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Review Paper

In-depth exploration of human gut microbiota: A review

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Abstract

Gut microbiota has a significant role in maintaining the overall health in humans and higher animals. Balanced diet, genetic makeup, and use of antibiotics highly influence the microbial population in the gastrointestinal tract. This review article presents a detailed background on the gut microbiota, including its composition and the various factors influencing its diversity and stability. Strategies for maintaining a healthy gut microbiota are explored, along with an examination of the role of neurotransmitters in regulating gut-brain communication. Research shows that machine learning has a huge potential in elucidating the gut microbiome. Wellbeing and health is directly associated with gut microbiome.

Introduction

The foundation of life on earth is made up of microbes. Our planet has been transformed by microbes from the beginning of time. They have inhabited every imaginable niche on the globe over billions of years (Cavalier-Smith et al., 2006). Oceans and the atmosphere were altered by microbes, creating environments that supported multicellular creatures (Gibbons and

Gilbert, 2015). It has been established that microbes in the ocean have just as much of an impact on the global climate as do those in cattle's gastrointestinal (GI) tracts. In addition, recent research is attributing new roles to human microbiome (King et al., 2019). The American microbiologist and Nobel laureate Joshua Lederberg is credited with coining the term "microbiome" in 2001 (Perciaccante and Donell, 2022). The word "microbiome" refers to the genome of all symbiotic and harmful bacteria found in and on all vertebrates. The collective genome of the bacteria, archaea, viruses, and fungi that live in the gut makes up the gut microbiome (Berg et al., 2020) . On the other hand, the collection of microorganisms found in a certain habitat is known as the microbiota. Lederberg and McCray were the first to use the word "microbiota," emphasizing the significance of the microorganisms that live inside the human body in both health and sickness (Marchesi and Ravel, 2015).

The collection of microbes that live in our digestive tract is known as the gut microbiota (Sokol H., 2019). The human gastrointestinal (GI) tract is one of the body's most extensive interfaces (250-400 m^2) with the outside world, foreign substances, and the immune system (Thursby and Juge, 2017). An estimated 60 tons of food travel through the human GI tract in a lifetime, along with numerous microbes that pose a serious threat to gut health (Akimbekov et al., 2020). The phrase "gut microbiota" refers to the assortment of bacteria, archaea, and eukarya that colonize the GI tract and has co-evolved with the host over thousands of years to develop an intricate and beneficial interaction (Quercia et al., 2014; Sekirov et al., 2010). The evolutionary history between the host and its gut microbial strain plays a quintessential role as the host-adapted gut microbiota has niche-specific modifications to colonize the microecological niche and promote health. The niche-specific modifications are brought about by genome specialization culminating in higher immune tolerance, resistance to enteropathogens, metabolic activity, and functionality within the host (Fassarella et al., 2021) .With a density of 10^{10}-10^{12} CFU/g of intestinal material, the gut microbiota has the highest number of cells in the colon and is the planet's densest and most diversified ecosystem (Martinez-Guryn et al., 2019; Quercia et al., 2014).In addition to bacteria, the microbiota also includes fungi, viruses, and protists. After birth, the microbiota progressively settles and is regarded as an adult around the age of three. Numerous environmental factors and the genetics of the host can influence the microbiota. Many human diseases are characterized by an unbalanced microbiota (dysbiosis), which has a function in many of them but varies in importance from one disease to another (Sokol, 2019).

The healthy gut microbiota has specialized roles in the host's food metabolism (Rowland et al., 2018), the metabolism of xenobiotics and drugs (Collins and Patterson, 2020),

the preservation of the structural and functional integrity of the gut mucosal barrier (Okumura and Takeda, 2018), immunomodulation (Liébana-García et al., 2021) and pathogen defense (Cheng et al., 2019). Fermentation of non-digestible substrates, such as food fibers and endogenous intestinal mucus, is made possible by the microbiota of the gut, which offers the necessary capacities for the process. This fermentation provides a favorable environment for the proliferation of specialized bacteria that are responsible for the production of short-chain fatty acids (SCFAs) (Figure 1) and gases. Acetate, propionate, and butyrate are the three primary SCFAs that are generated (Valdes et al., 2018).

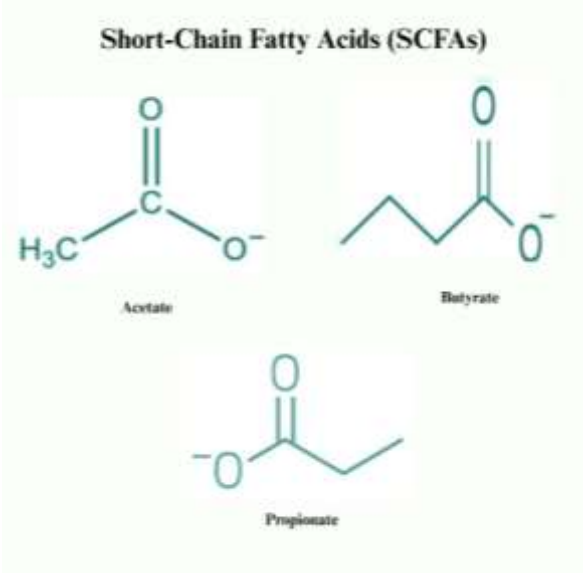

Figure 1. Short- Chain Fatty Acids; Acetate, Butyrate and Propionate

Human colonocytes mostly derive their energy from butyrate (Canani, 2011), which can also cause colon cancer cells to die (Chen et al., 2019) and promote intestinal gluconeogenesis (Ji et al., 2018), both of which have favorable impacts on glucose and energy homeostasis. To generate a condition of hypoxia that ensures the equilibrium of oxygen in the gut and prevents gut microbial dysbiosis, epithelial cells need butyrate in order to consume huge quantities of oxygen through the process of beta-oxidation (Gill et al., 2018; Salvi and Cowles, 2021).Propionate is transported to the liver, where it interacts with gut fatty acid receptors to control gluconeogenesis and satiety signaling (Bindels et al., 2012). Acetate, which is the most prevalent SCFA and a necessary metabolite for the growth of other bacteria, travels to the peripheral tissues, where it is employed in the metabolism of cholesterol and lipogenesis, and it may also have a role in the regulation of appetite in the central nervous system (Hernández et al., 2019; Schoeler and Caesar, 2019; Tsukuda et al., 2021). Bile acid metabolism is aided by gut microbial enzymes, which produce unconjugated and secondary bile acids that

act as metabolic regulators and signaling molecules to affect key host pathways (Cai et al., 2022).

However, gut microbiota can be negatively affected by environmental conditions, unhealthy food habits, and the use of medications (Hrncir, 2022). An imbalance in the natural microbiota of the gut has been connected with gastrointestinal disorders such as inflammatory bowel disease (IBD) (Alam et al., 2020) and irritable bowel syndrome (IBS) (Menees and Chey, 2018), as well as wider systemic manifestations of disease such as obesity (Mitev and Taleski, 2019), type 2 diabetes (Iatcu et al., 2021), and atopic dermatitis (Lee et al., 2018). Thus, it is extremely important to maintain a healthy balance of gut microbiota for better health. This has prompted researchers to extensively study the microbes and also its genetic machinery in order to delve into both their positive and negative aspects. This review attempts to give a detailed scenario of gut microbiota and its role in the onset of diseases. Efforts have also been made to illustrate the role of gut microbiota in the immune system and the beneficial role of probiotics in the improvement of intestinal flora also explaining the role of machine learning in the elucidation of healthy gut microbiota.

Composition of Gut microbiota

The gut microbiota has a very specific phylogenetic structure, which has led to the formation of a tree with few branches and a significant amount of branching at its extremities (Costello et al., 2009). Viruses, yeasts, and bacteria make up the gut microbiome. More than 1000 species of bacteria from six major phyla—*Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria,* and *Verrucomicrobia*—represent bacteria in the gastrointestinal tract (Stojanov et al., 2020). The bulk of the bacterial species that were found in the human gut microbiota belonged to the phyla known as *Firmicutes* and *Bacteroidetes* (King et al., 2019). More than 200 distinct genera, including *Lactobacillus, Bacillus, Clostridium, Enterococcus,* and *Ruminicoccus,* make up the Firmicutes phylum. 95% of the Firmicutes phylum is made up of the *Clostridium* genera. *Prevotella* and *Bacteroides* are two of the most common genera in the family *Bacteroidetes*. The *Bifidobacterium* genus dominates the *Actinobacteria* phylum, which is proportionally less common (Rinninella et al., 2019). The human gut microbiota varies taxonomically and functionally in each section of the gastrointestinal system (Hollister et al., 2014) and it also undergoes changes within the same individual because of infant transitions, age, and environmental influences like antibiotic use (Ahn and Hayes, 2021). The gut microbiota differs according to the different anatomical sections of the intestine, each of which has its own unique physiology, pH level, and oxygen tension, as well as digestive flow rates,

substrate availability, and host secretions (Flint et al., 2012) . The various gut microbes found in different locations of digestive tract are tabulated in Table 1 and shown in Figure 2.

Table 1: Variation of microbes in different positions of the gut.

S. No.	Location	Phylum	Bacterial species	Reference
1.	Oral cavity	Actinobacteria	*Corynebacterium*	(Esberg et al., 2020)
		Bacteroidetes	*Porphyromonas*	(Aleksijević et al., 2022)
		Firmicutes	*Streptococcus*	(Abranches et al., 2018)
			Veillonella sp	(Knapp et al., 2017)
		Fusobacteria	*Fusobacterium*	(Stokowa-Sołtys et al., 2021)
			Leptotrichia	(Eribe and Olsen, 2017)
		Proteobacteria	*Haemophilus*	(Gao et al., 2018)
2.	Esophagus	Actinobacteria	*Rothia*	(Greve et al., 2021)
		Bacteroidetes	*Prevotella*	(Dong et al., 2019)
		Firmicutes	*Streptococcus*	(T. Liu and Huang, 2019)
		Proteobacteria	*Actinobacillus*	(Dong et al., 2019)
3.	Stomach	Actinobacteria	*Rothia*	
		Bacteroidetes	*Prevotella*	(Yeoh et al., 2022)
		Firmicutes	*Streptococcus*	(Fukui et al., 2020)
			Enterococcus	(Siezen and Kleerebezem, 2011)
		Proteobacteria	*Helicobacter*	(Mladenova, 2021)
4.	Duodenum	Actinobacteria	*Bifidobacterium*	(Kerckhoffs et al., 2009)
		Bacteroidetes	*Prevotella*	(G. Li et al., 2015)
		Firmicutes	*Streptococcus*	(Sánchez et al., 2013)
			Lactobacillus	(Łubiech and Twarużek, 2020)
			Enterococcus	(Siezen and Kleerebezem, 2011)
		Proteobacteria	*Neisseria*	(D'Argenio et al., 2016)
5.	Jejunum	Actinobacteria	*Bifidobacterium*	(O'Callaghan and van Sinderen, 2016)
		Bacteroidetes	*Prevotella*	(Hedberg et al., 2013)
		Firmicutes	*Clostridium*	(Cooper and Songer, 2009)
			Lactobacillus	(Walter, 2008)
		Proteobacteria	*Escherichia*	(Sinha et al., 2018)
6.	Ileum	Actinobacteria	*Bifidobacterium*	(Wall et al., 2008)
		Bacteroidetes	*Bacteroides*	(Mailhe et al., 2016)
		Firmicutes	*Peptostreptococcus*	(Ahmed et al., 2007)
			Enterococcus	(Ghosh et al., 2013)
			Lactobacillus	(Wall et al., 2008)
7.	Colon	Actinobacteria	*Bifidobacterium*	(PICARD et al., 2005)
		Bacteroidetes	*Alistipes*	(Y. Yang and Jobin, 2017)
		Firmicutes	*Clostridium*	(Nanjappa et al., 2015)
			Ruminococcus	(Ze et al., 2012)

	Peptosteptococcus	(Tsoi et al., 2017)
Proteobacteria	*Escherichia coli*	(Y. Yang and Jobin, 2017)
	Bilophila	(McOrist et al., 2001)
	Helicobacter	(Ranjbar et al., 2022)

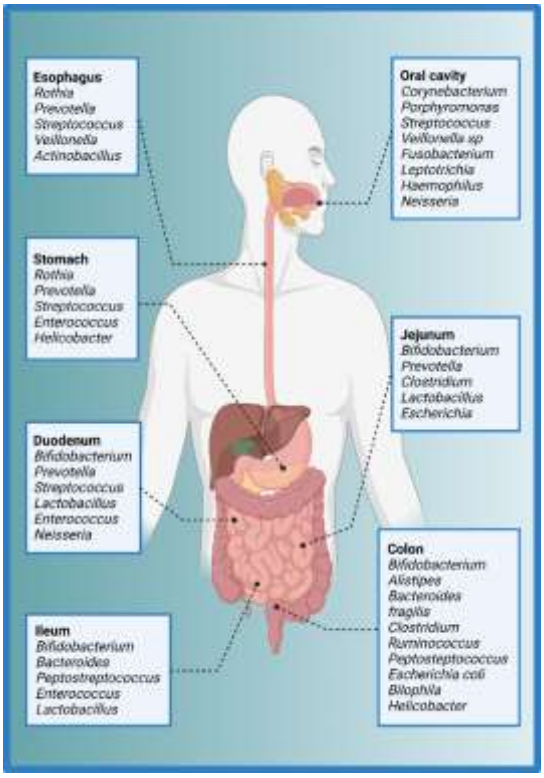

Figure 2. Different gut microbial strains

FACTORS AFFECTING GUT MICROBIOTA

Variation of Gut microbiota according to gestational age

The gut microbiota colonization process is heavily influenced by the gestational age at the time of birth (Yao et al., 2021). Preterm newborns, defined as those born at less than 37 weeks of gestation, have a unique microbiota composition compared to their term counterparts (Rinninella et al., 2019).After delivery, microbiota colonization can be difficult for premature newborns because of environmental influences such as the use of antibiotics, time spent in the hospital, and enteral feeding (Arboleya et al., 2012). Due to these factors, the preterm birth will have a significant impact on the maturation of the gut and the immune system after birth (Ren et al., 2018). An examination of the gut microbiota composition of preterm and term pigs revealed that the genera *Ruminococcus* spp., certain *Enterobacterium* spp., *Lachnospiraceae, Peptostreptococcaceae,* and *Clostridiaceae* were the most prevalent in both groups. On the other hand, a greater abundance of *Enterococcus* spp. was observed in preterm pig than in termed pig (Ren et al., 2018). It was also reported that Preterm newborns had lower concentrations of stringent anaerobes like *Bifidobacterium, Bacteroides,* and *Atopobium* and larger concentrations of facultative anaerobes (Arboleya et al., 2012).

Human milk composition and gut microbiota

Breastfeeding is the most important postnatal connection between mothers and newborns because it promotes microbial colonization, immune system development, and metabolic support, all of which play a significant part in infant health programming (Shamir, 2016). Since it is perfectly suited to newborn nutritional needs and promotes optimal child growth and development, human milk is the gold standard for infant (Selma-Royo et al., 2021). Human milk includes a staggering variety of microorganisms which help to seed the baby's gastrointestinal microbiota, affects the baby's immunological, metabolic developments and eventual health (Stinson et al., 2021). There are four phenotypes of human milk, each with a distinct proportion of oligosaccharides, depending on genetics, the mother's secretor, and the Lewis blood group (Gabrielli et al., 2011). It is observed that in preterm newborns of non-secretor moms, higher levels of *Proteobacteria* and lower levels of *Firmicutes* are observed (Underwood et al., 2015). Oligosaccharides in human milk promote the formation of *Bifidobacteria,* which helps shape the gut microbiota of babies (Łubiech and Twarużek, 2020). The prebiotic effects of human milk oligosaccharides in breast-fed infants are best recognized for the rise of *Bifidobacterium infantis, B. breve,* or *B. bifidum* strains because of their significant bifidogenic effects (Gueimonde et al., 2007). By directly attaching to epithelial surface receptors and preventing pathogens from accessing the mucosal surfaces, human milk oligosaccharides have demonstrated antibacterial and antiviral properties (Ayechu-Muruzabal et al., 2018). Human milk naturally contains lactoferrin (LF), which has antibacterial (Niaz et al., 2019), immunostimulatory (Czosnykowska-Łukacka et al., 2019), and immunomodulatory characteristics. It is reported that LF supports microbial ecology in newborns' guts that encourages the colonization of good bacteria ((Mastromarino et al., 2014).

