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Gastrointestinal microbiome: The two-way communication within us

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ABSTRACT

The gut is considered the largest organ with a significant function in regulating immune homeostasis throughout the life of an individual. The presence of "good" microbes in the gut tract makes the individual healthier, for example, in Parkinson's disease a decrease in beneficial microbes such as *Blautia* and *Roseburia* is observed contrary to a high population of *Akkermansia* and Verrucomicrobiaceae which is associated with mucin degradation. The first and foremost microbial colonization in the human gut occurs at the fetal stage *in utero*. Further, a vast amount of the resident microbial population is also transferred *in utero* from the oral cavity of the mother. The medical practices of birth, that is, the cesarean delivery or the vaginal delivery regulate the microbiome composition of the newborn. Unregulated dietary changes in human lifestyle along with antibiotics and environmental exposures can alter the gut microbiome. Typically, with less recognized implications for health and the likelihood of disease occurrence, the unhealthy gut impairs the normal functioning of the microbiota. Further, it has been extensively investigated that the intestinal tract harbors the largest and most diverse microbial population, and forms the Enteric Nervous System. Elucidation of the factors that influence this mutualistic relationship is therefore vital for understanding the Gut–Brain communication.

1. INTRODUCTION

The term gut, synonymous with gastrointestinal tract (GIT) is a passageway of an elaborate digestive system. It is the largest reservoir of microbes in the human body. Leading from the mouth and ending in the anus, the entire GIT comprises organs such as the stomach, liver, gall bladder, and pancreas, along with their secretions. The gut microflorae along with their DNA and the surrounding milieu in which these microbes reside, are referred to as the gut microbiome and, occasionally considered as a virtual organ of the body [1]. This gut microflorae with over 100 trillion microbes, includes the commensals and pathobionts and bacteria, viruses, and fungi that weigh around 200 g [2]. The organs along the GIT together perform intricate processes of mechanical and chemical digestion and absorption of digested food. It is also assigned the function of subsequent elimination of undigested food. The walls of the GIT are supplied with neurons, forming the enteric nervous system (ENS) very similar to the central nervous system (CNS). The gut, also referred to as the "second brain" has a significant function in the mental health of an individual. The microbes help in establishing a communication between the brain and the gut which is responsible for the neurological and immunological health of an individual [3]. However, it is the intestine that harbors the most diverse and abundant microbial community in the body [4]. This microbial population is dominant in bacteria that are from categories such as the Firmicutes, Bacteroidetes, and Actinobacteria [5]. Intestinal bacterial phyla are represented by Firmicutes (species, e.g., Clostridiales, *Lactobacillus, Enterococcus*) and Bacteroidetes (species, e.g., Bacteroides) that make up the larger proportion while the other phyla Actinobacteria (Bifidobacteria), Proteobacteria (*Escherichia coli*), Fusobacteria, and Verrucomicrobiota are represented in less numbers [6,7]. *Bifidobacterium* is a beneficial bacterium that helps to fight harmful bacteria [8]. It also helps in receiving the energy from diet in the adipose tissues, hence protecting the individual from diet-related obesity [9].

A decline in the diversity of microbes or loss of beneficial microbes leads to dysbiosis, a condition that makes an individual susceptible to various immune-mediated, metabolic, neural, and psychiatric diseases. A dysbiotic microbiota can further alter the barrier integrity and flood the tissues and organs with molecules/microbes/toxins, which negatively impact the metabolism. Since the gut microbes set an individual's metabolism, immunity, and overall health trajectory [10], it is imperative to know the communication between the microbiome and the body parameters. Investigations on gut microbial diversity are therefore, an emerging technology that facilitates insights into microbial ecosystems. The 16S ribosomal RNA (rRNA) amplification and whole-genome shotgun sequencing are the two most commonly used methods to study the diversity of the gut microbiota [11]. Lack of microflora diversity in the gut leads to various medical conditions,

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such as the gastroesophageal reflux or peptic ulcer diseases. This further involves treatments such as proton pump inhibitors and comprehensive digestive stool analysis. Moreover, it is evident that dietary-based modifications in the gut microbiome are the safest way to achieve a healthy self. Hence, the function of pre- and probiotics in the diet cannot be overlooked.

The present review provides a brief about the crucial role played by the gut microflora and the biological interactions within the body. It also reiterates the importance of a healthy lifestyle and diet in maintaining a balance of our gut microbiome. The state of imbalance or dysbiosis leads to health complications and therapeutic interventions. Further, the review also suggests some uncomplicated microbiome restoration strategies, thereby opening new avenues for preventive healthcare [Figure 1].

