome within the same geography? How critical does a set diet need to be to maintain a permanent healthy microbiome? Could a healthy microbiota be banked similar to stem cells to be used for future treatments? Could it be banked prior to an antibiotic treatment and replaced right after? Despite a substantial body of evidence, there is a lot of mystery around the human microbiome. None the less, it makes for a promising future for disease intervention.

Tour the Wellness Academy for valuable insights and resources to help you on your new health and wellness product development journey

REFERENCES

1. Agus A, Planchais J, Sokol H. Gut Microbiota Regulation of Tryptophan Metabolism in Health and Disease. *Cell Host Microbe.* 2018;23(6):716-724. doi:10.1016/j.chom.2018.05.003
2. Ait-Belgnaoui A, Durand H, Cartier C, et al. Prevention of gut leakiness by a probiotic treatment leads to attenuated HPA response to an acute psychological stress in rats. *Psychoneuroendocrinology.* 2012;37(11):1885-1895. doi:10.1016/j.psyneuen.2012.03.024
3. Allaband C, McDonald D, Vázquez-Baeza Y, et al. Microbiome 101: Studying, Analyzing, and Interpreting Gut Microbiome Data for Clinicians. *Clin Gastroenterol Hepatol.* 2019;17(2):218-230. doi:10.1016/j.cgh.2018.09.017
4. Alves-Santos AM, Sugizaki CSA, Lima GC, Naves MMV. Prebiotic effect of dietary polyphenols: A systematic review. *J Funct Foods.* 2020;74(104169):104169.
5. Arnold JW, Simpson JB, Roach J, Kwintkiewicz J, Azcarate-Peril MA. Intra-species Genomic and Physiological Variability Impact Stress Resistance in Strains of Probiotic Potential. *Front Microbiol.* 2018;9:242. doi:10.3389/fmicb.2018.00242
6. Arrieta MC, Stiemsma LT, Dimitriu PA, et al. Early infancy microbial and metabolic alterations affect risk of childhood asthma. *Sci Transl Med.* 2015;7(307):307ra152. doi:10.1126/scitranslmed.aab2271
7. Askari G, Ghavami A, Shahdadian F, Moravejolahkami AR. Effect of synbiotics and probiotics supplementation on autoimmune diseases: A systematic review and meta-analysis of clinical trials. *Clin Nutr.* 2021;40(5):3221-3234.
8. Azad MB, Konya T, Maughan H, et al. Infant gut microbiota and the hygiene hypothesis of allergic disease: impact of household pets and siblings on microbiota composition and diversity. *Allergy Asthma Clin Immunol.* 2013;9(1):15
9. Bäckhed F, Ley RE, Sonnenburg JL, Peterson DA, Gordon JI. Host-bacterial mutualism in the human intestine. *Science.* 2005;307(5717):1915-1920. doi:10.1126/science.1104816
10. Bailey MT, Dowd SE, Galley JD, Hufnagle AR, Allen RG, Lyte M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav Immun.* 2011;25(3):397-407. doi:10.1016/j.bbi.2010.10.023
11. Baj, A, Moro, E, Bistoletti, M, Orlandi, V, Crema, F, Giaroni, C. Glutamatergic signaling along the microbiota-gut-brain axis. Int J Mol Sci. 2019;20:1482. doi:10.3390/ijms20061482.
12. Barbosa PM, Barbosa ER. The gut brain-axis in neurological diseases. *Int J Cardiovasc Sci.* 2020;33(5). doi:10.36660/ijcs.20200039
13. Barouei J, Moussavi M, Hodgson DM. Effect of maternal probiotic intervention on HPA axis, immunity and gut microbiota in a rat model of irritable bowel syndrome. *PLoS One.* 2012;7(10):e46051. doi:10.1371/journal.pone.0046051
14. Barrett E, Ross RP, O'Toole PW, Fitzgerald GF, Stanton C. γ-Aminobutyric acid production by culturable bacteria from the human intestine [published correction appears in J Appl Microbiol. 2014 May;116(5):1384-6]. *J Appl Microbiol.* 2012;113(2):411-417. doi:10.1111/j.1365-2672.2012.05344.x
15. Bengmark S. Ecological control of the gastrointestinal tract. The role of probiotic flora. *Gut.* 1998;42(1):2-7. doi:10.1136/gut.42.1.2