Delivery and gut microbiota

The intestine is bacteria-free and sterile at birth (Glassner et al., 2020). Following birth, the mother's skin, vaginal and fecal microbiota, and environmental microbiota interactions create a rich and dynamic ecosystem (Moore and Townsend, 2019). Depending on the method of distribution, different microbiota gets colonized. Children born naturally have microbial communities that are similar to their mothers' vaginal microbiota (e.g., *Lactobacillus spp., Prevotella spp., Sneathia spp.).* This happens when the mother's vaginal-perianal bacteria are vertically transferred to the baby as it goes through the birth canal (Y. Yang and Jobin, 2017). On the other hand, children born via caesarean section have microbial communities that are similar to their mothers' skin microbiota (*Staphylococcus, Streptococcus,* and *Clostridium*) (Coelho et al., 2021). A newborn born by caesarean section has germs in its stomach that had

been horizontally transported from the skin surfaces of the mother, other people, and, to a lesser extent, the birth site. *Staphylococcus, Corynebacteria,* and *Propionibacterium spp.* are frequently more prevalent in newborn microbiomes as a result, while *Bifidobacteria* and *Bacteroides spp*. are typically in less amounts (Dominguez-Bello et al., 2010; Shin et al., 2015; B. Yang et al., 2015). Few bacterial species are found in the vaginal microbial communities, with *Lactobacilli* making up 50% of the entire microbial ecosystem, even during childbirth and in a geographically dependent way (Putignani et al., 2014). Moreover, Infants delivered by surgery had a less diverse gut microbiome than those delivered vaginally, in addition to differences in bacterial genera (Rutayisire et al., 2016). This could be significant because low diversity of microorganisms within the gut has been associated to several human disorders, including inflammatory bowel disease and obesity (Johnson and Loftus, 2021) whereas high diversity is generally thought to be protective (I. Yang et al., 2016).

Gut microbial composition and feeding methods

Compared to breastfed infants, formula-fed newborns are more likely to have *Escherichia coli, Bacteroides,* and *Clostridium difficile* colonization (Lees et al., 2016). It is also found that breastfeeding and formula milk have been linked to *Bifidobacterium* species abundance (Saturio et al., 2021). It was however found that formula-fed infants without probiotic supplements had lower levels of *Bifidobacterium longum* in their guts than breast milk-fed at full term (S. A. Lee et al., 2015). In addition, there are commensal bacteria such as *Lactobacilli, Lactococci, Enterococci,* and *Leuconostoc* spp. in the breast milk of healthy women (Cooke et al., 2005; Gueimonde et al., 2007).*Lactobacillus fermentum, Lactobacillus fermentum, Lactobacillus plantarum, Lactobacillus gasseri,* and *Enterococcus faecium* have all been found to be present in breast milk (Łubiech and Twarużek, 2020).

Gut microbiota and antibiotics use

Antibiotic use can change the composition of the gut microbiota. The use of broad-spectrum antibiotics has been found to increase the proportion of *Bacteroidetes* to *Firmicutes* (Ramirez et al., 2020). In another study, it was found that the administration of vancomycin-imipenem led to higher concentrations of arabinitol and carbohydrates (such as sucrose) in feces (Choo et al., 2017). Elevated levels of these compounds have been related to an increased vulnerability to *Clostridioides difficile* infection by serving as a growth substrate. Additionally, the relative abundance of the *Lachnospiraceae* and *Ruminococcaceae* bacteria that typically convert arabinitol to pentose sugars was reduced by vancomycin/imipenem (Haak et al., 2019).A separate study demonstrated that oral administration of vancomycin, ciprofloxacin and metronidazole resulted in a change in gut microbial diversity in healthy humans. It was

observed that there was a decrease in *Bacteriodetes* and an increase in *Firmicutes* in the phylum level. It was further observed that *Streptococcus* and *Lactobacillus* species were dramatically outgrown in antibiotic-treated patients on a genus level at day 9 of treatment, and obligately anaerobic taxa including *Bacteroides, Subdoligranulum,* and *Faecalibacterium* decreased. The abundance of the genera *Streptococcus* and *Lactobacillus* decreased, and the anaerobic communities were restored on day 49, showing a partial return to baseline; however, community composition often remained altered from its initial state (Lange et al., 2016; Haak et al., 2019).Various factors that affect the gut microbiota composition are shown in Figure 3.

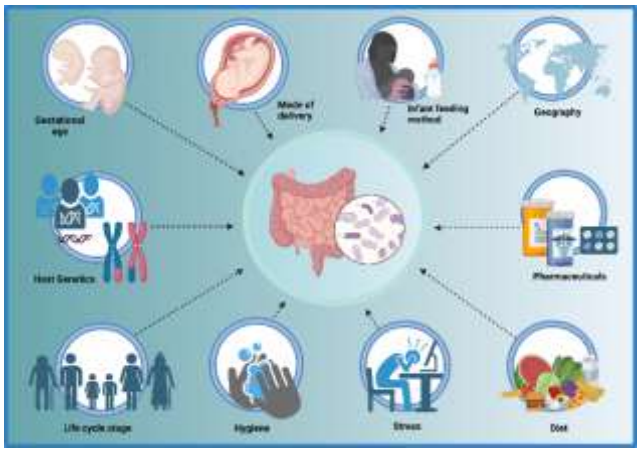

Figure 3. Factors affecting the gut microflora

METHODS TO STUDY HUMAN GUT MICROBIOTA

Microbial ecosystem of the human gut consists of about 100 trillion microbes (Grice and Segre 2012) which is influenced by an individual's diet (Turnbaugh et al. 2009). The presence of microbiota in the digestive system also impacts host metabolism and immunity (Tilg and Kaser 2011). The collection method for samples plays a crucial role in ensuring the integrity and stability of bacteria, facilitating the DNA extraction process (Lauber et al. 2010). The DNA extraction stage from feces is crucial for obtaining high-quality DNA and achieving accurate identification of microbial composition and relative abundance (Thomas, Gilbert, and Meyer 2014). Extracting bacterial DNA from fecal samples is particularly challenging due to the presence of dietary DNA, human DNA traces, and inhibitory substances that can hinder PCR amplification and NGS techniques (Nechvatal et al. 2008). Next-generation sequencing (NGS) is used to determine the bacterial composition in a sample by analyzing DNA fragments obtained from the total DNA isolate. Shotgun sequencing provides comprehensive data on the entire gene pool in the sample, but the large volume of data collected requires extensive bioinformatics work for sequence assembly, mapping, and analysis. For the analysis of bacterial community composition in various research fields, both clinical and environmental, sequencing of 16S rRNA gene amplicons is the preferred method, as it offers cost-effectiveness,

sufficient resolution, and sequencing depth (Sanschagrin and Yergeau 2014; Chen et al., 2021; Salipante et al. 2014; Sinclair et al. 2015; Janda and Abbott 2007).

There are several techniques to study gut microbiota. Some microorganisms can grow on culture, while others don't. Based on this, they are divided into two categories: culture-dependent and culture-independent.

Culture independent techniques:

Metagenomic studies

Metagenomics has played a pivotal role in identifying the phylogenetic composition of approximately 80% of uncultured microbes, leading to significant advancements in the study of human microflora over the past two decades (Wang et al., 2023). This technique involves sequencing the complete genetic material found in a sample, encompassing both bacterial and human DNA (Ye et al., 2019). It enables a comprehensive understanding of the microbial community and its functional capabilities within the microbiome. It also plays a significant role in studying the human gut microbiota by identifying microbial patterns associated with various health outcomes (Ye et al., 2019). For instance, research has demonstrated distinctions in the gut microbiota between obese and lean individuals, as well as the association of specific microbial taxa and metabolic pathways with obesity and its related conditions (Wang et al., 2023). To analyze the intricate gut microbial community, researchers employ a random sequencing approach to catalog all the genes associated with the bacterial population. (Gill et al. 2006; Turnbaugh et al. 2009; Qin et al. 2010)

To begin, fecal samples are used or the extraction of the complete DNA of all microorganisms. The total DNA samples are randomly fragmented using a technique known as the "shotgun" method before undergoing sequencing. Subsequently, the comprehensive sequences are scrutinized to generate species profiles utilizing phylogenetic markers such as 16S rDNA (Sunagawa et al. 2013) or genomic profiles using complete genomes (Tringe et al. 2005).

Metagenomics studies have the potential to identify potential probiotic strains and develop personalized microbiome-based therapies (Pigeyre et al., 2016). Through the identification of specific microorganisms that may be lacking or depleted in a patient's gut microbiota, researchers can employ targeted interventions to restore a healthy microbial balance and enhance health outcomes. According to initial metagenomic investigations that focused on analyzing environmental samples, it was discovered that 80% of the bacteria detected using metagenomics or by targeting the 16S rRNA gene through pyrosequencing had not been previously cultivated (Venter et al. 2004; Raman et al. 2005).

The evaluation of microbial relative abundance relies on various physiological and environmental factors. Descriptive metagenomics can reveal the community structure and variation of the microbiome. Functional metagenomics (analyzes encoded proteins functions from DNA of various microbial communities), on the other hand, involves the development of a predictive and dynamic ecosystem model through the examination of host-microbe and microbe-microbe interactions. These studies provide insights into the connections between the identity of a microbe or community and its specific roles in the environment (Faust and Raes 2012; Chistoserdova 2010).

In environmental sequencing, each genomic fragment is sequenced from a single species, even though samples often contain multiple species, many of which lack complete genomes. Identifying the species from which a particular sequence originated becomes challenging. Furthermore, environmental sequencing generates a significantly larger amount of sequence data compared to sequencing a single genome, with a difference of several orders of magnitude (Wooley, Godzik, and Friedberg 2010).

Approximately 80% of bacteria from the environment or the human gut microbiota were categorized as non-culturable (Thrash, 2019). In the case of complex ecosystems like the gut microbiota, which contains around 1012 bacteria per gram of stool, current metagenomic studies cannot detect bacteria at concentrations lower than 105 bacteria per gram (J. C. Lagier et al. 2012).

Real-time PCR

Quantitative PCR (qPCR) is a technique commonly employed for microbiome analysis, particularly in phylogenetic studies and to examine the ecological state of the environment in both normal individuals and those with obesity (Kieler et al. 2016). It allows for both quantitative and semi-quantitative assessment, depending on the specific applications. Furthermore, it has been utilized to gain insights into the functional microbial diversity of gut microbiota in relation to patient age and the impact of antibiotics on gut microbes (Zwielehner et al. 2009). For instance, qPCR can be used to quantify the DNA content in mucosal regions of gut. In this protocol, fluorescently labelled probes bind to the 16s RNA amplicons or double strands of DNA which is followed by a sharp signal emission, which is directly proportional to the DNA quantity in the sample (Riddle and Connor 2016).

The design of primers plays a critical role in the RT-PCR technique. Therefore, it is essential to ensure that the primers are specific to all species present in a given sample for bacterial phyla, and taxa (Carey et al. 2007). New bacterial strains cannot be identified via quantitative PCR as prior knowledge of primers or probes is required.

Genetic fingerprinting of gut microbiota

Microbial diversity can also be investigated by the probe-16S rRNA sequence hybridization and gel-based separation techniques. These techniques include temperature gradient gel electrophoresis (TGGE), denaturing gradient gel electrophoresis (DGGE), terminal restriction fragment length polymorphism (T-RFLP), and a combination of flow cytometry and FISH (Feng et al. 2018). These methods, often referred to as fingerprinting methods, have been commonly employed for studying microbial diversity. However, it is important to note that these techniques have a limitation and phylogenetic composition of the microbes in the alimentary canal can't be identified.

Temperature gradient gel electrophoresis

Temperature gradient gel electrophoresis (TGGE) is a molecular biology method utilized for the separation and examination of DNA fragments, relying on their distinctive melting patterns. This technique is frequently applied to investigate genetic variations, mutations, and disparities in DNA sequences. TGGE capitalizes on the principle that DNA fragments undergo denaturation (melting) at varying temperatures according to their specific sequence makeup. Melting temperature influences the stability of DNA. The higher the GC content of the DNA template, the more significant the hydrogen bonding, resulting in a higher melting temperature and improved DNA stability. This phenomenon can be attributed to the fact that G and C base pairing involves three hydrogen bonds, whereas A and T base pairing involves only two hydrogen bonds. In the context of TGGE, denaturant agents are substituted with a temperature gradient. The melting behavior and stability of amplicons influence the TGGE protocol, forming the foundation of this technique (Viglasky, 2013).

On passing the electric current, the stable DNA strands with high GC content are separated due to the temperature gradient while their motion is simultaneously restrained. Consequently, a unique banding pattern due to varying temperature conditions is produced (Fischer and Lerman 1980) which is referenced as fingerprinting.

Terminal restriction fragment length polymorphism (T-RFLP)

Two ecological communities are compared using T-RFLP (Li et al., 2007). In the T-RFLP, after DNA extraction, 16sRNA gene is amplified through PCR. Subsequently, these amplicons are treated with restriction enzymes which cleaves off these amplicons, resulting in restriction fragments of varying lengths (Osborne, 2014).These fragments are then separated using electrophoresis gel, where they move different distances based on their lengths and molecular weights, creating a unique banding pattern. The bands shown on the gel indicate individual species present in the alimentary canal, as the terminal fragments are fluorescently

labeled and identifiable. It is fast, and cost-effective. However, direct phylogenetic analysis of bacterial strains is not effective using this method.

Fluorescence in situ hybridization

This technique employs fluorescently labeled probes to specifically target bacterial taxa within a sample. From the microbial communities, after the DNA extraction, the 16S rRNA gene is amplified. The prepared amplicons and then allowed for denaturation in a solution. Subsequently, both fluorescent probes and DNA strands are introduced into the hybridization solution. Aldehyde and methanol are included and added to the reaction mixture and incubated at a temperature range of 65–75°C for 12 hours for the hybridization to occur (Lukumbuzya et al. 2019). The fluorescence intensity is measured after the hybridization, using a flow cytometer. Genomes of different species with a gut are compared using the combination of FISH and flow cytometer as it represents a high-throughput method (Swidsinski et al. 2008).

DNA Microarrays

DNA microarray technology, also known as the DNA chip method, is extensively utilized for studying the microbial ecosystem, particularly in the context of gut microbiota. Numerous fluorescent probes are immobilized on the solid surface which contains a lot of microscopic spots referred to as a small chip. The DNA to be detected on the microchip is in picograms and adequately binds with a small portion of its regulatory element on the cDNA on the DNA chip. The microarray protocol comprises several steps: firstly, the extracted DNA or 16S rRNA amplicon from the samples is treated in such a way to make them fluorescent. Subsequently, the microarray chip surface is immobilized with oligonucleotides probes (Ingber 2016).

The 16S rRNA amplicons and the fluorescent probes are then allowed to hybridize. The fluorescence intensity on hybridization is then quantified. In this way, expression of hundreds of genes is identified in a single experiment (Shankar et al. 2014). There are chances of cross-hybridization as numerous oligonucleotide probes bind to the single DNA fragment. A microarray is unable to detect a novel bacterial species, if the probe is not present.

Culture dependent techniques

A large number of Gram-negative bacterial species from the stool samples were discovered in the 1980s (DC 2001). Subsequently, numerous species have been identified and classified phylogenetically using fermentation profiling or in vitro bacterial species requirements. This advancement has significantly contributed to the identification of microbial agents and has given rise to a new field known as microbial ecology (Bäckhed et al. 2005).

In-depth exploration of human gut microbiota

Biochemical typing and culture were the only methods in the old times to identify novel bacterial species. To gain a deeper understanding of the diversity, composition, and associations of human gut microbes with various diseases, numerous other techniques have been developed. Genomic technologies followed by sequencing have recently achieved significant progress including metagenomics, proteomics and metatranscriptomics.

Culturomics

This traditional approach involves cultivating bacterial cells on selective media to separate and identify individual species found in a sample. However, conventional culture methods only manage to grow approximately 10% to 30% of the gut microbiota (Suau 1999; Tannock 2001; Sokol and Seksik 2010). In fact, new culturomics procedures are necessary to cultivate unculturable microbes, requiring diverse and favorable growth and incubation conditions. More than 50% bacterial species are identified again with the help of culturing which were previously identified through conventional 16S rRNA metagenomics (Lagier et al., 2015).Additionally, hundreds of new bacterial species in the gut can also be isolated using the same techniques in the future (Peter et al. 2014). It is a multi-step protocol that involves preparation of samples, growth under different conditions and inhibiting the growth of microbes while only allowing the growth of the growth of fastidious bacteria (Singh et al. 2016). Currently, culturomics has identified approximately 2,671 new species (Lagier et al. 2018). There are certain bacterial species present in the gut microbiota that cannot be cultured, and culturomics also has limitations such as the potential for bias in the selection of culture conditions used (Siezen 2011).