2. GUT MICROBIOME – THE SIGNATURE OF LONGEVITY

The diverse microbiome, besides microbes, also includes 50–100 fold more genes in the host. These additional genes contribute enzymes, not coded by the host. These enzymes play a crucial role in modulating host metabolism and hence are a significant part in the regulation of host physiology [12]. Certain bacteria, such as *Bacteroides fragilis*, *Eubacterium lentum, Enterobacter agglomerans, Serratia marcescens,* and *Enterococcus faecium* [13], anaerobically synthesize vitamin K2 (menaquinone) that is essential in decreasing vascular calcification, elevating high-density lipoprotein, and lowering cholesterol. All these are also significant in lowering the risk of cardiovascular disorders [14]. Gut bacteria also synthesize Vitamin B and Vitamin K, which have an important role in sugar and fat metabolism and maintenance of hemostatic functions. Further, the deficiency of Vitamin B5 and Vitamin B12, linked to disorders such as insomnia, neuropsychological disorders is regulated by the gut microbes [15,16].

Gut microflora is known for its function in the co-metabolism of bile acids with the host where they get associated with the liver to help detoxify and get rid of xenobiotics [17]. Furthermore, cholesterol-derived chemicals that are synthesized in the liver, conjugate with glycine or taurine, are subsequently stored in the gall bladder and then secreted in the duodenum where the digestive process is aided. About 95% of bile acids get reabsorbed at the distal ileum, and the remaining 5%, which are the unabsorbed primary bile acids, are bioconverted to secondary bile acids, deoxycholic acid, and lithocholic acid. The enzymes required for this conversion are provided by the colon bacteria such as *Clostridium scindens* [18]. Thus, these bacteria prove to regulate certain digestive conditions through the levels and bile acid profiles [19].

Microbes synthesize metabolites with pleiotropic effects. These metabolites further act as signaling molecules facilitating neuroendocrine crosstalks. This function physiologically links the gut with other systems. The gut and the central nervous system communicate through the vagus nerve that arises in the cranium. The gut microbiota establishes a connection with various pathways and metabolic processes such as the digestive, immune, and blood barrier systems. If the microbial diversity and/or population is disturbed, this communication falls apart. Leaky gut barrier is one of the reasons, another being dysbiosis which leads to low-grade systemic inflammation adversely affecting multiple organs [20]. The Gut–Brain Axis (GBA) is known for a significant role in diseases prevalent in elderly people, such as Alzheimer's, an old age-related disease. The neurotransmitters such as serotonin, dopamine, noradrenaline, and gamma-aminobutyric acid required for GBA communication are synthesized partly in specialized epithelial cells (enteroendocrine cells) of the gut. These cells are, in turn, influenced by the gut microflora [21,22]. The microbiota can directly synthesize neurotransmitters and influence the enzymes and transporters involved in neurotransmitter metabolism. Besides the neurotransmitters, there are other regulatory mechanisms in the communication that occur in the gut. While the vagus nerve strikes a direct connection, the gut environment is further sensed by the ENS. The signals sent by the ENS are transmitted to the brain which then controls the cognitive functions. The Gut-associated lymphoid tissue (GALT) with its immune system also assists in recognizing the signals given by the microbiota by releasing signaling molecules such as cytokines. These molecules cross blood–brain barrier along with the short-chain fatty acids (SCFAs) which actuate the release of hormones from the gut and are then carried to the brain.

3. GUT BARRIER - INTEGRITY AND DYSBIOSIS

The gut barrier or the mucosal barrier comprises a mucus layer and epithelium and is a link between the outside surroundings and the host internal milieu for the microbes. The gut microbiota such as *E. coli*, *Lactobacillus acidophilus*, *Clostridium perfringens* and several such species of the internal milieu and the host immune cells (external host environment) such as macrophages and neutrophils occupy different "niche" in the intestine. The latter are genetically tuned to attack invading alien organisms. As a result, the gut microbes can also be destroyed by host immune cells if they enter the external environment. It happens when the mucosal barrier is impaired. The leaky gut allows the microbes from the internal milieu to enter the mucosa with ease which are further attacked by the "resident" macrophages. This excessive immune response to gut microbes induces intestinal inflammation, the very cause of several gastrointestinal diseases [23].

The inflammation and dietary habits of an individual are intricately related to gut microbial imbalance and disease occurrence. Although majorly diet is known for maintaining beneficial microbe balance in the gut, the reverse cycle may also be true. Inflammation of the gut can also induce microbial imbalance or dysbiosis, leading to a pathological state. The diet rich in sugars and fats accelerates loss of intestinal membrane integrity leading to inflammation. In the reverse order dysbiosis and inflammation disrupt membrane integrity, which allows bacterial products to enter the bloodstream unfiltered, aggravating inflammation and causing diseases such as obesity and inflammatory bowel disease (IBD).