16. Bharwani A, Mian MF, Surette MG, Bienenstock J, Forsythe P. Oral treatment with Lactobacillus rhamnosus attenuates behavioural deficits and immune changes in chronic social stress. *BMC Med.* 2017;15(1):7. Published 2017 Jan 11. doi:10.1186/s12916-016-0771-7
17. Bisgaard H, Li N, Bonnelykke K, et al. Reduced diversity of the intestinal microbiota during infancy is associated with increased risk of allergic disease at school age. *J Allergy Clin Immunol.* 2011;128(3):646-52.e1-5.
18. Bonaz B, Bazin T, Pellissier S. The Vagus Nerve at the Interface of the Microbiota-Gut-Brain Axis. *Front Neurosci.* 2018;12(49):3389.
19. Bonaz B, Sinniger V, Pellissier S. Anti-inflammatory properties of the vagus nerve: potential therapeutic implications of vagus nerve stimulation: Anti-inflammatory effect of vagus nerve stimulation. *J Physiol.* 2016;594(20):5781-5790
20. Boudry G, Cheeseman CI, Perdue MH. Psychological stress impairs Na+-dependent glucose absorption and increases GLUT2 expression in the rat jejunal brush-border membrane. *Am J Physiol Regul Integr Comp Physiol.* 2007;292(2):R862-R867. doi:10.1152/ajpregu.00655.2006
21. Campbell JM, Fahey GC Jr, Wolf BW. Selected indigestible oligosaccharides affect large bowel mass, cecal and fecal short-chain fatty acids, pH and microflora in rats. *J Nutr.* 1997;127(1):130-136. doi:10.1093/jn/127.1.130
22. Caporaso JG, Lauber CL, Costello EK, et al. Moving pictures of the human microbiome. *Genome Biol.* 2011;12(5):R50. doi:10.1186/gb-2011-12-5-r50a
23. Carabotti M, Scirocco A, Maselli MA, Severi C. The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. *Ann Gastroenterol.* 2015;28(2):203-209.
24. Chattu VK, Manzar MD, Kumary S, Burman D, Spence DW, Pandi-Perumal SR. The Global Problem of Insufficient Sleep and Its Serious Public Health Implications. *Healthcare (Basel).* 2018;7(1):1. Published 2018 Dec 20. doi:10.3390/healthcare7010001
25. Chen, Y.; Xu, J.; Chen, Y. Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients* 2021, 13, 2099. https://doi.org/10.3390/nu13062099
26. Chrousos GP, Gold PW. The concepts of stress and stress system disorders. Overview of physical and behavioral homeostasis [published correction appears in JAMA 1992 Jul 8;268(2):200]. *JAMA.* 1992;267(9):1244-1252.
27. Clark A, Mach N. Exercise-induced stress behavior, gut-microbiota-brain axis and diet: a systematic review for athletes. *J Int Soc Sports Nutr.* 2016;13:43. Published 2016 Nov 24. doi:10.1186/s12970-016-0155-6
28. Clarke G, McKernan DP, Gaszner G, Quigley EM, Cryan JF, Dinan TG. A Distinct Profile of Tryptophan Metabolism along the Kynurenine Pathway Downstream of Toll-Like Receptor Activation in Irritable Bowel Syndrome. *Front Pharmacol.* 2012;3:90. Published 2012 May 21. doi:10.3389/fphar.2012.00090
29. Clarke SF, Murphy EF, O'Sullivan O, et al. Exercise and associated dietary extremes impact on gut microbial diversity. *Gut.* 2014;63(12):1913-1920. doi:10.1136/gutjnl-2013-306541
30. Collado MC, Isolauri E, Laitinen K, Salminen S. Effect of mother's weight on infant's microbiota acquisition, composition, and activity during early infancy: a prospective follow-up study initiated in early pregnancy. *Am J Clin Nutr.* 2010;92(5):1023-1030. doi:10.3945/ajcn.2010.29877
31. Conly JM, Stein K, Worobetz L, Rutledge-Harding S. The contribution of vitamin K2 (menaquinones) produced by the intestinal microflora to human nutritional requirements for vitamin K. *Am J Gastroenterol.* 1994;89(6):915-923.
32. Costantini L, Molinari R, Farinon B, Merendino N. Impact of Omega-3 Fatty Acids on the Gut Microbiota. *Int J Mol Sci.* 2017;18(12):2645. Published 2017 Dec 7. doi:10.3390/ijms18122645
33. Dalby MJ, Hall LJ. Recent advances in understanding the neonatal microbiome. *F1000Res.* 2020;9:F1000 Faculty Rev-422. Published 2020 May 22. doi:10.12688/f1000research.22355.1