Microfluidics assays

Gut microbiota is investigated using this assay. It is often referred to as gut-on-chip. Growth environment under specific conditions and nutritional requirements for bacterial growth are provided by this method which enables the identification of numerous uncultured microbes (Nichols et al. 2010).

Another chip consists of an array made up of microchambers which contain miniature cells and are used to cultivate bacteria. This is called iChip. It provides nutrients to each single bacterial cell on the chip equally (Jung et al. 2014). Microfluidics combines gel-based methods with sophisticated instruments. It involves the initial cultivation of a single bacterial cell, followed by genome amplification and sequencing, facilitating the identification of new species (Arnold, Roach, and Azcarate-Peril 2016).

Mass spectrometry

The advancement of mass spectrometry and the implementation of matrix-assisted laser desorption ionization- time of flight MALDI-TOF in bacteriology laboratories enabled rapid identification of any bacterium species, provided that its spectrum was stored in the database of the mass spectrometer (Seng et al. 2009). The utilization of mass spectrometry in the study of the human gut microbiota includes the identification of biomarkers for illness or treatment response. By comparing the metabolites present in the gut microbiota of healthy individuals with those of individuals with diseases, researchers can discover potential targets for diagnostic or therapeutic interventions.

Mass spectrometry has also been used in research to identify and quantify the metabolic byproducts of specific bacterial species present in the gut microbiota (Heaney, 2020). This approach aids in understanding the functional characteristics of different bacterial strains and their potential impact on human health and disease. This method is valuable for investigating the metabolic processes of the microbiota and its interactions with the host. Mass spectrometry has been employed to study the production of metabolites by the human gut microbiota, including short-chain fatty acids (SCFAs), bile acids, and amino acids. These metabolites play important roles as signaling molecules, influencing various physiological functions of the host, such as immune response, energy metabolism, and gastrointestinal motility (Verhaar et al., 2020).

MALDI-TOF MS

MALDI-TOF MS was utilized for the identification of archaeal species. In a study by Dridi et al. (2012), they successfully identified *Methanosphaera stadtmanae, Methanobrevibacter oralis*, *Methanobrevibacter smithii* and the recently discovered *Methanomassiliicoccus luminyensis* using MALDI-TOF MS (Dridi et al., 2012). It offers a fast and precise method for identifying species at the protein level. Furthermore, it aids in the identification of various bacterial species present in the gut and their relative abundance. Significantly, a study by (Seng et al. 2013) using MALDI-TOF MS found that 77% of the bacterial species, which were rarely reported as human pathogens and identified based on their phenotypes, were accurately identified. Isolates can be grouped using MALDI-TOF MS based on their phenotypic characteristics, including pathogenicity, serogroup, and antibiotic resistance. Studies have utilized this method to categorize isolates according to their phenotypic traits, such as pathogenicity (Pinto et al. 2017), serogroup (Clark et al. 2013; Kuhns et al. 2012), and antibiotic resistance (Berrazeg et al. 2013).

The MALDI-TOF MS technique has proven to be effective in identifying coagulase-negative *staphylococci* and *Staphylococcus aureus* (Seng et al. 2013). Two separate studies

conducted by Dupont et al. and Carpaij et al., involving 234 and 62 coagulase-negative *Staphylococcus* strains, respectively, reported accurate identification rates ranging from 93.2% to 100% compared to the reference molecular technique used (Dupont et al. 2010; Carpaij et al. 2011).

For instance, current metagenomic analysis techniques are unable to detect *Salmonella enterica serovar Typhi,* a highly dangerous pathogen (Lagier et al. 2012). Similarly, metagenomics and culturomics yield comparable numbers of species, achieved through the diversification of culture conditions and identification using matrix-assisted laser desorption ionization-time of flight mass spectrometry (MALDI-TOF MS) to enhance the bacterial repertoire.

Degand et al. reported that MALDI-TOF MS successfully identified 549 non-fermenting Gram-negative bacteria from clinical samples, although 9 strains of the *Burkholderia cepacia* complex could not be identified to the species level (Degand et al. 2008). The effectiveness of this method in identification was further demonstrated in two studies conducted with anaerobes in the same laboratory. In 2011, La Scola, Fournier, and Raoult (2011) identified 61% of 544 isolates using MALDI-TOF. Then, in 2013, the same group tested 1,325 anaerobic species using the same cutoff, achieving accurate species-level identification for 92.5% of the strains (La Scola et al., 2011). In 2013, the same research group utilized the same threshold to evaluate 1,325 anaerobic species, achieving accurate identification at the species level for 92.5% of the strains (Barreau et al., 2013).

Functional analysis:

Next generation sequencing based methodology

Next-generation sequencing (NGS) has multiple applications, including phylogenetic classification and functional analysis of microbial communities. One PCR-based massively parallel sequencing platform called pyrosequencing, such as Roche/454 pyrosequencing, is used to investigate gut microbiota (Wu et al., 2010). Pyrosequencing requires a small amount of DNA, is cost-effective and a high-throughput technique. However, it has a limitation of producing short reads, which makes it unsuitable for comparing species within the same genus and for bioinformatics analysis (Rhodes 1998). In addition to pyrosequencing, several other next-generation sequencing platforms such as SOLiD, Illumina, Ion Torrent, Oxford Nanopore, and single-molecule real-time circular consensus sequencing equipment from Pacific Biosciences have been developed for DNA sequencing (Wagner et al. 2016). These advanced technologies have greatly facilitated microbiome analysis, making it faster and easier while accumulating genomic data for phylogenetic analysis.

Metatranscriptomics

This method involves sequencing the messenger RNA (mRNA) found in a sample of microbial community, allowing for an understanding of the active gene expression. Complementary microarray chips were used initially to measure RNA expression levels for transcriptomics analysis (Lowe et al., 2017). Fluorescent probes are immobilized on the microarray chips and different microbial communities are investigated. RNA encoded by the metagenome are studied under metatranscriptomics for a certain population of a region such as microbiota of gut etc. Nowadays, the RNA-seq method has been utilized to study the metatranscriptome, proving to be highly suitable for confirming gene expression across the entire metagenome in the sample, thereby providing fundamental data for proteomics and metabolomics (Franzosa et al. 2014).

Metaproteomics

This approach involves the identification and quantification of the proteins expressed by the microbial community, providing insights into the functional activity of the microbiome (Callegari, 2016; Long et al., 2017). The protein complements expressed by the metagenome of the microbiota of a specific region of body comes under the study of metaproteomics which is also known as community proteomics.

Proteomics methods are of two types: gel-independent method and gel-dependent method. Gel-independent method is also known as shotgun proteomics that relies on two-dimensional liquid chromatography with nanospray mass spectrometry and bioinformatics data analysis pipelines whereas the gel-dependent method involves the combination of 2D gel-electrophoresis, bioinformatics and mass-spectrometry only. In the context of human gut proteome, these types of technologies generate extensive protein analysis data (Xiong et al. 2015).

Metabolomics

This approach involves the examination of the metabolic byproducts generated by the microbiome, which yields insights into the functional activity of the microbiome. Metabolites, resulting from gene expression, exhibit high uniqueness specifically within the gut microbiota (Hou et al., 2022). To study metabolomics advanced technologies are needed that includes secondary ion mass spectrometry, matrix-assisted laser desorption time of flight, Fourier transform ion cyclotron resonance MS etc. (Scholz et al. 2016). The functionality and physiology of a microbial community can be understood via comprehensive annotation of the metabolome derived from the metagenome. Metabolome analysis enables the exploration of functional gene products within a sample, facilitating the functional analysis of microbes within

a microbial niche (Alseekh et al., 2021). Figure 4 shows how multi-omics profiling helps in the functional analysis of gut microflora.

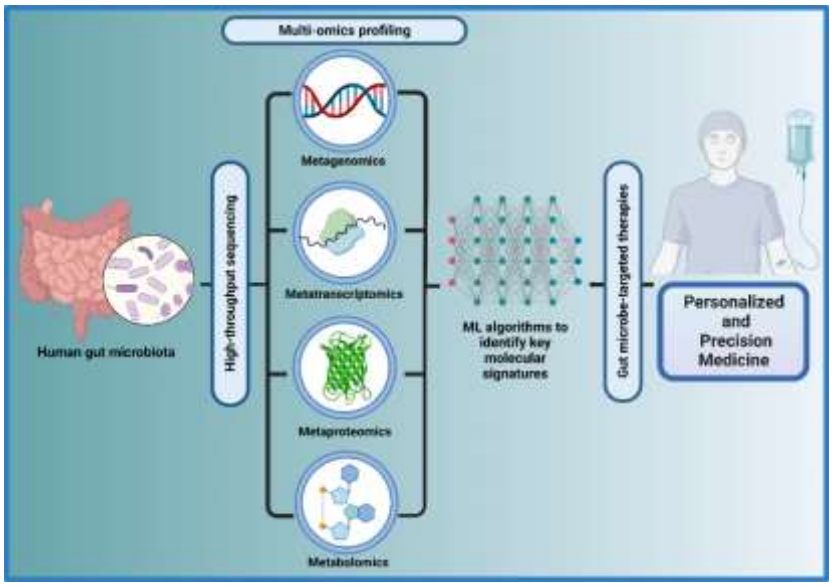

Figure 4. Functional analysis of gut microbiota using multi-omics profiling

NEUROTRANSMITTERS MODULATION BY GUT MICROBIOTA

Neurotransmitters play a vital role in the maintenance of homeostasis and are not restricted to a "fight or flight" response, but it controls gut physiology. Neurotransmitters are produced and modulated by host microbiota which resides in the gastrointestinal tract of humans (Mittal, Debs et al. 2017). Gut microbiota plays an important role in immune activation (Yoo et al., 2020), brain activity (Chen et al., 2021; Dicks et al., 2021) and cognitive functions (Dicks, 2022) along with digestion of food. Gut flora has an impact on mental health through neurotransmitter modulation in the host (Dicks, 2022). It is known that mental disorders can prevail if there is disturbance in level of neurotransmitters production and regulation (Dicks et al., 2021). General gut dysbiosis can result in the onset of depression, anxiety and other related disorders (Strandwitz 2018). Gut microbiota regulates the neurotransmitter production in different ways. The enteric nervous system is regarded as the second brain, or an endocrine organ produces numerous neurotransmitters which are also present in the central nervous system (Chen et al., 2021). Bacteria in gut microbiota produces a variety of neurotransmitters including serotonin, dopamine, GABA and norepinephrine (Strandwitz, 2018). The *Lactobacillus plantarum* and *Lactobacillus rhamnosus* in gut are shown to increase the levels of serotonin, dopamine, and GABA respectively. 90% of body serotonin is synthesized by gut microbiota in human digestive tract and 50 % of dopamine (T. Liu and Huang, 2019). Gut

microbiota is also reported to produce histamine and acetylcholine (Cryan et al., 2020; Mou et al., 2021).

Mechanism of Communication along Gut-Brain Axis

Main goal of gut microbiota study is to dissect out routes of communication between host and gut microbiota. Gut microbiota has influence along gut brain axis for which several mechanisms have been identified such as secretion of short chain fatty acids, vagus nerve stimulation and ability to modulate and produce neurotransmitters (Chen et al., 2021).

Dopamine

The right balance of dopamine is important to a person's overall well-being. Dopamine is one of important neurotransmitters which is precursor for epinephrine and norepinephrine and has role in memory and behavior (Borodovitsyna et al., 2017). Dopamine deficiency can cause certain ailments such as depression and anxiety (T. Liu et al., 2020). Gut microbiota influences the production of dopamine and norepinephrine in gut lumen. It is not completely understood how microbiota modulates dopamine but studies suggested germ free mice have relatively low levels of dopamine and levels are restored by colonization of gut different species of *Clostridium* but mode of modulation is still unknown (Asano et al., 2012). One of mechanisms is that *Clostridium* produces compound 4-cresol which increases dopamine enhance signaling. Dopamine levels increase in the presence of probiotic bacteria. The levels of dopamine increased when germ free mice are supplemented with *L. plantarum* and *B. oklahamensis*. The *S. thermophilus* also increased serotonin with dopamine (T. Liu and Huang, 2019). In addition, *S. cerevisiae*, *H. alvei*, *K. pneumoniae*, *S. aureus*, and *P. vulgaris* are potential candidates for production dopamine in gut (Rich et al., 2022). The *Lactobacillus* and *Bifidobacterium,* probiotic bacteria supplementation in gut to elevated levels of dopamine with improving depression. The strains of *Escherichia coli,* in gut produce an enzyme called tyrosine decarboxylase which converts the amino acid tyrosine into tyramine, which can then be further metabolized into dopamine (Shishov et al., 2009). *Bacillus sp. JPJ* is also capable of producing dopamine (Surwase and Jadhav, 2011) .

Norepinephrine

Norepinephrine is neurotransmitter that is synthesized from dopamine and plays important role in stress and arousal (Scardaci et al., 2022). It is associated with alertness, attention and fight or flight mode. It is produced from the action of enzyme dopamine beta-hydroxylase. The disturbance in level of norepinephrine can lead to development of post-traumatic stress disorder (PTSD) and depression (Morilak et al., 2005). Several bacterial species from are reported to produce norepinephrine in gut of mice. It is also produced by *E.*

coli in in vitro model (Scardaci et al., 2021).Certain strains of *S. marcescens* and *P. vulagris* and of *Bacillus* such as *B. subtilis* and *B. mycoides* also produce norepinephrine (T. Liu et al., 2020).

Serotonin

Serotonin is the second most important neurotransmitter that controls most of the body's functions including respiration, behavior, appetite, neurological functions, and peristalsis (Stasi et al., 2019). Serotonin has main role in eating behaviors (Jones et al., 2020) . Increased and decreased levels are associated with reduced appetite and binging. Serotonin also produces pro-inflammatory cytokines by activating immune cells. Most of serotonin, about 95%, is produced in gastrointestinal tract microbiota (Yano et al., 2015). There are cells called enterochromaffin in gut lumen which convert tryptophan into serotonin (Bertrand and Bertrand, 2010). And gut microbiota stimulates the release of serotonin from these cells. Some strains of *E.coli* have a special enzyme, tryptophan hydroxylase which produces serotonin from amino acid tryptophan (O'Mahony et al., 2015). In this case tryptophan availability is key factor in serotonin synthesis. When bacteria consume tryptophan there is decrease in serotonin synthesis. In such situation host has mechanism which produces short chain fatty acids (SCFAs) which will signal enterochromaffin cells to produce serotonin by expression of tryptophan hydroxylase(Yano et al., 2015b). It is also seen that bacterial toxins also stimulate the serotonin from EC cells (D'Amelio and Sassi, 2018). Gut microbiota influences the serotonin by secreting various metabolites in gut still unknown except SCFAs and tryptophan and toll like receptors (Strandwitz 2018). Certain strains of *Lactobacillus*, *Candida* and *Helicobactor pylori* are associated with serotonin secretion in lumen of gut. Administration of probiotic strains *Lactobacillus planatarum* increased serotonin and improved depression symptoms (T. Liu et al., 2020). Spore forming *Bacillus uniformus* also promotes serotonin synthesis from enterochromaffin cells in gut lumen. In animal model, *B. oklahomensis, A. baumannii* and *B. cereus*, are potential candidate for serotonin secretion (Valles-Colomer et al., 2019). In vitro studies shown that *K. pneumoniae, M. morganii, H. alvei*, *L. lactis* and *S. thermophilus* has ability to produce serotonin (Jones et al., 2020).Similarly, some species of *Candida* and *S. cerevisiae* are also shown to modulate serotonin synthesis in gut (Shishov et al., 2009).

Gamma-Aminobutyric Acid

The gut bacteria are involved in many mechanisms such as synthesis of essential vitamins, production of short chain fatty acids and antimicrobials (Möhler, 2012). Recent studies have shown the evidence of presence of certain bacteria in human gut that produce neurotransmitters like serotonin, dopamine, tryptamine along with γ-aminobutyric acid

(GABA) (Otaru et al., 2021)These neurotransmitters can affect and modulate the gastrointestinal tract along with the central nervous system that is also known as the gut-brain axis (Quillin et al., 2021).