Several studies have indicated that a change in diet can bring rapid changes to gut microbial communities. For example, a high-fat diet leads to mucus production impairment and increases barrier-disrupting microbial population which increases intestinal permeability [24].

Clinically, the membrane integrity can be tested by the Dual Sugar Absorption Test. In this test, sugars such as lactulose and mannitol are administered orally, and urinary excretion is measured. The blood biomarkers, such as zonulin, fatty-acid-binding proteins, and lipopolysaccharide-binding proteins in the samples provide indirect evidence for impaired integrity [25].

To understand the physiological implications of a leaky gut, it is necessary to know the structure of the barrier system. The mucosal barrier comprises four functional components: mechanical, chemical, immune, and biological, that work in a coordinated manner to maintain functional stability between the outside and the inside world [Figure 2]. The epithelial cells, including goblet cells, paneth cells, and absorptive cells, provide the defense layer of the intestinal mucosa [26]. These

cells remain joined by junctional complexes, and include tight junctions (TJs), gap junctions, adherens junctions, and desmosomes that contribute to the mechanical barrier [27]. The intercellular TJ proteins are important for determining paracellular permeability, which is the movement of molecules through the intercellular spaces. The other route for microbes is the transcellular passage across epithelial cells. The paracellular route is significant for the transport of solutes or hydrophilic molecules that are smaller than 600 Da in size. This size limitation of proteinaceous molecules and other molecules, such as antigens, restricts their movement through the paracellular route [28]. However, when the intestinal integrity is compromised, pathogens, pro-inflammatory substances, and antigens enter the bloodstream. Such alteration in the environment might trigger a disease or an inflammation

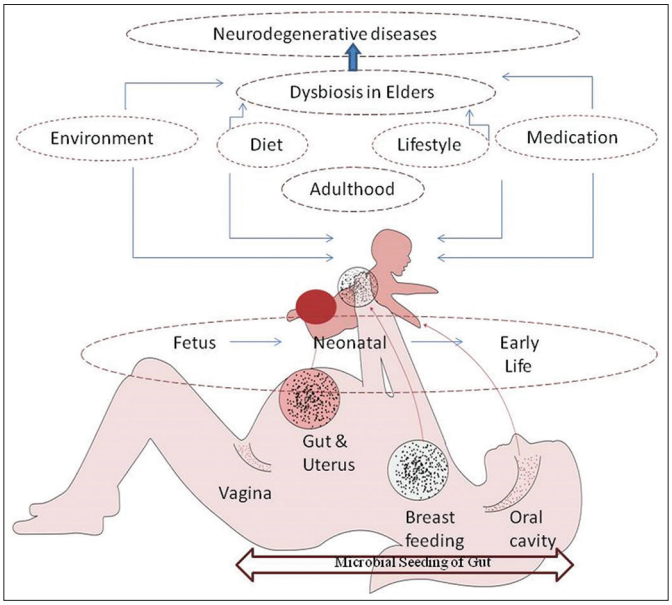

Figure 1: Microbial colonization pathways converging over lifespan.

[29-31]. The TJ proteins bind to the actomyosin cytoskeleton and are in charge of the increased permeability to electrolytes and small molecules upon contraction [32].

Mucus in the intestine performs a critical function in the chemical barrier. It brings about bacteriolysis, meant to inhibit the invasion of pathogenic bacteria. This barrier is created by the digestive acids released by GIT digestive enzymes, along with other molecules, namely, mucopolysaccharides, glycoproteins, and glycolipids. GALT and secretory immunoglobulin A along with other cell types such as macrophages, the natural killer cells, and intraepithelial lymphocytes, constitute the immune barrier. This is necessary for maintaining intestinal immunity homeostasis [33,34].

A biological barrier is a stable and interrelated microecosystem composed of resident intestinal flora. The obligate anaerobes comprise the dominant bacterial community in the gut with less oxygen availability. It represents a mutually dependent relationship that continues to evolve with the host [35]. As a "virtual organ," the gut microbiota is associated with metabolic processes, promotion of immune system maturation, and protection of neural function, and directly or indirectly also regulates both the physiological and pathological processes [36].