34. Dart A. Gut microbiota bile acid metabolism controls cancer immunosurveillance. *Nat Rev Microbiol.* 2018;16(8):453. doi:10.1038/s41579-018-0053-9

35. David LA, Maurice CF, Carmody RN, et al. Diet rapidly and reproducibly alters the human gut microbiome. *Nature.* 2014;505(7484):559-563. doi:10.1038/nature12820

36. De Palma G, Blennerhassett P, Lu J, et al.Microbiota and host determinants of behavioural phenotype in maternally separated mice. *Nat Commun.* 2015;6:7735. doi:10.1038/ncomms8735

37. De Pessemier B, Grine L, Debaere M, Maes A, Paetzold B, Callewaert C. Gut-Skin Axis: Current Knowledge of the Interrelationship between Microbial Dysbiosis and Skin Conditions. *Microorganisms.* 2021;9(2):353. Published 2021 Feb 11. doi:10.3390/microorganisms9020353

38. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud DJ, Bakker BM. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J Lipid Res.* 2013;54(9):2325-2340. doi:10.1194/jlr.R036012

39. Delzenne NM, Neyrinck AM, Cani PD. Modulation of the gut microbiota by nutrients with prebiotic properties: consequences for host health in the context of obesity and metabolic syndrome. *Microb Cell Fact.* 2011;10 Suppl 1(Suppl 1):S10. doi:10.1186/1475-2859-10-S1-S10

40. Desbonnet L, Garrett L, Clarke G, Kiely B, Cryan JF, Dinan TG. Effects of the probiotic Bifidobacterium infantis in the maternal separation model of depression. *Neuroscience.* 2010;170(4):1179-1188. doi:10.1016/j.neuroscience.2010.08.005

41. Dethlefsen L, Relman DA. Incomplete recovery and individualized responses of the human distal gut microbiota to repeated antibiotic perturbation. *Proc Natl Acad Sci U S A.* 2011;108 Suppl 1(Suppl 1):4554-4561. doi:10.1073/pnas.1000087107

42. Drissi F, Merhej V, Angelakis E, et al. Comparative genomics analysis of Lactobacillus species associated with weight gain or weight protection. *Nutr Diabetes.* 2014;4(2):e109.

43. Eckburg PB, Bik EM, Bernstein CN. Microbiology: diversity of the human intestinal microbial flora. *Science.* 2005;308:1635–1638

44. Ellis SR, Nguyen M, Vaughn AR, et al. The Skin and Gut Microbiome and Its Role in Common Dermatologic Conditions. *Microorganisms.* 2019;7(11):550. Published 2019 Nov 11. doi:10.3390/microorganisms7110550

45. Everard A, Lazarevic V, Derrien M, et al. Responses of gut microbiota and glucose and lipid metabolism to prebiotics in genetic obese and diet-induced leptin-resistant mice [published correction appears in Diabetes. 2011 Dec;60(12):3307. Muccioli, Giulio M [corrected to Muccioli, Giulio G]]. *Diabetes.* 2011;60(11):2775-2786. doi:10.2337/db11-0227

46. Falony G., Joossens M., Vieira-Silva S., Wang J., Darzi Y., Faust K., Kurilshikov A., Bonder M.J., Valles-Colomer M., Vandeputte D., et al. Population-level analysis of gut microbiome variation. *Science.* 2016;352:560–564. doi: 10.1126/science.aad3503