GABA is Gamma-aminobutyric acid, it is an amino acid that plays a role as a neurotransmitter inhibitor in brain and spinal cord. Its supplements are used to relax hyperactivity of nerve cells in case of fear, anxiety or stress (Möhler, 2012). Disordering GABA signaling can result in multiple neurological disorders like epilepsy, anxiety and depression. GABA receptors are of two major classes: $GABA^A$ and $GABA^B$ (Della Vecchia et al., 2022; Thoeringer et al., 2010).

Certain bacterial species of human gut, for instance *Lactobacilli* and *Bifidobacteria* can alter the functioning of central nervous system by producing various compounds (Duranti et al., 2020). These strains are commonly referred to as psychobiotics. Similarly, GABA is produced by such psychobiotics residing in the human gut that modulate neural signals which ultimately influence sleep, mood, cognition and appetite (Duranti et al., 2020; Otaru et al., 2021)

Genetic research concludes that a *gad* gene present in *Bifidobacteria* and *Lactic Acid Bacteria* (LAB) is responsible for production of glutamic acid decarboxylase. Gut bacteria contain a glutamate decarboxylase (GAD) enzyme which uses pyridocal-5′-phosphate (PLP) as a cofactor (Mousavi et al., 2022). GABA is synthesized by consumption of a cytoplasmic proton along with irreversible α-decarboxylation of L-glutamate in Lactic Acid Bacteria (LAB) for instance *Lactobacillus* species and *Lactococcus* species have been widely studied in production of GABA (Duranti et al., 2020; Thoeringer et al., 2010).

Acetylcholine

Acetylcholine is an excitatory neurotransmitter that is involved in memory, muscle contraction and regulation of autonomic nervous system. It works simultaneously with dopamine (T. Liu and Huang, 2019). Gut microbiota regulates the secretion of acetylcholine in host in which strains of *L. plantarum* are potential candidate (Özoğul et al., 2012) . *Bacillus subtilis* and *E. coli* has ability to secrete acetylcholine(Horiuchi et al., 2003). *A. hydrogeniformans* is seen to produce acetylcholine in host (Valles-Colomer et al., 2019).

ROLE OF MACHINE LEARNING IN HUMAN GUT MICROBIOME

Recent research has emphasized the critical part that the gut microbiota plays in several human diseases (Salim et al., 2023).High-throughput technology has made it possible for researchers to characterize gut microorganisms using several kinds of molecular profiling data (Cammarota et al., 2020). Machine learning (ML) algorithms have tremendously helped the interpretation of such data, allowing for the identification of important genetic fingerprints, the

discovery of patient stratifications, and the precise prediction of specific phenotypes. To find connections between microorganisms and diseases, it is especially important to analyse the huge datasets produced by multi-omics human intestinal microbiota research using machine learning and statistical methods.

Oncology stands to gain considerably from the investigation of gut microbiota powered by machine learning. With the integration of numerous large-scale datasets from diverse omic systems and the mounting evidence tying the microbiome to cancer, there is a chance to create strategies for preventing, detecting, and treating cancer. Because certain microbial signatures have been shown to promote the development of cancer and have an impact on the safety, tolerability, and effectiveness of cancer therapies, research has suggested that the gut microbiota can affect the natural progression of malignancies (Cammarota et al., 2020). In this section, we'll examine a few critical areas where machine learning might improve our comprehension and use of gut microbiota data in a variety of contexts, such as disease diagnosis and prediction, identifying the microorganisms in the gut that cause disease, clinical intervention, and drug discovery.

The availability of more transparent data and accessible analytical tools has improved data availability and study reproducibility in recent years. These advancements, combined with ML approaches, have the potential to revolutionize our understanding and utilization of gut microbiota data in the context of oncology and pave the way for innovative strategies in cancer prevention, diagnosis, and treatment.

ML in identification of gut-related diseases

To provide more precise diagnosis and prognosis, ML algorithms can analyse gut microbiome data to uncover patterns and fingerprints linked to diseases (Beam and Kohane, 2018). Machine learning as demonstrated potential in the diagnosis of diseases, particularly in identifying the gut microbiome that may cause dysbiosis to cause cancer. By evaluating the strength of microbiome-brain region associations, studies have used ML-based frameworks to jointly analyze paired host transcriptomic and gut microbiome profiles from colonic mucosal samples of patients with colorectal cancer, irritable bowel syndrome, and inflammatory bowel disease (Priya et al., 2022). Although the brain was previously thought to be independent from the rest of the body, new research indicates that the gut microbiome, which is made up of the microorganisms that live there, may have an impact on how the brain functions and how people behave. While the brain was traditionally considered separate from the rest of the body, emerging evidence suggests that the microbes residing in our gut, known as the gut microbiome, can influence brain function and behavior through various mechanisms.

The network of bidirectional communication between the gut and its microbiota and the brain is known as the gut-brain axis. It involves intricate interactions between the immunological, endocrine, and neurological systems. Numerous substances, including neurotransmitters, neuropeptides, and metabolites that can affect brain function, can be produced, and released by the gut bacteria. ML models have also been used to reveal microbiome-immunotherapy interactions that may ultimately improve cancer patient outcomes (S. Long et al., 2020) also differentiating cachectic from non-cachectic cancer patients (Gou et al., 2021). The extraction of characteristics important for classification using interpretable ML techniques has revealed fundamental biological pathways that account for the changes in the microbiome's functional landscape from a healthy gut to adenoma and colorectal cancer (Casimiro-Soriguer et al., 2022). In an effort to discover gut microbe-targeted medicines and advance personalized and precision medicine, ML is now being used to analyze the gut microbiome (Xiao et al., 2021).

Elucidating disease-causing microbes in the gut

By identifying the individual microorganisms or microbial characteristics that contribute to the onset and progression of diseases, ML methods can help identify possible treatment targets (Lin and Lane, 2017). Machine learning algorithms can be used to find the microbial biomarkers that cause inflammatory bowel disease, colon cancer, and irritable bowel syndrome (M. Zhang et al., 2017). In order to examine the population of microorganisms living in the small intestine and colon, metagenomic analysis of the intestinal microbiome involves obtaining DNA from an environmental sample, such as gut or faeces. Isolated, cleaned, and sequenced DNA is used. Using marker gene surveys, which analyze short segments of DNA (called markers), it is affordable to examine vast amounts of DNA in environmental samples. A bacterial census can be created using the 16S ribosomal RNA (16S rRNA) gene as a universal marker gene for bacteria (Caporaso et al., 2011). A 2020 study found that by combining machine learning with human cohort data, a potent mix of gut bacteria linked to type 2 diabetes was discovered (Gou et al., 2021). In terms of predicting type 2 diabetes, the mix of gut microbes performed better than host genetics or conventional risk factors. The Faecal Microbiota Transfer Experiment demonstrated the influence of the microbe mixture on the emergence of type 2 diabetes. The link between the risk score and type 2 diabetes by body fat distribution is modifiable, as evidenced by the identification of potential modifying factors for microbiome traits associated with type 2 diabetes (Gou et al., 2021). In a cross-sectional study, ML studies showed that microbial variations strongly affect insulin resistance (H. Wu et al., 2020).

Clinical intervention using machine learning data

Machine learning models can assist in personalized treatment planning by leveraging gut microbiota data alongside clinical variables, enabling more tailored and effective interventions (Xiao et al., 2021). Machine learning can help to detect diseases at an early stage. The data can be used to control and treat diseases timely. A study demonstrated the potential of utilizing supervised machine learning models to train with gut microbiome data for accurately diagnosing inflammatory bowel syndrome, which includes Crohn's Disease and Ulcerative Colitis (Manandhar et al., 2021). Discovery of new drug targets or repurposing existing drugs by considering the interactions between gut microbes and host physiology can be done by using ML (Angermueller et al., 2016; Beam and Kohane, 2018). Machine learning algorithms can help optimize interventions, such as prebiotics, probiotics, or fecal microbiota transplantation, to enhance the composition and function of the gut microbiota for improved patient outcomes (Bhadra et al., 2018).

The research shows how machine learning can detect the adverse effects of drugs on gut microbiota (McCoubrey et al., 2021). In the research thirteen ML models were developed to predict drug-induced growth impairment of 40 gut bacterial strains using over 18,600 drug-bacteria interactions. Random forest, Extra trees, and multilayer perceptron (MLP) were used as the top baseline ML techniques, indicating the need for models accommodating nonlinear data relationships. After hyperparameter tuning, the best-performing model utilized extra trees, achieving impressive metrics and the model accurately predicted the impact on all 40 gut bacteria within 0.53 seconds, while identifying the top 10 important chemical features, highlighting valency's role (McCoubrey et al., 2021). This ML model aids in predicting unknown drug-microbiome effects, benefiting drug development. This experiment shows how fast and powerful ML learning is and it’s potential in disease diagnosis and drug development.

Conclusion

Research on human gut microbiota has garnered significant attention due to its huge impact on human health. The review article provides a comprehensive analysis of the human gut microbiota, highlighting its significance in maintaining human health. By examining its composition, factors influencing its stability, strategies for maintenance, and the role of neurotransmitters in gut-brain communication, this review offers valuable insights into the intricate dynamics of the gut microbiota. Additionally, the emerging role of machine learning in unraveling the complexities of the gut microbiota is discussed, showcasing its potential for advancing our understanding in this field.

The work underscores the critical importance of a diverse and stable gut microbiota for overall well-being. The intricate interplay between the gut microbiota, neurotransmitters, and the central nervous system emphasizes the gut-brain axis as a promising avenue for therapeutic interventions. Furthermore, the integration of machine learning techniques holds great promise for unraveling the intricate interactions within the gut microbiota, enabling personalized approaches to optimize gut health. Continued exploration of the gut microbiota will undoubtedly deepen our understanding of its profound influence on human health and open new avenues for developing targeted interventions against diseases and disorders associated with microbiota dysregulation. This review contributes to the growing body of knowledge in this field, providing valuable insights for researchers and individuals seeking to enhance their gut health and overall well-being.

References

Abranches, J., Zeng, L., Kajfasz, J. K., Palmer, S. R., Chakraborty, B., Wen, Z. T., Richards, V. P., Brady, L. J., and Lemos, J. A. (2018). Biology of Oral Streptococci. *Microbiology Spectrum,* 6(5). https://doi.org/10.1128/microbiolspec.GPP3-0042-2018

Ahmed, S., Macfarlane, G. T., Fite, A., McBain, A. J., Gilbert, P., and Macfarlane, S. (2007). Mucosa-Associated Bacterial Diversity in Relation to Human Terminal Ileum and Colonic Biopsy Samples. *Applied and Environmental Microbiology*, 73(22), 7435–7442. https://doi.org/10.1128/AEM.01143-07

Ahn, J., and Hayes, R. B. (2021). Environmental Influences on the Human Microbiome and Implications for Non-communicable Disease. *Annual Review of Public Health*, 42(1), 277–292. https://doi.org/10.1146/annurev-publhealth-012420-105020

Akimbekov, N. S., Digel, I., Sherelkhan, D. K., Lutfor, A. B., and Razzaque, M. S. (2020). Vitamin D and the Host-Gut Microbiome: A Brief Overview. *ACTA HISTOCHEMICA ET CYTOCHEMICA*, 53(3), 33–42. https://doi.org/10.1267/ahc.20011

Alam, M. T., Amos, G. C. A., Murphy, A. R. J., Murch, S., Wellington, E. M. H., and Arasaradnam, R. P. (2020). Microbial imbalance in inflammatory bowel disease patients at different taxonomic levels. Gut Pathogens, 12(1), 1. https://doi.org/10.1186/s13099-019-0341-6

Aleksijević, L. H., Aleksijević, M., Škrlec, I., Šram, M., Šram, M., and Talapko, J. (2022). Porphyromonas gingivalis Virulence Factors and Clinical Significance in Periodontal Disease and Coronary Artery Diseases. *Pathogens*, *11*(10), 1173. https://doi.org/10.3390/pathogens11101173

Alseekh, S., Aharoni, A., Brotman, Y., Contrepois, K., D'Auria, J., Ewald, J., C. Ewald, J., Fraser, P. D., Giavalisco, P., Hall, R. D., Heinemann, M., Link, H., Luo, J., Neumann, S., Nielsen, J., Perez de Souza, L., Saito, K., Sauer, U., Schroeder, F. C., … Fernie, A. R. (2021). Mass spectrometry-based metabolomics: a guide for annotation, quantification and best reporting practices. *Nature Methods*, *18*(7), 747–756. https://doi.org/10.1038/s41592-021-01197-1

Angermueller, C., Pärnamaa, T., Parts, L., and Stegle, O. (2016). Deep learning for computational biology. *Molecular Systems Biology*, *12*(7). https://doi.org/10.15252/msb.20156651

Arboleya, S., Binetti, A., Salazar, N., Fernández, N., Solís, G., Hernández-Barranco, A., Margolles, A., los Reyes-Gavilán, C. G., and Gueimonde, M. (2012). Establishment and development of intestinal microbiota in preterm neonates. *FEMS Microbiology Ecology*, *79*(3), 763–772. https://doi.org/10.1111/j.1574-6941.2011.01261.x

Arnold, J. W., Roach, J., and Azcarate-Peril, M. A. (2016). Emerging Technologies for Gut Microbiome Research. *Trends in Microbiology*, *24*(11), 887–901. https://doi.org/10.1016/j.tim.2016.06.008

Asano, Y., Hiramoto, T., Nishino, R., Aiba, Y., Kimura, T., Yoshihara, K., Koga, Y., and Sudo, N. (2012). Critical role of gut microbiota in the production of biologically active, free catecholamines in the gut lumen of mice. *American Journal of Physiology. Gastrointestinal and Liver Physiology*, *303*(11). https://doi.org/10.1152/AJPGI.00341.2012

Ayechu-Muruzabal, V., van Stigt, A. H., Mank, M., Willemsen, L. E. M., Stahl, B., Garssen, J., and van't Land, B. (2018). Diversity of Human Milk Oligosaccharides and Effects on Early Life Immune Development. *Frontiers in Pediatrics*, *6*. https://doi.org/10.3389/fped.2018.00239

Bäckhed, F., Ley, R. E., Sonnenburg, J. L., Peterson, D. A., and Gordon, J. I. (2005). Host-bacterial mutualism in the human intestine. *Science*, *307*(5717), 1915–1920. https://doi.org/10.1126/science.1104816

Barreau, M., Pagnier, I., and La Scola, B. (2013). Improving the identification of anaerobes in the clinical microbiology laboratory through MALDI-TOF mass spectrometry. *Anaerobe*, *22*, 123–125. https://doi.org/10.1016/j.anaerobe.2013.04.011

Beam, A. L., and Kohane, I. S. (2018). Big Data and Machine Learning in Health Care. *JAMA*, *319*(13), 1317. https://doi.org/10.1001/jama.2017.18391

Berg, G., Rybakova, D., Fischer, D., Cernava, T., Vergès, M.-C. C., Charles, T., Chen, X., Cocolin, L., Eversole, K., Corral, G. H., Kazou, M., Kinkel, L., Lange, L., Lima, N., Loy, A., Macklin, J. A., Maguin, E., Mauchline, T., McClure, R., … Schloter, M. (2020). Microbiome definition re-visited: old concepts and new challenges. *Microbiome*, *8*(1), 103. https://doi.org/10.1186/s40168-020-00875-0

Berrazeg, M., Diene, S. M., Drissi, M., Kempf, M., Richet, H., Landraud, L., and Rolain, J. M. (2013). Biotyping of Multidrug-Resistant Klebsiella pneumoniae Clinical Isolates from France and Algeria Using MALDI-TOF MS. *PLoS ONE*, *8*(4). https://doi.org/10.1371/journal.pone.0061428

Bertrand, P. P., and Bertrand, R. L. (2010). Serotonin release and uptake in the gastrointestinal tract. *Autonomic Neuroscience*, *153*(1–2), 47–57. https://doi.org/10.1016/J.AUTNEU.2009.08.002

Bhadra, P., Yan, J., Li, J., Fong, S., and Siu, S. W. I. (2018). AmPEP: Sequence-based prediction of antimicrobial peptides using distribution patterns of amino acid properties and random forest. *Scientific Reports*, *8*(1), 1697. https://doi.org/10.1038/s41598-018-19752-w