The intestinal integrity and intact epithelium are important for protecting the host against several diseases [10]. If this integrity is lost, the gut becomes leaky and permeable [Figure 3a and b]. In a leaky gut, the probability of leakage of bacterial components such as lipopolysaccharides (LPS) from the cell wall of Gram-negative bacteria is more, leading to a condition referred to as metabolic "endotoxemia" [37]. This increases the chances of inflammation, due to colonization and growth of pathogenic (pathobionts) microbes such as *Clostridioides difficile*, *Helicobacter pylori*, *Helicobacter hepaticus, E. coli*, and *Proteus mirabilis*. A similar leakage of commensal microbes contributes to allergy and autoimmune disorders [38]. These conditions of an imbalanced microbial population lead to diseases such as IBD, *Clostridium difficile* infection, celiac disease, obesity,

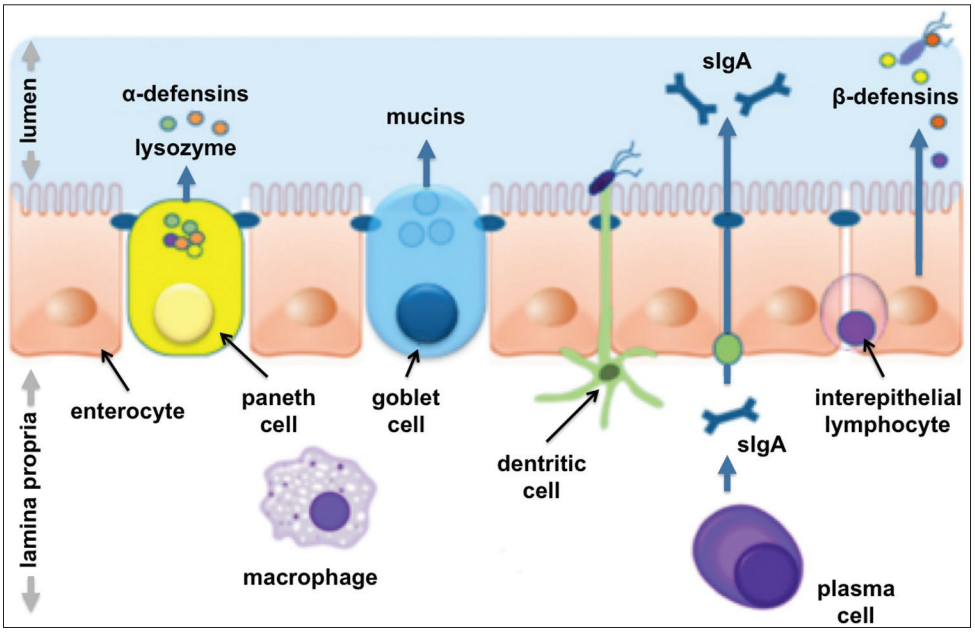

Figure 2: Key defense mechanisms of intestinal mucosa: Structural, immune, biochemical. Reference: Stephan C Bischoff DOI: 10.1186/s12876-014-0189-7© Bischoff *et al*.; license BioMed Central Ltd. 2014.

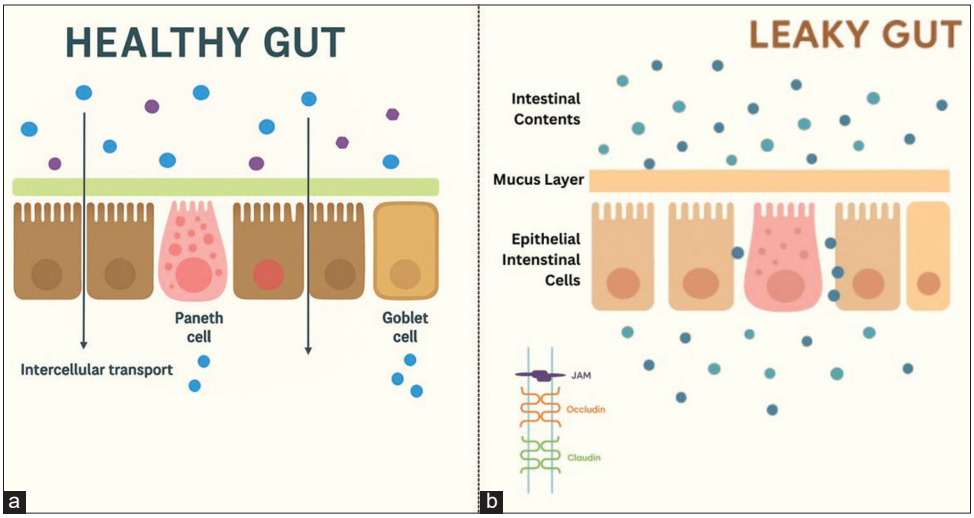

Figure 3: (a and b) Intact mucosal barrier in "a" and a state of dysbiosis due to loss of integrity of mucosal barrier in "b".