47. Flint HJ, Duncan SH, Scott KP, Louis P. Links between diet, gut microbiota composition and gut metabolism. *Proc Nutr Soc.* 2015;74(1):13-22. doi:10.1017/S0029665114001463

48. Foster JA, McVey Neufeld KA. Gut-brain axis: how the microbiome influences anxiety and depression. *Trends Neurosci.* 2013;36(5):305-312. doi:10.1016/j.tins.2013.01.005

49. Fredricks DN, Fiedler TL, Marrazzo JM. Molecular identification of bacteria associated with bacterial vaginosis. *The New England journal of medicine.* 2005;353:1899–1911. doi: 10.1056/NEJMoa043802.

50. Galland L. The gut microbiome and the brain. *J Med Food.* 2014;17(12):1261-1272. doi:10.1089/jmf.2014.7000

51. Gao K, Mu CL, Farzi A, Zhu WY. Tryptophan Metabolism: A Link Between the Gut Microbiota and Brain. *Adv Nutr.* 2020;11(3):709-723. doi:10.1093/advances/nmz127

52. Gareau MG, Silva MA, Perdue MH. Pathophysiological mechanisms of stress-induced intestinal damage. *Curr Mol Med.* 2008;8(4):274-281. doi:10.2174/156652408784533760

53. Gibson G.R., Scott K.P., Rastall R.A., Tuohy K.M., Hotchkiss A., Dubert-Ferrandon A., Gareau M., Murphy E.F., Saulnier D., Loh G., et al.Dietary prebiotics: Current status and new definition. *Food Sci. Technol. Bull. Funct. Foods.* 2010;7:1–19. doi: 10.1616/1476-2137.15880

54. Hakansson A, Molin G. Gut microbiota and inflammation. *Nutrients.* 2011;3(6):637-682. doi:10.3390/nu3060637

55. Hodge S, Bunting BP, Carr E, Strain JJ, Stewart-Knox BJ. Obesity, whole blood serotonin and sex differences in healthy volunteers. *Obes Facts.* 2012;5(3):399-407. doi:10.1159/000339981

56. Hsu YJ, Chiu CC, Li YP, et al. Effect of intestinal microbiota on exercise performance in mice. *J Strength Cond Res.* 2015;29(2):552-558. doi:10.1519/JSC.0000000000000644

57. Huang BL, Chandra S, Shih DQ. Skin manifestations of inflammatory bowel disease. *Front Physiol.* 2012;3:13. Published 2012 Feb 6. doi:10.3389/fphys.2012.00013

58. Human Microbiome Project Consortium. A framework for human microbiome research. *Nature.* 2012a;486(7402):215-221. doi:10.1038/nature11209

59. Human Microbiome Project Consortium. Structure, function and diversity of the healthy human microbiome. *Nature.* 2012b;486(7402):207-214. doi:10.1038/nature11234

60. Isolauri E. Development of healthy gut microbiota early in life: Microbiota and health in early life. *J Paediatr Child Health.* 2012;48 Suppl 3:1-6

61. Jašarević E, Howerton CL, Howard CD, Bale TL. Alterations in the Vaginal Microbiome by Maternal Stress Are Associated With Metabolic Reprogramming of the Offspring Gut and Brain. *Endocrinology.* 2015;156(9):3265-3276. doi:10.1210/en.2015-1177

62. Ellis JL, Karl JP, Oliverio AM, et al. Dietary vitamin K is remodeled by gut microbiota and influences community composition. *Gut Microbes.* 2021;13(1):1-16

63. Jernberg C, Löfmark S, Edlund C, Jansson JK. Long-term ecological impacts of antibiotic administration on the human intestinal microbiota [published correction appears in *ISME J.* 2013 Feb;7(2):456]. ISME J. 2007;1(1):56-66. doi:10.1038/ismej.2007.3

64. Jie Z, Xia H, Zhong SL, et al. The gut microbiome in atherosclerotic cardiovascular disease. *Nat Commun.* 2017;8(1):845. Published 2017 Oct 10. doi:10.1038/s41467-017-00900-1