Bindels, L. B., Porporato, P., Dewulf, E. M., Verrax, J., Neyrinck, A. M., Martin, J. C., Scott, K. P., Buc Calderon, P., Feron, O., Muccioli, G. G., Sonveaux, P., Cani, P. D., and Delzenne, N. M. (2012). Gut microbiota-derived propionate reduces cancer cell proliferation in the liver. *British Journal of Cancer*, *107*(8), 1337–1344. https://doi.org/10.1038/bjc.2012.409

Borodovitsyna, O., Flamini, M., and Chandler, D. (2017). Noradrenergic Modulation of Cognition in Health and Disease. *Neural Plasticity*, *2017*. https://doi.org/10.1155/2017/6031478

Cahana, I., and Iraqi, F. A. (2020). Impact of host genetics on gut microbiome: Take-home lessons from human and mouse studies. *Animal Models and Experimental Medicine*, *3*(3), 229. https://doi.org/10.1002/AME2.12134

Cai, J., Rimal, B., Jiang, C., Chiang, J. Y. L., and Patterson, A. D. (2022). Bile acid metabolism and signaling, the microbiota, and metabolic disease. *Pharmacology and Therapeutics*, *237*, 108238. https://doi.org/10.1016/j.pharmthera.2022.108238

Callegari, E. A. (2016). *Shotgun Proteomics Analysis of Estrogen Effects in the Uterus Using Two-Dimensional Liquid Chromatography and Tandem Mass Spectrometry* (pp. 131–148). https://doi.org/10.1007/978-1-4939-3127-9_11

Cammarota, G., Ianiro, G., Ahern, A., Carbone, C., Temko, A., Claesson, M. J., Gasbarrini, A., and Tortora, G. (2020). Gut microbiome, big data and machine learning to promote precision medicine for cancer. *Nature Reviews Gastroenterology and Hepatology*, *17*(10), 635–648. https://doi.org/10.1038/s41575-020-0327-3

Canani, R. B. (2011). Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World Journal of Gastroenterology*, *17*(12), 1519. https://doi.org/10.3748/wjg.v17.i12.1519

Caporaso, J. G., Lauber, C. L., Walters, W. A., Berg-Lyons, D., Lozupone, C. A., Turnbaugh, P. J., Fierer, N., and Knight, R. (2011). Global patterns of 16S rRNA diversity at a depth of millions of sequences per sample. *Proceedings of the National Academy of Sciences*, *108*(supplement_1), 4516–4522. https://doi.org/10.1073/pnas.1000080107

Carey, C. M., Kirk, J. L., Ojha, S., and Kostrzynska, M. (2007). Current and future uses of real-time polymerase chain reaction and microarrays in the study of intestinal microbiota, and probiotic use and effectiveness. *Canadian Journal of Microbiology*, *53*(5), 537–550. https://doi.org/10.1139/W07-039

Carpaij, N., Willems, R. J. L., Bonten, M. J. M., and Fluit, A. C. (2011). Comparison of the identification of coagulase-negative staphylococci by matrix-assisted laser desorption ionization time-of-flight mass spectrometry and tuf sequencing. *European Journal of Clinical Microbiology and Infectious Diseases*, *30*(10), 1169–1172. https://doi.org/10.1007/s10096-011-1204-3

Casimiro-Soriguer, C. S., Loucera, C., Peña-Chilet, M., and Dopazo, J. (2022). Towards a metagenomics machine learning interpretable model for understanding the transition from adenoma to colorectal cancer. *Scientific Reports*, *12*(1), 450. https://doi.org/10.1038/s41598-021-04182-y

Cavalier-Smith, T., Brasier, M., and Embley, T. M. (2006). Introduction: how and when did microbes change the world? *Philosophical Transactions of the Royal Society B: Biological Sciences*, *361*(1470), 845–850. https://doi.org/10.1098/rstb.2006.1847

Chen, Y., Xu, J., and Chen, Y. (2021). Regulation of Neurotransmitters by the Gut Microbiota and Effects on Cognition in Neurological Disorders. *Nutrients*, *13*(6). https://doi.org/10.3390/NU13062099

Chen, Y., Zhou, J., and Wang, L. (2021). Role and Mechanism of Gut Microbiota in Human Disease. *Frontiers in Cellular and Infection Microbiology*, *11*(March), 1–12. https://doi.org/10.3389/fcimb.2021.625913

Cheng, H.-Y., Ning, M.-X., Chen, D.-K., and Ma, W.-T. (2019). Interactions Between the Gut Microbiota and the Host Innate Immune Response Against Pathogens. *Frontiers in Immunology*, *10*. https://doi.org/10.3389/fimmu.2019.00607

Chistoserdova, L. (2010). Recent progress and new challenges in metagenomics for biotechnology. Biotechnology Letters, 32(10), 1351–1359. https://doi.org/10.1007/s10529-010-0306-9

Choo, J. M., Kanno, T., Zain, N. M. M., Leong, L. E. X., Abell, G. C. J., Keeble, J. E., Bruce, K. D., Mason, A. J., and Rogers, G. B. (2017). Divergent Relationships between Fecal Microbiota and Metabolome following Distinct Antibiotic-Induced Disruptions. *MSphere*, *2*(1). https://doi.org/10.1128/mSphere.00005-17

Clark, C. G., Kruczkiewicz, P., Guan, C., McCorrister, S. J., Chong, P., Wylie, J., van Caeseele, P., Tabor, H. A., Snarr, P., Gilmour, M. W., Taboada, E. N., and Westmacott, G. R. (2013). Evaluation of MALDI-TOF mass spectroscopy methods for determination of Escherichia coli pathotypes. Journal of Microbiological Methods, 94(3), 180–191. https://doi.org/10.1016/j.mimet.2013.06.020

Coelho, G. D. P., Ayres, L. F. A., Barreto, D. S., Henriques, B. D., Prado, M. R. M. C., and Passos, C. M. Dos. (2021). Acquisition of microbiota according to the type of birth: an integrative review. Revista Latino-Americana de Enfermagem, 29. https://doi.org/10.1590/1518.8345.4466.3446

Collins, S. L., and Patterson, A. D. (2020). The gut microbiome: an orchestrator of xenobiotic metabolism. Acta Pharmaceutica Sinica B, 10(1), 19–32. https://doi.org/10.1016/j.apsb.2019.12.001

Cooke, G., Behan, J., Clarke, N., Gorman, W., and Costello, M. (2005). Comparing the gut flora of Irish breastfed and formula-fed neonates aged between birth and 6 weeks old. Microbial Ecology in Health and Disease, 17(3), 163–168. https://doi.org/10.1080/08910600500430664

Cooper, K. K., and Songer, J. G. (2009). Necrotic enteritis in chickens: A paradigm of enteric infection by Clostridium perfringens type A. Anaerobe, 15(1–2), 55–60. https://doi.org/10.1016/j.anaerobe.2009.01.006

Costello, E. K., Lauber, C. L., Hamady, M., Fierer, N., Gordon, J. I., and Knight, R. (2009). Bacterial Community Variation in Human Body Habitats Across Space and Time. Science, 326(5960), 1694–1697. https://doi.org/10.1126/science.1177486

Cryan, J. F., O'Riordan, K. J., Sandhu, K., Peterson, V., and Dinan, T. G. (2020). The gut microbiome in neurological disorders. The Lancet Neurology, 19(2), 179–194. https://doi.org/10.1016/S1474-4422(19)30356-4

Czosnykowska-Łukacka, Orczyk-Pawiłowicz, Broers, and Królak-Olejnik. (2019). Lactoferrin in Human Milk of Prolonged Lactation. Nutrients, 11(10), 2350. https://doi.org/10.3390/nu11102350

D'Amelio, P., and Sassi, F. (2018). Gut Microbiota, Immune System, and Bone. Calcified Tissue International, 102(4), 415–425. https://doi.org/10.1007/S00223-017-0331-Y

D'Argenio, V., Casaburi, G., Precone, V., Pagliuca, C., Colicchio, R., Sarnataro, D., Discepolo, V., Kim, S. M., Russo, I., Del Vecchio Blanco, G., Horner, D. S., Chiara, M., Pesole, G., Salvatore, P., Monteleone, G., Ciacci, C., Caporaso, G. J., Jabrì, B., Salvatore, F., and Sacchetti, L. (2016). Metagenomics Reveals Dysbiosis and a Potentially Pathogenic N. flavescens Strain in Duodenum of Adult Celiac Patients. American Journal of Gastroenterology, 111(6), 879–890. https://doi.org/10.1038/ajg.2016.95

DC, S. (2001). Microbial biota of the human intestine: a tribute to some pioneering scientists. Curr Issues Intest Microbiol., 1–15.

Degand, N., Carbonnelle, E., Dauphin, B., Beretti, J. L., Le Bourgeois, M., Sermet-Gaudelus, I., Segonds, C., Berche, P., Nassif, X., and Ferroni, A. (2008). Matrix-assisted laser desorption ionization-time of flight mass spectrometry for identification of nonfermenting gram-negative bacilli isolated from cystic fibrosis patients. Journal of Clinical Microbiology, 46(10), 3361–3367. https://doi.org/10.1128/JCM.00569-08

Della Vecchia, A., Arone, A., Piccinni, A., Mucci, F., and Marazziti, D. (2022). GABA System in Depression: Impact on Pathophysiology and Psychopharmacology. Current Medicinal Chemistry, 29(36), 5710–5730. https://doi.org/10.2174/0929867328666211115124149

Dicks, L. M. T. (2022). Gut Bacteria and Neurotransmitters. Microorganisms, 10(9). https://doi.org/10.3390/MICROORGANISMS10091838

Dicks, L. M. T., Hurn, D., and Hermanus, D. (2021). Gut bacteria and neuropsychiatric disorders. Microorganisms, 9(12). https://doi.org/10.3390/MICROORGANISMS9122583

Dominguez-Bello, M. G., Costello, E. K., Contreras, M., Magris, M., Hidalgo, G., Fierer, N., and Knight, R. (2010). Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. Proceedings of the National Academy of Sciences, 107(26), 11971–11975. https://doi.org/10.1073/pnas.1002601107

Dong, L.-N., Wang, M., Guo, J., and Wang, J.-P. (2019). Role of intestinal microbiota and metabolites in inflammatory bowel disease. Chinese Medical Journal, 132(13), 1610–1614. https://doi.org/10.1097/CM9.0000000000000290

Dridi, B., Raoult, D., and Drancourt, M. (2012). Matrix-assisted laser desorption/ionization time-of-flight mass spectrometry identification of Archaea: Towards the universal identification of living organisms. Apmis, 120(2), 85–91. https://doi.org/10.1111/j.1600-0463.2011.02833.x

Dupont, C., Sivadon-Tardy, V., Bille, E., Dauphin, B., Beretti, J. L., Alvarez, A. S., Degand, N., Ferroni, A., Rottman, M., Herrmann, J. L., Nassif, X., Ronco, E., and Carbonnelle, E. (2010). Identification of clinical coagulase-negative staphylococci, isolated in microbiology laboratories, by matrix-assisted laser desorption/ionization-time of flight mass spectrometry and two automated systems. Clinical Microbiology and Infection, 16(7), 998–1004. https://doi.org/10.1111/j.1469-0691.2009.03036.x

Duranti, S., Ruiz, L., Lugli, G. A., Tames, H., Milani, C., Mancabelli, L., Mancino, W., Longhi, G., Carnevali, L., Sgoifo, A., Margolles, A., Ventura, M., Ruas-Madiedo, P., and

Turroni, F. (2020). Bifidobacterium adolescentis as a key member of the human gut microbiota in the production of GABA. Scientific Reports, 10(1), 14112. https://doi.org/10.1038/s41598-020-70986-z

Eribe, E. R. K., and Olsen, I. (2017). Leptotrichia species in human infections II. Journal of Oral Microbiology, 9(1), 1368848. https://doi.org/10.1080/20002297.2017.1368848

Esberg, A., Barone, A., Eriksson, L., Lif Holgerson, P., Teneberg, S., and Johansson, I. (2020). Corynebacterium matruchotii Demography and Adhesion Determinants in the Oral Cavity of Healthy Individuals. Microorganisms, 8(11), 1780. https://doi.org/10.3390/microorganisms8111780

Fassarella, M., Blaak, E. E., Penders, J., Nauta, A., Smidt, H., and Zoetendal, E. G. (2021). Gut microbiome stability and resilience: elucidating the response to perturbations in order to modulate gut health. Gut, 70(3), 595–605. https://doi.org/10.1136/GUTJNL-2020-321747

Faust, K., and Raes, J. (2012). Microbial interactions: From networks to models. Nature Reviews Microbiology, 10(8), 538–550. https://doi.org/10.1038/nrmicro2832

Feng, X. wei, Ding, W. ping, Xiong, L. yun, Guo, L., Sun, J. ming, and Xiao, P. (2018). Recent Advancements in Intestinal Microbiota Analyses: A Review for Non-Microbiologists. Current Medical Science, 38(6), 949–961. https://doi.org/10.1007/s11596-018-1969-z

Fischer, S. G., and Lerman, L. S. (1980). Separation of random fragments of DNA according to properties of their sequences. Proceedings of the National Academy of Sciences of the United States of America, 77(8), 4420–4424. https://doi.org/10.1073/pnas.77.8.4420

Flint, H. J., Scott, K. P., Louis, P., and Duncan, S. H. (2012). The role of the gut microbiota in nutrition and health. Nature Reviews Gastroenterology and Hepatology, 9(10), 577–589. https://doi.org/10.1038/nrgastro.2012.156

Franzosa, E. A., Morgan, X. C., Segata, N., Waldron, L., Reyes, J., Earl, A. M., Giannoukos, G., Boylan, M. R., Ciulla, D., Gevers, D., Izard, J., Garrett, W. S., Chan, A. T., and Huttenhower, C. (2014). Relating the metatranscriptome and metagenome of the human gut. Proceedings of the National Academy of Sciences of the United States of America, 111(22). https://doi.org/10.1073/pnas.1319284111

Fukui, A., Takagi, T., Naito, Y., Inoue, R., Kashiwagi, S., Mizushima, K., Inada, Y., Inoue, K., Harusato, A., Dohi, O., Okayama, T., Katada, K., Kamada, K., Uchiyama, K., Ishikawa, T., Handa, O., Itoh, Y., and Nakagawa, M. (2020). Higher Levels of andlt;bandgt;andlt;iandgt;Streptococcusandlt;/iandgt;andlt;/bandgt; in Upper Gastrointestinal Mucosa Associated with Symptoms in Patients with Functional Dyspepsia. Digestion, 101(1), 38–45. https://doi.org/10.1159/000504090

Gabrielli, O., Zampini, L., Galeazzi, T., Padella, L., Santoro, L., Peila, C., Giuliani, F., Bertino, E., Fabris, C., and Coppa, G. V. (2011). Preterm Milk Oligosaccharides During the First Month of Lactation. Pediatrics, 128(6), e1520–e1531. https://doi.org/10.1542/peds.2011-1206

Gao, L., Xu, T., Huang, G., Jiang, S., Gu, Y., and Chen, F. (2018). Oral microbiomes: more and more importance in oral cavity and whole body. Protein and Cell, 9(5), 488–500. https://doi.org/10.1007/s13238-018-0548-1

Ghosh, A., Borst, L., Stauffer, S. H., Suyemoto, M., Moisan, P., Zurek, L., and Gookin, J. L. (2013). Mortality in Kittens Is Associated with a Shift in Ileum Mucosa-Associated Enterococci from Enterococcus hirae to Biofilm-Forming Enterococcus faecalis and Adherent Escherichia coli. Journal of Clinical Microbiology, 51(11), 3567–3578. https://doi.org/10.1128/JCM.00481-13

Gibbons, S. M., and Gilbert, J. A. (2015). Microbial diversity — exploration of natural ecosystems and microbiomes. Current Opinion in Genetics and Development, 35, 66–72. https://doi.org/10.1016/j.gde.2015.10.003

Gill, P. A., van Zelm, M. C., Muir, J. G., and Gibson, P. R. (2018). Review article: short chain fatty acids as potential therapeutic agents in human gastrointestinal and inflammatory disorders. Alimentary Pharmacology and Therapeutics, 48(1), 15–34. https://doi.org/10.1111/apt.14689

Gill, S. R., Pop, M., DeBoy, R. T., Eckburg, P. B., Turnbaugh, P. J., Samuel, B. S., Gordon, J. I., Relman, D. A., Fraser-Liggett, C. M., and Nelson, K. E. (2006). Metagenomic Analysis of the Human Distal Gut Microbiome\r10.1126/science.1124234. Science, 312(5778), 1355–1359.

Glassner, K. L., Abraham, B. P., and Quigley, E. M. M. (2020). The microbiome and inflammatory bowel disease. The Journal of Allergy and Clinical Immunology, 145(1), 16–27. https://doi.org/10.1016/J.JACI.2019.11.003

Gou, W., Ling, C., He, Y., Jiang, Z., Fu, Y., Xu, F., Miao, Z., Sun, T., Lin, J., Zhu, H., Zhou, H., Chen, Y., and Zheng, J.-S. (2021). Interpretable Machine Learning Framework Reveals Robust Gut Microbiome Features Associated With Type 2 Diabetes. Diabetes Care, 44(2), 358–366. https://doi.org/10.2337/dc20-1536

Greve, D., Moter, A., Kleinschmidt, M. C., Pfäfflin, F., Stegemann, M. S., Kursawe, L., Grubitzsch, H., Falk, V., and Kikhney, J. (2021). Rothia aeria and Rothia dentocariosa as biofilm builders in infective endocarditis. International Journal of Medical Microbiology, 311(2), 151478. https://doi.org/10.1016/j.ijmm.2021.151478

Grice, E. A., and Segre, J. A. (2012). The human microbiome: Our second genome. Annual Review of Genomics and Human Genetics, 13(May), 151–170. https://doi.org/10.1146/annurev-genom-090711-163814

Gueimonde, M., Laitinen, K., Salminen, S., and Isolauri, E. (2007). Breast Milk: A Source of Bifidobacteria for Infant Gut Development and Maturation? Neonatology, 92(1), 64–66. https://doi.org/10.1159/000100088

Haak, B. W., Lankelma, J. M., Hugenholtz, F., Belzer, C., de Vos, W. M., and Wiersinga, W. J. (2019). Long-term impact of oral vancomycin, ciprofloxacin and metronidazole on the gut microbiota in healthy humans. Journal of Antimicrobial Chemotherapy, 74(3), 782–786. https://doi.org/10.1093/jac/dky471

Heaney, L. M. (2020). Applying mass spectrometry-based assays to explore gut microbial metabolism and associations with disease. Clinical Chemistry and Laboratory Medicine (CCLM), 58(5), 719–732. https://doi.org/10.1515/cclm-2019-0974

Hedberg, M. E., Israelsson, A., Moore, E. R. B., Svensson-Stadler, L., Wai, S. N., Pietz, G., Sandström, O., Hernell, O., Hammarström, M.-L., and Hammarström, S. (2013). Prevotella jejuni sp. nov., isolated from the small intestine of a child with coeliac

disease. International Journal of Systematic and Evolutionary Microbiology, 63(Pt_11), 4218–4223. https://doi.org/10.1099/ijs.0.052647-0

Hernández, Canfora, Jocken, and Blaak. (2019). The Short-Chain Fatty Acid Acetate in Body Weight Control and Insulin Sensitivity. Nutrients, 11(8), 1943. https://doi.org/10.3390/nu11081943

Hollister, E. B., Gao, C., and Versalovic, J. (2014). Compositional and Functional Features of the Gastrointestinal Microbiome and Their Effects on Human Health. Gastroenterology, 146(6), 1449–1458. https://doi.org/10.1053/j.gastro.2014.01.052

Horiuchi, Y., Kimura, R., Kato, N., Fujii, T., Seki, M., Endo, T., Kato, T., and Kawashima, K. (2003). Evolutional study on acetylcholine expression. Life Sciences, 72(15), 1745–1756. https://doi.org/10.1016/S0024-3205(02)02478-5

Hou, K., Wu, Z.-X., Chen, X.-Y., Wang, J.-Q., Zhang, D., Xiao, C., Zhu, D., Koya, J. B., Wei, L., Li, J., and Chen, Z.-S. (2022). Microbiota in health and diseases. Signal Transduction and Targeted Therapy, 7(1), 135. https://doi.org/10.1038/s41392-022-00974-4

Hrncir, T. (2022). Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options. Microorganisms, 10(3), 578. https://doi.org/10.3390/microorganisms10030578

Iatcu, C. O., Steen, A., and Covasa, M. (2021). Gut Microbiota and Complications of Type-2 Diabetes. Nutrients, 14(1), 166. https://doi.org/10.3390/nu14010166

Ingber, D. E. (2016). Reverse Engineering Human Pathophysiology with Organs-on-Chips. Cell, 164(6), 1105–1109. https://doi.org/10.1016/j.cell.2016.02.049

Janda, J. M., and Abbott, S. L. (2007). 16S rRNA gene sequencing for bacterial identification in the diagnostic laboratory: Pluses, perils, and pitfalls. Journal of Clinical Microbiology, 45(9), 2761–2764. https://doi.org/10.1128/JCM.01228-07

Johnson, A., and Loftus, E. (2021). Obesity in inflammatory bowel disease: A review of its role in the pathogenesis, natural history, and treatment of IBD. Saudi Journal of Gastroenterology, 27(4), 183. https://doi.org/10.4103/sjg.sjg_30_21

Jones, L. A., Sun, E. W., Martin, A. M., and Keating, D. J. (2020). The ever-changing roles of serotonin. The International Journal of Biochemistry and Cell Biology, 125. https://doi.org/10.1016/J.BIOCEL.2020.105776

Jung, D., Seo, E. Y., Epstein, S. S., Joung, Y., Han, J., Parfenova, V. V., Belykh, O. I., Gladkikh, A. S., and Ahn, T. S. (2014). Application of a new cultivation technology, I-tip, for studying microbial diversity in freshwater sponges of Lake Baikal, Russia. FEMS Microbiology Ecology, 90(2), 417–423. https://doi.org/10.1111/1574-6941.12399

Kerckhoffs, A. P., Samsom, M., Rest, M. E. van der, Vogel, J. de, Knol, J., Ben-Amor, K., and Akkermans, L. M. (2009). Lower Bifidobacteria counts in both duodenal mucosa-associated and fecal microbiota in irritable bowel syndrome patients. World Journal of Gastroenterology, 15(23), 2887. https://doi.org/10.3748/wjg.15.2887

Kieler, I. N., Mølbak, L., Hansen, L. L., Hermann-Bank, M. L., and Bjornvad, C. R. (2016). Overweight and the feline gut microbiome - a pilot study. Journal of Animal Physiology and Animal Nutrition, 100(3), 478–484. https://doi.org/10.1111/JPN.12409

King, C. H., Desai, H., Sylvetsky, A. C., LoTempio, J., Ayanyan, S., Carrie, J., Crandall, K. A., Fochtman, B. C., Gasparyan, L., Gulzar, N., Howell, P., Issa, N., Krampis, K., Mishra,

L., Morizono, H., Pisegna, J. R., Rao, S., Ren, Y., Simonyan, V., … Mazumder, R. (2019). Baseline human gut microbiota profile in healthy people and standard reporting template. PLOS ONE, 14(9), e0206484. https://doi.org/10.1371/journal.pone.0206484

Knapp, S., Brodal, C., Peterson, J., Qi, F., Kreth, J., and Merritt, J. (2017). Natural Competence Is Common among Clinical Isolates of Veillonella parvula and Is Useful for Genetic Manipulation of This Key Member of the Oral Microbiome. Frontiers in Cellular and Infection Microbiology, 7. https://doi.org/10.3389/fcimb.2017.00139

Kuhns, M., Zautner, A. E., Rabsch, W., Zimmermann, O., Weig, M., Bader, O., and Groß, U. (2012). Rapid discrimination of Salmonella enterica serovar typhi from other serovars by MALDI-TOF mass spectrometry. PLoS ONE, 7(6), 1–6. https://doi.org/10.1371/journal.pone.0040004

La Scola, B., Fournier, P. E., and Raoult, D. (2011). Burden of emerging anaerobes in the MALDI-TOF and 16S rRNA gene sequencing era. Anaerobe, 17(3), 106–112. https://doi.org/10.1016/j.anaerobe.2011.05.010

Lagier, J. C., Armougom, F., Million, M., Hugon, P., Pagnier, I., Robert, C., Bittar, F., Fournous, G., Gimenez, G., Maraninchi, M., Trape, J. F., Koonin, E. V., La Scola, B., and Raoult, D. (2012). Microbial culturomics: Paradigm shift in the human gut microbiome study. Clinical Microbiology and Infection, 18(12), 1185–1193. https://doi.org/10.1111/1469-0691.12023

Lagier, J. C., Dubourg, G., Million, M., Cadoret, F., Bilen, M., Fenollar, F., Levasseur, A., Rolain, J. M., Fournier, P. E., and Raoult, D. (2018). Culturing the human microbiota and culturomics. Nature Reviews Microbiology, 16(9), 540–550. https://doi.org/10.1038/s41579-018-0041-0

Lagier, J.-C., Hugon, P., Khelaifia, S., Fournier, P.-E., La Scola, B., and Raoult, D. (2015). The Rebirth of Culture in Microbiology through the Example of Culturomics To Study Human Gut Microbiota. Clinical Microbiology Reviews, 28(1), 237–264. https://doi.org/10.1128/CMR.00014-14

Lange, K., Buerger, M., Stallmach, A., and Bruns, T. (2016). Effects of Antibiotics on Gut Microbiota. Digestive Diseases (Basel, Switzerland), 34(3), 260–268. https://doi.org/10.1159/000443360

Lauber, C. L., Zhou, N., Gordon, J. I., Knight, R., and Fierer, N. (2010). Effect of storage conditions on the assessment of bacterial community structure in soil and human-associated samples. FEMS Microbiology Letters, 307(1), 80–86. https://doi.org/10.1111/j.1574-6968.2010.01965.x

Lee, S. A., Lim, J. Y., Kim, B.-S., Cho, S. J., Kim, N. Y., Kim, O. Bin, and Kim, Y. (2015). Comparison of the gut microbiota profile in breast-fed and formula-fed Korean infants using pyrosequencing. Nutrition Research and Practice, 9(3), 242. https://doi.org/10.4162/nrp.2015.9.3.242

Lee, S.-Y., Lee, E., Park, Y. M., and Hong, S.-J. (2018). Microbiome in the Gut-Skin Axis in Atopic Dermatitis. Allergy, Asthma and Immunology Research, 10(4), 354. https://doi.org/10.4168/aair.2018.10.4.354

Lees, E. A., Miyajima, F., Pirmohamed, M., and Carrol, E. D. (2016). The role of Clostridium difficile in the paediatric and neonatal gut — a narrative review. European Journal of

Clinical Microbiology and Infectious Diseases, 35(7), 1047–1057. https://doi.org/10.1007/s10096-016-2639-3

Li, F., Hullar, M. A. J., and Lampe, J. W. (2007). Optimization of terminal restriction fragment polymorphism (TRFLP) analysis of human gut microbiota. Journal of Microbiological Methods, 68(2), 303–311. https://doi.org/10.1016/j.mimet.2006.09.006

Li, G., Yang, M., Zhou, K., Zhang, L., Tian, L., Lv, S., Jin, Y., Qian, W., Xiong, H., Lin, R., Fu, Y., and Hou, X. (2015). Diversity of Duodenal and Rectal Microbiota in Biopsy Tissues and Luminal Contents in Healthy Volunteers. Journal of Microbiology and Biotechnology, 25(7), 1136–1145. https://doi.org/10.4014/jmb.1412.12047

Liébana-García, R., Olivares, M., Bullich-Vilarrubias, C., López-Almela, I., Romaní-Pérez, M., and Sanz, Y. (2021). The gut microbiota as a versatile immunomodulator in obesity and associated metabolic disorders. Best Practice and Research Clinical Endocrinology and Metabolism, 35(3), 101542. https://doi.org/10.1016/j.beem.2021.101542

Lin, E., and Lane, H.-Y. (2017). Machine learning and systems genomics approaches for multi-omics data. Biomarker Research, 5(1), 2. https://doi.org/10.1186/s40364-017-0082-y

Liu, P., Wang, Y., Yang, G., Zhang, Q., Meng, L., Xin, Y., and Jiang, X. (2021). The role of short-chain fatty acids in intestinal barrier function, inflammation, oxidative stress, and colonic carcinogenesis. Pharmacological Research, 165, 105420. https://doi.org/10.1016/j.phrs.2021.105420

Liu, T., and Huang, Z. (2019). Evidence-based analysis of neurotransmitter modulation by gut microbiota. Lecture Notes in Computer Science (Including Subseries Lecture Notes in Artificial Intelligence and Lecture Notes in Bioinformatics), 11837 LNCS, 238–249. https://doi.org/10.1007/978-3-030-32962-4_22/COVER

Liu, T., Feenstra, K. A., Heringa, J., and Huang, Z. (2020). Influence of Gut Microbiota on Mental Health via Neurotransmitters: A Review. Journal of Artificial Intelligence for Medical Sciences, 1(1–2), 1–14. https://doi.org/10.2991/JAIMS.D.200420.001

Long, S. L., Gahan, C. G. M., and Joyce, S. A. (2017). Interactions between gut bacteria and bile in health and disease. Molecular Aspects of Medicine, 56, 54–65. https://doi.org/10.1016/j.mam.2017.06.002

Lowe, R., Shirley, N., Bleackley, M., Dolan, S., and Shafee, T. (2017). Transcriptomics technologies. PLOS Computational Biology, 13(5), e1005457. https://doi.org/10.1371/journal.pcbi.1005457

Łubiech, K., and Twarużek, M. (2020). Lactobacillus Bacteria in Breast Milk. Nutrients, 12(12), 3783. https://doi.org/10.3390/nu12123783

Lukumbuzya, M., Schmid, M., Pjevac, P., and Daims, H. (2019). A multicolor fluorescence in situ hybridization approach using an extended set of fluorophores to visualize microorganisms. Frontiers in Microbiology, 10(JUN), 1–13. https://doi.org/10.3389/fmicb.2019.01383

Mailhe, M., Ricaboni, D., Vitton, V., Fournier, P.-E., Khelaifia, S., and Raoult, D. (2016). ‘ Bacteroides mediterraneensis ’ sp. nov., a new human-associated bacterium isolated from ileum specimen. New Microbes and New Infections, 13, 48–50. https://doi.org/10.1016/j.nmni.2016.06.003

Manandhar, I., Alimadadi, A., Aryal, S., Munroe, P. B., Joe, B., and Cheng, X. (2021). Gut microbiome-based supervised machine learning for clinical diagnosis of inflammatory

bowel diseases. American Journal of Physiology-Gastrointestinal and Liver Physiology, 320(3), G328–G337. https://doi.org/10.1152/ajpgi.00360.2020

Marchesi, J. R., and Ravel, J. (2015). The vocabulary of microbiome research: a proposal. Microbiome, 3(1), 31. https://doi.org/10.1186/s40168-015-0094-5

Martinez-Guryn, K., Leone, V., and Chang, E. B. (2019). Regional Diversity of the Gastrointestinal Microbiome. Cell Host and Microbe, 26(3), 314–324. https://doi.org/10.1016/j.chom.2019.08.011

Mastromarino, P., Capobianco, D., Campagna, G., Laforgia, N., Drimaco, P., Dileone, A., and Baldassarre, M. E. (2014). Correlation between lactoferrin and beneficial microbiota in breast milk and infant's feces. BioMetals, 27(5), 1077–1086. https://doi.org/10.1007/s10534-014-9762-3

McCoubrey, L. E., Elbadawi, M., Orlu, M., Gaisford, S., and Basit, A. W. (2021). Machine Learning Uncovers Adverse Drug Effects on Intestinal Bacteria. Pharmaceutics, 13(7), 1026. https://doi.org/10.3390/pharmaceutics13071026

McOrist, A. L., Warhurst, M., McOrist, S., and Bird, A. R. (2001). Colonic Infection by Bilophila wadsworthia in Pigs. Journal of Clinical Microbiology, 39(4), 1577–1579. https://doi.org/10.1128/JCM.39.4.1577-1579.2001

Menees, S., and Chey, W. (2018). The gut microbiome and irritable bowel syndrome. F1000Research, 7, 1029. https://doi.org/10.12688/f1000research.14592.1

Mitev, K., and Taleski, V. (2019). Association between the Gut Microbiota and Obesity. Open Access Macedonian Journal of Medical Sciences, 7(12), 2050–2056. https://doi.org/10.3889/oamjms.2019.586

Mladenova, I. (2021). Clinical Relevance of Helicobacter pylori Infection. Journal of Clinical Medicine, 10(16), 3473. https://doi.org/10.3390/jcm10163473