65. Jin M, Qian Z, Yin J, Xu W, Zhou X. The role of intestinal microbiota in cardiovascular disease. *J Cell Mol Med.* 2019;23(4):2343-2350. doi:10.1111/jcmm.14195

66. Jung SE, Joo NS, Han KS, Kim KN. Obesity Is Inversely Related to Hydrogen-Producing Small Intestinal Bacterial Overgrowth in Non-Constipation Irritable Bowel Syndrome. *J Korean Med Sci.* 2017;32(6):948-953. doi:10.3346/jkms.2017.32.6.948

67. Kalliomäki M, Collado MC, Salminen S, Isolauri E. Early differences in fecal microbiota composition in children may predict overweight. Am J Clin Nutr. 2008 Mar;87(3):534-8. doi: 10.1093/ajcn/87.3.534. PMID: 18326589.

68. Kałużna-Czaplińska J, Gątarek P, Chirumbolo S, Chartrand MS, Bjørklund G. How important is tryptophan in human health?. *Crit Rev Food Sci Nutr.* 2019;59(1):72-88. doi:10.1080/10408398.2017.1357534

69. Kayama H, Takeda K. Functions of innate immune cells and commensal bacteria in gut homeostasis. *J Biochem.* 2016;159(2):141-149. doi:10.1093/jb/mvv119

70. Knauf C, Abot A, Wemelle E, Cani P, D: Targeting the Enteric Nervous System to Treat Metabolic Disorders? “Enterosynes” as Therapeutic Gut Factors. Neuroendocrinology 2020;110:139-146. doi: 10.1159/000500602

71. Knowles SR, Nelson EA, Palombo EA. Investigating the role of perceived stress on bacterial flora activity and salivary cortisol secretion: a possible mechanism underlying susceptibility to illness. *Biol Psychol.* 2008;77(2):132-137. doi:10.1016/j.biopsycho.2007.09.010

72. Krutmann J. Pre-and probiotics for human skin. *J. Dermatol. Sci.* 2009;54:1–5. doi: 10.1016/j.jdermsci.2009.01.002

73. Kubota T, Shimojo N, Nonaka K, et al. Prebiotic consumption in pregnant and lactating women increases IL-27 expression in human milk. *British Journal of Nutrition.* 2014;111(4):625-632. doi:10.1017/S0007114513003036

74. Kumar Singh A, Cabral C, Kumar R, et al. Beneficial Effects of Dietary Polyphenols on Gut Microbiota and Strategies to Improve Delivery Efficiency. *Nutrients.* 2019;11(9):2216. doi:10.3390/nu11092216

75. Kumari R, Palaniyandi S, Hildebrandt GC. Microbiome: An Emerging New Frontier in Graft-Versus-Host Disease. *Dig Dis Sci.* 2019;64(3):669-677. doi:10.1007/s10620-018-5369-9

76. LeBlanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, Ventura M. Bacteria as vitamin suppliers to their host: a gut microbiota perspective. *Curr Opin Biotechnol.* 2013;24(2):160-168. doi:10.1016/j.copbio.2012.08.005

77. Lee DE, Huh CS, Ra J, et al. Clinical Evidence of Effects of Lactobacillus plantarum HY7714 on Skin Aging: A Randomized, Double Blind, Placebo-Controlled Study. *J Microbiol Biotechnol.* 2015;25(12):2160-2168. doi:10.4014/jmb.1509.09021

78. Lee YK, Mazmanian SK. Has the microbiota played a critical role in the evolution of the adaptive immune system?. *Science.* 2010;330(6012):1768-1773. doi:10.1126/science.1195568

79. Ley RE, Hamady M, Lozupone C, et al.Evolution of mammals and their gut microbes [published correction appears in Science. 2008 Nov 21;322(5905):1188]. *Science.* 2008;320(5883):1647-1651. doi:10.1126/science.1155725

80. Liu RT. The microbiome as a novel paradigm in studying stress and mental health. *Am Psychol.* 2017;72(7):655-667. doi:10.1037/amp0000058