Möhler, H. (2012). The GABA system in anxiety and depression and its therapeutic potential. Neuropharmacology, 62(1), 42–53. https://doi.org/10.1016/J.NEUROPHARM.2011.08.040

Moore, R. E., and Townsend, S. D. (2019). Temporal development of the infant gut microbiome. Open Biology, 9(9), 190128. https://doi.org/10.1098/rsob.190128

Morilak, D. A., Barrera, G., Echevarria, D. J., Garcia, A. S., Hernandez, A., Ma, S., and Petre, C. O. (2005). Role of brain norepinephrine in the behavioral response to stress. Progress in Neuro-Psychopharmacology and Biological Psychiatry, 29(8), 1214–1224. https://doi.org/10.1016/J.PNPBP.2005.08.007

Mou, Z., Yang, Y., Hall, A. B., and Jiang, X. (2021). The taxonomic distribution of histamine-secreting bacteria in the human gut microbiome. BMC Genomics, 22(1), 1–11. https://doi.org/10.1186/S12864-021-08004-3/FIGURES/3

Mousavi, R., Mottawea, W., Audet, M.-C., and Hammami, R. (2022). Survival and Interplay of γ-Aminobutyric Acid-Producing Psychobiotic Candidates with the Gut Microbiota in a Continuous Model of the Human Colon. Biology, 11(9), 1311. https://doi.org/10.3390/biology11091311

Nanjappa, S., Shah, S., and Pabbathi, S. (2015). Clostridium septicum Gas Gangrene in Colon Cancer: Importance of Early Diagnosis. Case Reports in Infectious Diseases, 2015, 1–3. https://doi.org/10.1155/2015/694247

Nechvatal, J. M., Ram, J. L., Basson, M. D., Namprachan, P., Niec, S. R., Badsha, K. Z., Matherly, L. H., Majumdar, A. P. N., and Kato, I. (2008). Fecal collection, ambient preservation, and DNA extraction for PCR amplification of bacterial and human markers from human feces. Journal of Microbiological Methods, 72(2), 124–132. https://doi.org/10.1016/j.mimet.2007.11.007

Niaz, B., Saeed, F., Ahmed, A., Imran, M., Maan, A. A., Khan, M. K. I., Tufail, T., Anjum, F. M., Hussain, S., and Suleria, H. A. R. (2019). Lactoferrin (LF): a natural antimicrobial protein. International Journal of Food Properties, 22(1), 1626–1641. https://doi.org/10.1080/10942912.2019.1666137

Nichols, D., Cahoon, N., Trakhtenberg, E. M., Pham, L., Mehta, A., Belanger, A., Kanigan, T., Lewis, K., and Epstein, S. S. (2010). Use of ichip for high-throughput in situ cultivation of "uncultivable microbial species▽. Applied and Environmental Microbiology, 76(8), 2445–2450. https://doi.org/10.1128/AEM.01754-09

O'Callaghan, A., and van Sinderen, D. (2016). Bifidobacteria and Their Role as Members of the Human Gut Microbiota. Frontiers in Microbiology, 7. https://doi.org/10.3389/fmicb.2016.00925

O'Mahony, S. M., Clarke, G., Borre, Y. E., Dinan, T. G., and Cryan, J. F. (2015). Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural Brain Research, 277, 32–48. https://doi.org/10.1016/J.BBR.2014.07.027

Okumura, R., and Takeda, K. (2018). Maintenance of intestinal homeostasis by mucosal barriers. Inflammation and Regeneration, 38(1), 5. https://doi.org/10.1186/s41232-018-0063-z

Osborne, C. A. (2014). Terminal Restriction Fragment Length Polymorphism (T-RFLP) Profiling of Bacterial 16S rRNA Genes (pp. 57–69). https://doi.org/10.1007/978-1-62703-712-9_5

Otaru, N., Ye, K., Mujezinovic, D., Berchtold, L., Constancias, F., Cornejo, F. A., Krzystek, A., de Wouters, T., Braegger, C., Lacroix, C., and Pugin, B. (2021). GABA Production by Human Intestinal Bacteroides spp.: Prevalence, Regulation, and Role in Acid Stress Tolerance. Frontiers in Microbiology, 12. https://doi.org/10.3389/FMICB.2021.656895

Özoğul, F. (2004). Production of biogenic amines by Morganella morganii, Klebsíella pneumoniae and Hafnia alvei using a rapid HPLC method. European Food Research and Technology, 219(5), 465–469. https://doi.org/10.1007/S00217-004-0988-0/TABLES/3

Özoğul, F., Kuley, E., Özoğul, Y., and Özoğul, I. (2012). The Function of Lactic Acid Bacteria on Biogenic Amines Production by Food-Borne Pathogens in Arginine Decarboxylase Broth. Food Science and Technology Research, 18(6), 795–804. https://doi.org/10.3136/FSTR.18.795

PERCIACCANTE, A., and DONELL, S. T. (2022). Microbiome: an old history of a new paradigm. Minerva Gastroenterology, 67(4). https://doi.org/10.23736/S2724-5985.21.02905-3

Peter, A., Jacob, D. J., Logan, J. A., and Link, C. (2014). The Making of the Microbial Body. Strategic Management Journal, 35(1), 1–23.

PICARD, C., FIORAMONTI, J., FRANCOIS, A., ROBINSON, T., NEANT, F., and MATUCHANSKY, C. (2005). Review article: bifidobacteria as probiotic agents -

physiological effects and clinical benefits. Alimentary Pharmacology and Therapeutics, 22(6), 495–512. https://doi.org/10.1111/j.1365-2036.2005.02615.x

Pigeyre, M., Yazdi, F. T., Kaur, Y., and Meyre, D. (2016). Recent progress in genetics, epigenetics and metagenomics unveils the pathophysiology of human obesity. Clinical Science, 130(12), 943–986. https://doi.org/10.1042/CS20160136

Pinto, T. C. A., Costa, N. S., Castro, L. F. S., Ribeiro, R. L., Botelho, A. C. N., Neves, F. P. G., Peralta, J. M., and Teixeira, L. M. (2017). Potential of MALDI-TOF MS as an alternative approach for capsular typing Streptococcus pneumoniae isolates. Scientific Reports, 7(December 2016), 1–5. https://doi.org/10.1038/srep45572

Priya, S., Burns, M. B., Ward, T., Mars, R. A. T., Adamowicz, B., Lock, E. F., Kashyap, P. C., Knights, D., and Blekhman, R. (2022). Identification of shared and disease-specific host gene–microbiome associations across human diseases using multi-omic integration. Nature Microbiology, 7(6), 780–795. https://doi.org/10.1038/s41564-022-01121-z

Putignani, L., Del Chierico, F., Petrucca, A., Vernocchi, P., and Dallapiccola, B. (2014). The human gut microbiota: a dynamic interplay with the host from birth to senescence settled during childhood. Pediatric Research, 76(1), 2–10. https://doi.org/10.1038/pr.2014.49

Qin, J., Li, R., Raes, J., Arumugam, M., Burgdorf, K. S., Manichanh, C., Nielsen, T., Pons, N., Levenez, F., Yamada, T., Mende, D. R., Li, J., Xu, J., Li, S., Li, D., Cao, J., Wang, B., Liang, H., Zheng, H., … Zoetendal, E. (2010). A human gut microbial gene catalogue established by metagenomic sequencing. Nature, 464(7285), 59–65. https://doi.org/10.1038/nature08821

Quercia, S., Candela, M., Giuliani, C., Turroni, S., Luiselli, D., Rampelli, S., Brigidi, P., Franceschi, C., Bacalini, M. G., Garagnani, P., and Pirazzini, C. (2014). From lifetime to evolution: timescales of human gut microbiota adaptation. Frontiers in Microbiology, 5. https://doi.org/10.3389/fmicb.2014.00587

Quillin, S. J., Tran, P., and Prindle, A. (2021). Potential Roles for Gamma-Aminobutyric Acid Signaling in Bacterial Communities. Bioelectricity, 3(2), 120–125. https://doi.org/10.1089/BIOE.2021.0012

Raman, R., Thomas, R. G., Weiner, M. W., Jack, C. R., Ernstrom, K., Aisen, P. S., Tariot, P. N., and Quinn, J. F. (2005). Diversity of the Human Intestinal Microbial Flora. Science, 308(5728), 1635–1638.

Ramirez, J., Guarner, F., Bustos Fernandez, L., Maruy, A., Sdepanian, V. L., and Cohen, H. (2020). Antibiotics as Major Disruptors of Gut Microbiota. Frontiers in Cellular and Infection Microbiology, 10. https://doi.org/10.3389/fcimb.2020.572912

Ranjbar, J., Geramizadeh, B., Bagheri Lankarani, K., Jowkar, Z., Mirzai, M., and Moazamian, E. (2022). Is the Presence of Helicobacter Pylori in the Colonic Mucosa, Provocative of Activity in Ulcerative Colitis? Clinical Pathology, 15, 2632010X2210966. https://doi.org/10.1177/2632010X221096660

Ren, S., Hui, Y., Obelitz-Ryom, K., Brandt, A. B., Kot, W., Nielsen, D. S., Thymann, T., Sangild, P. T., and Nguyen, D. N. (2018). Neonatal gut and immune maturation is determined more by postnatal age than by postconceptional age in moderately preterm pigs. American Journal of Physiology-Gastrointestinal and Liver Physiology, 315(5), G855–G867. https://doi.org/10.1152/ajpgi.00169.2018

Rhodes, A. N. (1998). Identification of bacterial isolates obtained from intestinal contents associated with 12,000-year-old mastodon remains. Applied Environmental Microbiology, .651-658.

Rich, B. E., Jackson, J. C., de Ora, L. O., Long, Z. G., Uyeda, K. S., and Bess, E. N. (2022). Alternative pathway for dopamine production by acetogenic gut bacteria that O-Demethylate 3-Methoxytyramine, a metabolite of catechol O-Methyltransferase. Journal of Applied Microbiology, 133(3), 1697. https://doi.org/10.1111/JAM.15682

Riddle, M. S., and Connor, B. A. (2016). The Traveling Microbiome. Current Infectious Disease Reports, 18(9). https://doi.org/10.1007/s11908-016-0536-7

Rinninella, E., Raoul, P., Cintoni, M., Franceschi, F., Miggiano, G. A. D., Gasbarrini, A., and Mele, M. C. (2019). What is the Healthy Gut Microbiota Composition? A Changing Ecosystem across Age, Environment, Diet, and Diseases. Microorganisms, 7(1). https://doi.org/10.3390/MICROORGANISMS7010014

Rowland, I., Gibson, G., Heinken, A., Scott, K., Swann, J., Thiele, I., and Tuohy, K. (2018). Gut microbiota functions: metabolism of nutrients and other food components. European Journal of Nutrition, 57(1), 1–24. https://doi.org/10.1007/s00394-017-1445-8

Rutayisire, E., Huang, K., Liu, Y., and Tao, F. (2016). The mode of delivery affects the diversity and colonization pattern of the gut microbiota during the first year of infants' life: a systematic review. BMC Gastroenterology, 16(1), 86. https://doi.org/10.1186/s12876-016-0498-0

Salim, F., Mizutani, S., Zolfo, M., and Yamada, T. (2023). Recent advances of machine learning applications in human gut microbiota study: from observational analysis toward causal inference and clinical intervention. Current Opinion in Biotechnology, 79, 102884. https://doi.org/10.1016/j.copbio.2022.102884

Salipante, S. J., Kawashima, T., Rosenthal, C., Hoogestraat, D. R., Cummings, L. A., Sengupta, D. J., Harkins, T. T., Cookson, B. T., and Hoffman, N. G. (2014). Performance comparison of Illumina and Ion Torrent next-generation sequencing platforms for 16S rRNA-based bacterial community profiling. Applied and Environmental Microbiology, 80(24), 7583–7591. https://doi.org/10.1128/AEM.02206-14

Salvi, P. S., and Cowles, R. A. (2021). Butyrate and the Intestinal Epithelium: Modulation of Proliferation and Inflammation in Homeostasis and Disease. Cells, 10(7), 1775. https://doi.org/10.3390/cells10071775

Sánchez, E., Donat, E., Ribes-Koninckx, C., Fernández-Murga, M. L., and Sanz, Y. (2013). Duodenal-Mucosal Bacteria Associated with Celiac Disease in Children. Applied and Environmental Microbiology, 79(18), 5472–5479. https://doi.org/10.1128/AEM.00869-13

Sanschagrin, S., and Yergeau, E. (2014). Next-generation sequencing of 16S ribosomal RNA gene amplicons. Journal of Visualized Experiments, 90, 1–7. https://doi.org/10.3791/51709

Saturio, S., Nogacka, A. M., Alvarado-Jasso, G. M., Salazar, N., de los Reyes-Gavilán, C. G., Gueimonde, M., and Arboleya, S. (2021). Role of Bifidobacteria on Infant Health. Microorganisms, 9(12), 2415. https://doi.org/10.3390/microorganisms9122415

Scardaci, R., Bietto, F., Racine, P.-J., Boukerb, A. M., Lesouhaitier, O., Feuilloley, M. G. J., Scutera, S., Musso, T., Connil, N., and Pessione, E. (2022). Norepinephrine and Serotonin Can Modulate the Behavior of the Probiotic Enterococcus faecium NCIMB10415 towards the Host: Is a Putative Surface Sensor Involved? Microorganisms, 10(3). https://doi.org/10.3390/microorganisms10030487

Scardaci, R., Varese, F., Manfredi, M., Marengo, E., Mazzoli, R., and Pessione, E. (2021). Enterococcus faecium NCIMB10415 responds to norepinephrine by altering protein profiles and phenotypic characters. Journal of Proteomics, 231. https://doi.org/10.1016/J.JPROT.2020.104003

Schoeler, M., and Caesar, R. (2019). Dietary lipids, gut microbiota and lipid metabolism. Reviews in Endocrine and Metabolic Disorders, 20(4), 461–472. https://doi.org/10.1007/s11154-019-09512-0

Scholz, M., Ward, D. V., Pasolli, E., Tolio, T., Zolfo, M., Asnicar, F., Truong, D. T., Tett, A., Morrow, A. L., and Segata, N. (2016). Strain-level microbial epidemiology and population genomics from shotgun metagenomics. Nature Methods, 13(5), 435–438. https://doi.org/10.1038/nmeth.3802

Sekirov, I., Russell, S. L., Antunes, L. C. M., and Finlay, B. B. (2010). Gut Microbiota in Health and Disease. Physiological Reviews, 90(3), 859–904. https://doi.org/10.1152/physrev.00045.2009

Selma-Royo, M., Calvo Lerma, J., Cortés-Macías, E., and Collado, M. C. (2021). Human milk microbiome: From actual knowledge to future perspective. Seminars in Perinatology, 45(6), 151450. https://doi.org/10.1016/j.semperi.2021.151450

Seng, P., Abat, C., Rolain, J. M., Colson, P., Lagier, J. C., Gouriet, F., Fournier, P. E., Drancourt, M., Scola, B. La, and Raoult, D. (2013). Identification of rare pathogenic bacteria in a clinical microbiology laboratory: Impact of matrix-assisted laser desorption ionization-time of flight mass spectrometry. Journal of Clinical Microbiology, 51(7), 2182–2194. https://doi.org/10.1128/JCM.00492-13

Seng, P., Drancourt, M., Gouriet, F., Scola, B. La, Fournier, P. E., Rolain, J. M., and Raoult, D. (2009). Ongoing revolution in bacteriology: Routine identification of bacteria by matrix-assisted laser desorption ionization time-of-flight mass spectrometry. Clinical Infectious Diseases, 49(4), 543–551. https://doi.org/10.1086/600885

Shamir, R. (2016). The Benefits of Breast Feeding (pp. 67–76). https://doi.org/10.1159/000442724

Shankar, V., Hamilton, M. J., Khoruts, A., Kilburn, A., Unno, T., Paliy, O., and Sadowsky, M. J. (2014). Species and genus level resolution analysis of gut microbiota in Clostridium difficile patients following fecal microbiota transplantation. Microbiome, 2(1), 1–10. https://doi.org/10.1186/2049-2618-2-13

Shin, H., Pei, Z., Martinez, K. A., Rivera-Vinas, J. I., Mendez, K., Cavallin, H., and Dominguez-Bello, M. G. (2015). The first microbial environment of infants born by C-section: the operating room microbes. Microbiome, 3(1), 59. https://doi.org/10.1186/s40168-015-0126-1

Shishov, V. A., Kirovskaya, T. A., Kudrin, V. S., and Oleskin, A. V. (2009). Amine neuromediators, their precursors, and oxidation products in the culture of Escherichia

coli k-12. Applied Biochemistry and Microbiology, 45(5), 494–497. https://doi.org/10.1134/S0003683809050068/METRICS

Siezen RJ, K. M. (2011). The human gut microbiome: are we our enterotypes? Microbial Biotechnology, 550–553.

Siezen, R. J., and Kleerebezem, M. (2011). The human gut microbiome: are we our enterotypes? Microbial Biotechnology, 4(5), 550. https://doi.org/10.1111/J.1751-7915.2011.00290.X

Sinclair, L., Osman, O. A., Bertilsson, S., and Eiler, A. (2015). Microbial community composition and diversity via 16S rRNA gene amplicons: Evaluating the illumina platform. PLoS ONE, 10(2), 1–18. https://doi.org/10.1371/journal.pone.0116955

Singh, J., Kumar, M., Sharma, A., Pandey, G., Chae, K., and Lee, S. (2016). Genomic Techniques Used to Investigate the Human Gut Microbiota. Intech, 11(tourism), 13.

Sinha, R., Sahoo, N. R., Kumar, P., Qureshi, S., Kumar, A., Ravikumar, G. V. P. P. S., and Bhushan, B. (2018). Comparative jejunal expression of MUC 13 in Indian native pigs differentially adhesive to diarrhoeagenic E. coli. Journal of Applied Animal Research, 46(1), 107–111. https://doi.org/10.1080/09712119.2016.1267009

Sokol H. (2019). Définition et rôles du microbiote intestinal [Definition and roles of the gut microbiota]. La Revue Du Praticien, 69(7).

Sokol, H., and Seksik, P. (2010). The intestinal microbiota in inflammatory bowel diseases: Time to connect with the host. Current Opinion in Gastroenterology, 26(4), 327–331. https://doi.org/10.1097/MOG.0b013e328339536b

Stasi, C., Sadalla, S., and Milani, S. (2019). The Relationship Between the Serotonin Metabolism, Gut-Microbiota and the Gut-Brain Axis. Current Drug Metabolism, 20(8), 646–655. https://doi.org/10.2174/1389200220666190725115503

Stinson, L. F., Sindi, A. S. M., Cheema, A. S., Lai, C. T., Mühlhäusler, B. S., Wlodek, M. E., Payne, M. S., and Geddes, D. T. (2021). The human milk microbiome: who, what, when, where, why, and how? Nutrition Reviews, 79(5), 529–543. https://doi.org/10.1093/nutrit/nuaa029

Stojanov, S., Berlec, A., and Štrukelj, B. (2020). The Influence of Probiotics on the Firmicutes/Bacteroidetes Ratio in the Treatment of Obesity and Inflammatory Bowel disease. Microorganisms, 8(11), 1715. https://doi.org/10.3390/microorganisms8111715

Stokowa-Sołtys, K., Wojtkowiak, K., and Jagiełło, K. (2021). Fusobacterium nucleatum – Friend or foe? Journal of Inorganic Biochemistry, 224, 111586. https://doi.org/10.1016/j.jinorgbio.2021.111586

Strandwitz, P. (2018). Neurotransmitter modulation by the gut microbiota. Brain Research, 1693(Pt B), 128–133. https://doi.org/10.1016/J.BRAINRES.2018.03.015

Strandwitz, P., Kim, K. H., Terekhova, D., Liu, J. K., Sharma, A., Levering, J., McDonald, D., Dietrich, D., Ramadhar, T. R., Lekbua, A., Mroue, N., Liston, C., Stewart, E. J., Dubin, M. J., Zengler, K., Knight, R., Gilbert, J. A., Clardy, J., and Lewis, K. (2019). GABA-modulating bacteria of the human gut microbiota. Nature Microbiology, 4(3), 396–403. https://doi.org/10.1038/S41564-018-0307-3

Suau, A. (1999). Direct analysis of genes encoding 16S rRNA from complex communities reveals many novel molecular species within the human gut. Appl Environ Microbiol., 4799–4807.

Sunagawa, S., Mende, D. R., Zeller, G., Izquierdo-Carrasco, F., Berger, S. A., Kultima, J. R., Coelho, L. P., Arumugam, M., Tap, J., Nielsen, H. B., Rasmussen, S., Brunak, S., Pedersen, O., Guarner, F., De Vos, W. M., Wang, J., Li, J., Doré, J., Dusko Ehrlich, S., … Bork, P. (2013). Metagenomic species profiling using universal phylogenetic marker genes. Nature Methods, 10(12), 1196–1199. https://doi.org/10.1038/nmeth.2693

Surwase, S. N., and Jadhav, J. P. (2011). Bioconversion of L-tyrosine to L-DOPA by a novel bacterium Bacillus sp. JPJ. Amino Acids, 41(2), 495–506. https://doi.org/10.1007/S00726-010-0768-Z

Swidsinski, A., Loening-Baucke, V., Vaneechoutte, M., and Doerffel, Y. (2008). Active Crohn's disease and ulcerative colitis can be specifically diagnosed and monitored based on the biostructure of the fecal flora. Inflammatory Bowel Diseases, 14(2), 147–161. https://doi.org/10.1002/ibd.20330

Tannock, G. W. (2001). Molecular assessment of intestinal microflora. American Journal of Clinical Nutrition, 73(2 SUPPL.), 410–414. https://doi.org/10.1093/ajcn/73.2.410s

Thoeringer, C. K., Erhardt, A., Sillaber, I., Mueller, M. B., Ohl, F., Holsboer, F., and Keck, M. E. (2010). Long-term anxiolytic and antidepressant-like behavioural effects of tiagabine, a selective GABA transporter-1 (GAT-1) inhibitor, coincide with a decrease in HPA system activity in C57BL/6 mice. Journal of Psychopharmacology, 24(5), 733–743. https://doi.org/10.1177/0269881109103091

Thomas, T., Gilbert, J., and Meyer, F. (2014). Metagenomics: A guide from sampling to data analysis. The Role of Bioinformatics in Agriculture, Figure 1, 357–383. https://doi.org/10.1201/b16568

Thrash, J. C. (2019). Culturing the Uncultured: Risk versus Reward. MSystems, 4(3). https://doi.org/10.1128/MSYSTEMS.00130-19

Thursby, E., and Juge, N. (2017). Introduction to the human gut microbiota. Biochemical Journal, 474(11), 1823–1836. https://doi.org/10.1042/BCJ20160510

Tilg, H., and Kaser, A. (2011). Gut microbiome, obesity, and metabolic dysfunction. Journal of Clinical Investigation, 121(6), 2126–2132. https://doi.org/10.1172/JCI58109

Tringe, S. G., Von Mering, C., Kobayashi, A., Salamov, A. A., Chen, K., Chang, H. W., Podar, M., Short, J. M., Mathur, E. J., Detter, J. C., Bork, P., Hugenholtz, P., and Rubin, E. M. (2005). Comparative metagenomics of microbial communities. Science, 308(5721), 554–557. https://doi.org/10.1126/science.1107851

Tsoi, H., Chu, E. S. H., Zhang, X., Sheng, J., Nakatsu, G., Ng, S. C., Chan, A. W. H., Chan, F. K. L., Sung, J. J. Y., and Yu, J. (2017). Peptostreptococcus anaerobius Induces Intracellular Cholesterol Biosynthesis in Colon Cells to Induce Proliferation and Causes Dysplasia in Mice. Gastroenterology, 152(6), 1419-1433.e5. https://doi.org/10.1053/j.gastro.2017.01.009

Tsukuda, N., Yahagi, K., Hara, T., Watanabe, Y., Matsumoto, H., Mori, H., Higashi, K., Tsuji, H., Matsumoto, S., Kurokawa, K., and Matsuki, T. (2021). Key bacterial taxa and metabolic pathways affecting gut short-chain fatty acid profiles in early life. The ISME Journal, 15(9), 2574–2590. https://doi.org/10.1038/s41396-021-00937-7

Turnbaugh, P. J., Ridaura, V. K., Faith, J. J., Rey, F. E., Knight, R., and Gordon, J. I. (2009). The effect of diet on the human gut microbiome: A metagenomic analysis in humanized

gnotobiotic mice. Science Translational Medicine, 1(6). https://doi.org/10.1126/scitranslmed.3000322

Underwood, M. A., Gaerlan, S., De Leoz, M. L. A., Dimapasoc, L., Kalanetra, K. M., Lemay, D. G., German, J. B., Mills, D. A., and Lebrilla, C. B. (2015). Human milk oligosaccharides in premature infants: absorption, excretion, and influence on the intestinal microbiota. Pediatric Research, 78(6), 670–677. https://doi.org/10.1038/pr.2015.162

Valdes, A. M., Walter, J., Segal, E., and Spector, T. D. (2018). Role of the gut microbiota in nutrition and health. BMJ, k2179. https://doi.org/10.1136/bmj.k2179

Valles-Colomer, M., Falony, G., Darzi, Y., Tigchelaar, E. F., Wang, J., Tito, R. Y., Schiweck, C., Kurilshikov, A., Joossens, M., Wijmenga, C., Claes, S., Van Oudenhove, L., Zhernakova, A., Vieira-Silva, S., and Raes, J. (2019). The neuroactive potential of the human gut microbiota in quality of life and depression. Nature Microbiology, 4(4), 623–632. https://doi.org/10.1038/S41564-018-0337-X

Venter, J. C., Remington, K., Heidelberg, J. F., Halpern, A. L., Rusch, D., Eisen, J. A., Wu, D., Paulsen, I., Nelson, K. E., Nelson, W., Fouts, D. E., Levy, S., Knap, A. H., Lomas, M. W., Nealson, K., White, O., Peterson, J., Hoffman, J., Parsons, R., … Smith, H. O. (2004). Environmental Genome Shotgun Sequencing of the Sargasso Sea. Science, 304(5667), 66–74. https://doi.org/10.1126/science.1093857

Verhaar, B. J. H., Prodan, A., Nieuwdorp, M., and Muller, M. (2020). Gut Microbiota in Hypertension and Atherosclerosis: A Review. Nutrients, 12(10), 2982. https://doi.org/10.3390/nu12102982

Viglasky, V. (2013). Polyacrylamide Temperature Gradient Gel Electrophoresis (pp. 159–171). https://doi.org/10.1007/978-1-62703-565-1_10

Wagner, J., Coupland, P., Browne, H. P., Lawley, T. D., Francis, S. C., and Parkhill, J. (2016). Evaluation of PacBio sequencing for full-length bacterial 16S rRNA gene classification. BMC Microbiology, 16(1), 1–17. https://doi.org/10.1186/s12866-016-0891-4

Wall, R., Hussey, S. G., Ryan, C. A., O'Neill, M., Fitzgerald, G., Stanton, C., and Ross, R. P. (2008). Presence of two Lactobacillus and Bifidobacterium probiotic strains in the neonatal ileum. The ISME Journal, 2(1), 83–91. https://doi.org/10.1038/ismej.2007.69

Walter, J. (2008). Ecological Role of Lactobacilli in the Gastrointestinal Tract: Implications for Fundamental and Biomedical Research. Applied and Environmental Microbiology, 74(16), 4985–4996. https://doi.org/10.1128/AEM.00753-08

Wang, J., Dong, P., Zheng, S., Mai, Y., Ding, J., Pan, P., Tang, L., Wan, Y., and Liang, H. (2023). Advances in gut microbiome in metabonomics perspective: based on bibliometrics methods and visualization analysis. Frontiers in Cellular and Infection Microbiology, 13. https://doi.org/10.3389/fcimb.2023.1196967

Wooley, J. C., Godzik, A., and Friedberg, I. (2010). A primer on metagenomics. PLoS Computational Biology, 6(2). https://doi.org/10.1371/journal.pcbi.1000667

Wu, G. D., Lewis, J. D., Hoffmann, C., Chen, Y.-Y., Knight, R., Bittinger, K., Hwang, J., Chen, J., Berkowsky, R., Nessel, L., Li, H., and Bushman, F. D. (2010). Sampling and pyrosequencing methods for characterizing bacterial communities in the human gut using 16S sequence tags. BMC Microbiology, 10(1), 206. https://doi.org/10.1186/1471-2180-10-206

Wu, H., Tremaroli, V., Schmidt, C., Lundqvist, A., Olsson, L. M., Krämer, M., Gummesson, A., Perkins, R., Bergström, G., and Bäckhed, F. (2020). The Gut Microbiota in Prediabetes and Diabetes: A Population-Based Cross-Sectional Study. Cell Metabolism, 32(3), 379-390.e3. https://doi.org/10.1016/j.cmet.2020.06.011

Xiao, Y., Zhai, Q., Zhang, H., Chen, W., and Hill, C. (2021Chen). Gut Colonization Mechanisms of Lactobacillus and Bifidobacterium : An Argument for Personalized Designs. Annual Review of Food Science and Technology, 12(1), 213–233. https://doi.org/10.1146/annurev-food-061120-014739

Xiong, W., Abraham, P. E., Li, Z., Pan, C., and Hettich, R. L. (2015). Microbial metaproteomics for characterizing the range of metabolic functions and activities of human gut microbiota. Proteomics, 15(20), 3424–3438. https://doi.org/10.1002/pmic.201400571

Yang, B., Feng, L., Wang, F., and Wang, L. (2015). Enterohemorrhagic Escherichia coli senses low biotin status in the large intestine for colonization and infection. Nature Communications, 6(1), 6592. https://doi.org/10.1038/ncomms7592

Yang, I., Corwin, E. J., Brennan, P. A., Jordan, S., Murphy, J. R., and Dunlop, A. (2016). The Infant Microbiome. Nursing Research, 65(1), 76–88. https://doi.org/10.1097/NNR.0000000000000133

Yang, Y., and Jobin, C. (2017). Novel insights into microbiome in colitis and colorectal cancer. Current Opinion in Gastroenterology, 33(6), 422–427. https://doi.org/10.1097/MOG.0000000000000399

Yano, J. M., Yu, K., Donaldson, G. P., Shastri, G. G., Ann, P., Ma, L., Nagler, C. R., Ismagilov, R. F., Mazmanian, S. K., and Hsiao, E. Y. (2015). Indigenous Bacteria from the Gut Microbiota Regulate Host Serotonin Biosynthesis. Cell, 161(2), 264–276. https://doi.org/10.1016/J.CELL.2015.02.047

Yao, Y., Cai, X., Ye, Y., Wang, F., Chen, F., and Zheng, C. (2021). The Role of Microbiota in Infant Health: From Early Life to Adulthood. Frontiers in Immunology, 12. https://doi.org/10.3389/fimmu.2021.708472

Ye, S. H., Siddle, K. J., Park, D. J., and Sabeti, P. C. (2019). Benchmarking Metagenomics Tools for Taxonomic Classification. Cell, 178(4), 779–794. https://doi.org/10.1016/j.cell.2019.07.010

Yeoh, Y. K., Sun, Y., Ip, L. Y. T., Wang, L., Chan, F. K. L., Miao, Y., and Ng, S. C. (2022). Prevotella species in the human gut is primarily comprised of Prevotella copri, Prevotella stercorea and related lineages. Scientific Reports, 12(1), 9055. https://doi.org/10.1038/s41598-022-12721-4

Yoo, J. Y., Groer, M., Dutra, S. V. O., Sarkar, A., and McSkimming, D. I. (2020). Gut Microbiota and Immune System Interactions. Microorganisms, 8(10), 1–22. https://doi.org/10.3390/MICROORGANISMS8101587

Ze, X., Duncan, S. H., Louis, P., and Flint, H. J. (2012). Ruminococcus bromii is a keystone species for the degradation of resistant starch in the human colon. The ISME Journal, 6(8), 1535–1543. https://doi.org/10.1038/ismej.2012.4

Zhang, M., Sun, K., Wu, Y., Yang, Y., Tso, P., and Wu, Z. (2017). Interactions between Intestinal Microbiota and Host Immune Response in Inflammatory Bowel Disease. Frontiers in Immunology, 8. https://doi.org/10.3389/fimmu.2017.00942

Zwielehner, J., Liszt, K., Handschur, M., Lassl, C., Lapin, A., and Haslberger, A. G. (2009). Combined PCR-DGGE fingerprinting and quantitative-PCR indicates shifts in fecal population sizes and diversity of Bacteroides, bifidobacteria and Clostridium cluster IV in institutionalized elderly. Experimental Gerontology, 44(6–7), 440–446. https://doi.org/10.1016/j.exger.2009.04.002