81. Ma C, Han M, Heinrich B, et al. Gut microbiome-mediated bile acid metabolism regulates liver cancer via NKT cells. *Science.* 2018;360(6391):eaan5931. doi:10.1126/science.aan5931

82. Mach N, Fuster-Botella D. Endurance exercise and gut microbiota: A review. *J Sport Health Sci.* 2017;6(2):179-197. doi:10.1016/j.jshs.2016.05.00

83. Mackie RI, Sghir A, Gaskins HR. Developmental microbial ecology of the neonatal gastrointestinal tract. *Am J Clin Nutr.* 1999;69(5):1035S-1045S. doi:10.1093/ajcn/69.5.1035s

84. Magnúsdóttir S, Ravcheev D, de Crécy-Lagard V, Thiele I. Systematic genome assessment of B-vitamin biosynthesis suggests co-operation among gut microbes. *Front Genet.* 2015;6:148. doi:10.3389/fgene.2015.00148

85. Marchesi, J.R., Ravel, J. The vocabulary of microbiome research: a proposal. *Microbiome* 3, 31;2015. https://doi.org/10.1186/s40168-015-0094-5

86. McFadzean R. Exercise can help modulate human gut microbiota. *CU Scholar.* 2014. Undergraduate honors thesis 155

87. Mika A, Fleshner M. Early-life exercise may promote lasting brain and metabolic health through gut bacterial metabolites. *Immunol Cell Biol.* 2016;94(2):151-157

88. Mills S, Stanton C, Lane JA, Smith GJ, Ross RP. Precision Nutrition and the Microbiome, Part I: Current State of the Science. *Nutrients.* 2019;11(4):923. Published 2019 Apr 24. doi:10.3390/nu11040923

89. Misiak B, Łoniewski I, Marlicz W, et al. The HPA axis dysregulation in severe mental illness: Can we shift the blame to gut microbiota?. *Prog Neuropsychopharmacol Biol Psychiatry.* 2020;102:109951. doi:10.1016/j.pnpbp.2020.109951

90. Murri M, Leiva I, Gomez-Zumaquero JM, et al. Gut microbiota in children with type 1 diabetes differs from that in healthy children: a case-control study. *BMC Med.* 2013;11:46. Published 2013 Feb 21. doi:10.1186/1741-7015-11-46

91. Nguyen TT, Zhang X, Wu TC, Liu J,Le C, Tu XM, Knight R and Jeste DV. Association of Loneliness and Wisdom With Gut Microbial Diversity and Composition: An Exploratory Study. *Front. Psychiatry* 2021;12:648475

92. Obesity and overweight. Who.int. https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight. Accessed September 1, 2021.

93. Panda S, El khader I, Casellas F, et al. Short-term effect of antibiotics on human gut microbiota. *PLoS One.* 2014;9(4):e95476. doi:10.1371/journal.pone.0095476

94. Peguet-Navarro J, Dezutter-Dambuyant C, Buetler T, Leclaire J, Smola H, Blum S, Bastien P, Breton L, Gueniche A. Supplementation with oral probiotic bacteria protects human cutaneous immune homeostasis after UV exposure-double blind, randomized, placebo controlled clinical trial. Eur J Dermatol. 2008 Sep-Oct;18(5):504-11. doi: 10.1684/ejd.2008.0496.

95. Pellissier S, Dantzer C, Mondillon L, et al. Relationship between vagal tone, cortisol, TNF-alpha, epinephrine and negative affects in Crohn’s disease and irritable bowel syndrome. *PLoS One.* 2014;9(9):e105328. Published 2014 Sep 10. doi:10.1371/journal.pone.0105328

96. Qin J, Li R, Raes J, Arumugam M, et al.: A human gut microbial gene catalogue established by metagenomic sequencing. Nature. 2010; 464: 59–65.

97. Queipo-Ortuño MI, Seoane LM, Murri M, et al. Gut microbiota composition in male rat models under different nutritional status and physical activity and its association with serum leptin and ghrelin levels. *PLoS One.* 2013;8(5):e65465. Published 2013 May 28. doi:10.1371/journal.pone.0065465

98. Rothschild D, Weissbrod O, Barkan E, et al. Environment dominates over host genetics in shaping human gut microbiota. *Nature.* 2018;555(7695):210-215. doi:10.1038/nature25973

99. Russell SL, Gold MJ, Hartmann M, et al. Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep.* 2012;13(5):440-447. Published 2012 May 1. doi:10.1038/embor.2012.32

100. Sakkas H, Bozidis P, Touzios C, et al. Nutritional Status and the Influence of the Vegan Diet on the Gut Microbiota and Human Health. *Medicina (Kaunas).* 2020;56(2):88. doi:10.3390/medicina56020088

101. Salem I, Ramser A, Isham N, Ghannoum MA. The Gut Microbiome as a Major Regulator of the Gut-Skin Axis. *Front Microbiol.* 2018;9:1459. doi:10.3389/fmicb.2018.01459

102. Sarkar A, Lehto SM, Harty S, Dinan TG, Cryan JF, Burnet PWJ. Psychobiotics and the Manipulation of Bacteria-Gut-Brain Signals. *Trends Neurosci.* 2016;39(11):763-781. doi:10.1016/j.tins.2016.09.002

103. Sarkar A, Yoo JY, Valeria Ozorio Dutra S, Morgan KH, Groer M. The Association between Early-Life Gut Microbiota and Long-Term Health and Diseases. *Journal of Clinical Medicine.* 2021;10(3):459. https://doi.org/10.3390/jcm10030459

104. Schaafsma A, Mallee L, van den Belt M, et al. The Effect of A Whey-Protein and Galacto-Oligosaccharides Based Product on Parameters of Sleep Quality, Stress, and Gut Microbiota in Apparently Healthy Adults with Moderate Sleep Disturbances: A Randomized Controlled Cross-Over Study. *Nutrients.* 2021;13(7):2204. Published 2021 Jun 27. doi:10.3390/nu13072204

105. Schellekens H, Torres-Fuentes C, van de Wouw M, et al. Bifidobacterium longum counters the effects of obesity: Partial successful translation from rodent to human. *EBioMedicine.* 2021;63(103176):103176.

106. Shao Y, Forster SC, Tsaliki E, et al. Stunted microbiota and opportunistic pathogen colonization in caesarean-section birth. *Nature.* 2019;574(7776):117-121. doi:10.1038/s41586-019-1560-1

107. Smith MI, Yatsunenko T, Manary MJ, et al. Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. *Science.* 2013;339(6119):548-554. doi:10.1126/science.1229000

108. Smits L., Bouter K., De Vos W., Borody T., Nieuwdorp M. Therapeutic potential of fecal microbiota transplantation. *Gastroenterology.* 2013;145: 946–953

109. Söderholm JD, Perdue MH. Stress and gastrointestinal tract. II. Stress and intestinal barrier function. *Am J Physiol Gastrointest Liver Physiol.* 2001;280(1):G7-G13. doi:10.1152/ajpgi.2001.280.1.G7

110. Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. *Nature.* 2016;535:56–16. doi:10.1038/nature18846.

111. Staffas A, Burgos da Silva M, van den Brink MR. The intestinal microbiota in allogeneic hematopoietic cell transplant and graft-versus-host disease [published correction appears in Blood. 2017 Apr 13;129(15):2204]. *Blood.* 2017;129(8):927-933. doi:10.1182/blood-2016-09-691394

112. Sudo N, Chida Y, Aiba Y, et al. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J Physiol.* 2004;558(Pt 1):263-275. doi:10.1113/jphysiol.2004.063388

113. Sun LJ, Li JN, Nie YZ. Gut hormones in microbiota-gut-brain cross-talk. *Chin Med J (Engl).* 2020;133(7):826-833. doi:10.1097/CM9.0000000000000706

114. Tanaka M, Nakayama J. Development of the gut microbiota in infancy and its impact on health in later life. *Allergol Int.* 2017;66(4):515-522. doi:10.1016/j.alit.2017.07.010

115. Tandon D, Haque MM, Gote M, et al. A prospective randomized, double-blind, placebo-controlled, dose-response relationship study to investigate efficacy of fructo-oligosaccharides (FOS) on human gut microflora. *Sci Rep.* 2019;9(1):5473. Published 2019 Apr 2. doi:10.1038/s41598-019-41837-3

116. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. *Nature.* 2016;535(7610):65-74. doi:10.1038/nature1884

117. Tomasello G, Mazzola M, Leone A, et al. Nutrition, oxidative stress and intestinal dysbiosis: Influence of diet on gut microbiota in inflammatory bowel diseases. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub.* 2016;160(4):461-466. doi:10.5507/bp.2016.052

118. Trompette A, Gollwitzer ES, Yadava K, et al. Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med.* 2014;20(2):159-166. doi:10.1038/nm.3444

119. Turnbaugh PJ, Bäckhed F, Fulton L, Gordon JI. Diet-induced obesity is linked to marked but reversible alterations in the mouse distal gut microbiome. *Cell Host Microbe.* 2008;3(4):213-223. doi:10.1016/j.chom.2008.02.015

120. Turnbaugh PJ, Hamady M, Yatsunenko T, et al. A core gut microbiome in obese and lean twins. *Nature.* 2009;457(7228):480-484. doi:10.1038/nature07540

121. Turnbaugh PJ, Ley RE, Mahowald MA, Magrini V, Mardis ER, Gordon JI. An obesity-associated gut microbiome with increased capacity for energy harvest. *Nature.* 2006;444(7122):1027-1031. doi:10.1038/nature05414

122. Turroni F, Milani C, Duranti S, et al.: Bifidobacteria and the infant gut: An example of co-evolution and natural selection. Cell Mol Life Sci. 2018; 75(1): 103-18.

123. Walker AW, Ince J, Duncan SH, et al. Dominant and diet-responsive groups of bacteria within the human colonic microbiota. *ISME J.* 2011;5(2):220-230. doi:10.1038/ismej.2010.118

124. Wang S, Xiao Y, Tian F, et al. Rational use of prebiotics for gut microbiota alterations: Specific bacterial phylotypes and related mechanisms. J Funct Foods. 2020;66(103838):103838.

125. Wilder-Smith CH, Olesen SS, Materna A, Drewes AM. Breath methane concentrations and markers of obesity in patients with functional gastrointestinal disorders. *United European Gastroenterol J.* 2018;6(4):595-603. doi:10.1177/2050640617744457

126. Wu GD, Chen J, Hoffmann C, et al. Linking long-term dietary patterns with gut microbial enterotypes. *Science.* 2011;334(6052):105-108. doi:10.1126/science.1208344

127. Yang Q, Lin SL, Kwok MK, Leung GM, Schooling CM. The Roles of 27 Genera of Human Gut Microbiota in Ischemic Heart Disease, Type 2 Diabetes Mellitus, and Their Risk Factors: A Mendelian Randomization Study. *Am J Epidemiol.* 2018;187(9):1916-1922. doi:10.1093/aje/kwy096

128. Belkaid Y, Hand TW. Role of the Microbiota in immunity and inflammation. *Cell.* 2014;157(1):121-141

129. Yatsunenko T, Rey FE, Manary MJ, et al. Human gut microbiome viewed across age and geography. *Nature.* 2012;486(7402):222-227. doi:10.1038/nature11053

130. Yu X, Wu X, Qiu L, et al. Analysis of the intestinal microbial community structure of healthy and long-living elderly residents in Gaotian Village of Liuyang City. *Appl Microbiol Biotechnol.* 2015;99(21):9085-9095. doi:10.1007/s00253-015-6888-3

131. Zareie M, Johnson-Henry K, Jury J, et al. Probiotics prevent bacterial translocation and improve intestinal barrier function in rats following chronic psychological stress. *Gut.* 2006;55(11):1553-1560. doi:10.1136/gut.2005.080739

132. Zheng D, Liwinski T, Elinav E. Interaction between microbiota and immunity in health and disease. *Cell Res.* 2020;30(6):492-506.

133. Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol.* 2019;16(1):35-56.