colorectal cancer, and autism spectrum disorder. Further, studies reveal that besides the internal factors that make gut leaky, factors such as increased consumption of sugar, protein, or food additives, alcohol, drugs, lack of hygiene, anxiety, and stress also bring about bacterial translocation [39]. The bacterial species commonly translocated under such circumstances include *E. coli*, *Klebsiella, Proteus*, *Enterobacter*, *Shigella*, *Salmonella,* and *Serratia.* The leaky gut is responsible for the entry of LPS in the bloodstream and triggering low-grade inflammation, which further manifests in obesity. Furthermore, fat metabolism that leads to the formation of new fats and their storage in the adipose tissue is disturbed [40]. The SCFAs related to fat oxidation are also altered. The diet, too, correlates with dysbiosis. This is evidenced by the fact that during dysbiosis, bacteria present in the gut extract energy from indigestible carbohydrates of the diet. This leads to increased calorie absorption and obesity.

4. ESTABLISHING MATERNAL-FETUS GUT MICROFLORA

Earlier studies suggested that fetuses (37–42 weeks) were sterile [41] and the bacterial colonization of the neonate's GIT occurred after the child transited through the birth canal [42-44]. A sterile fetal gut is indicated by the absence of microbiota in the placenta, amniotic fluid, or oral cavity and a sterile womb. Various evidence have been put forth to support the sterile womb hypothesis, such as 16S rRNA sequencing, culture, and microscopic studies, which do not detect any microbial populations *in utero* [45]. If any bacterial populations were detected in cord blood or placenta, they were the microbes that were frequent contaminants of clinical specimens. In a survey, around 62% of meconium samples collected from healthy and fit pregnant women showed the absence of microbes in aerobic and anaerobic cultures. Even the amniotic fluid and placental fluid did not show any bacterial population with the progression of the pregnancy. Hence, the "sterile womb hypothesis" was considered valid and appropriate for the available evidence [46]. However, this concept was later challenged by the presence of the low-level microbes that were reported from the placenta [47].

Recent studies have demonstrated that colonization and/or contact of the fetus and the maternal GIT starts *in utero*. In the uterus, the fetus occasionally ingests/swallows amniotic fluid, which contains a plethora of bacteria and bacterial products of the maternal origin, (e.g., glycoproteins, genetic material including both DNA and RNA), which are the source for the microbes to enter the gut of the developing fetus [48]. In the fetal gut, the microbes stay in a dormant form. Further, the fetus starts to swallow the amniotic fluid just around 10 weeks post-conception [49] when the esophagus is innervated. By 13 weeks [50], the fetus is immersed in about 100 mL of amniotic fluid. However, in the third trimester of pregnancy, around 700 and 1000 mL of amniotic fluid is swallowed per day by the human fetus [51]. That the womb is not sterile but has its own microbiome has been tested using various techniques. The studies on DNA profiling of bacteria in the first-pass meconium and amniotic fluid of pregnant women, and analyses of placental and umbilical cord blood indicate that the womb has its own microflora. Besides these, the mid-gestation amniocentesis provides recent evidence that bacterial exposure occurs before birth [49,52]. These studies are in conjunction with the studies of Park and Yun [48] based on the data obtained from vaginal discharge and amniotic fluid in pregnant women, and that of umbilical cord blood, gastric liquid, and meconium from neonates.

As the human fetus gut microbiome starts developing before birth, it is imperative that the gestation period has a significant role in maintaining maternal health and fetal development. The maternal factors include maternal oral microbiome, maternal diet and mode of delivery, breastfeeding, environmental exposures, gestational factors, and genetics, all of which influence the GIT of the newborn [53,54]. Even sterilization procedures, which lead to the mother being exposed to disinfection by-products (DBPs), may prevent the infant from obtaining the vaginal microflora, otherwise indispensable for infant health. The studies conducted on pregnant women reveal that antibiotics and several drugs may alter the fetus's microbiome [55].

The initial seeding and maturation of fetal/neonatal GIT is a partially controlled transfer of maternal blood through the placenta to the fetus through the paracellular pathway of the placental barrier. Evidence to this observation is provided by isolation of bacteria such as *Lactobacillus* sp. from umbilical cord blood [56], amniotic fluid, meconium, and placental and fetal membranes [Figure 4]. The medical practices adopted for childbirth also affect the microbial population.

The healthy pregnant women, when compared to non-pregnant women, experience higher intestinal permeability [57]. This increased permeability is due to a combination of physiological, metabolic, and anatomical changes that occur during pregnancy, which include uterine

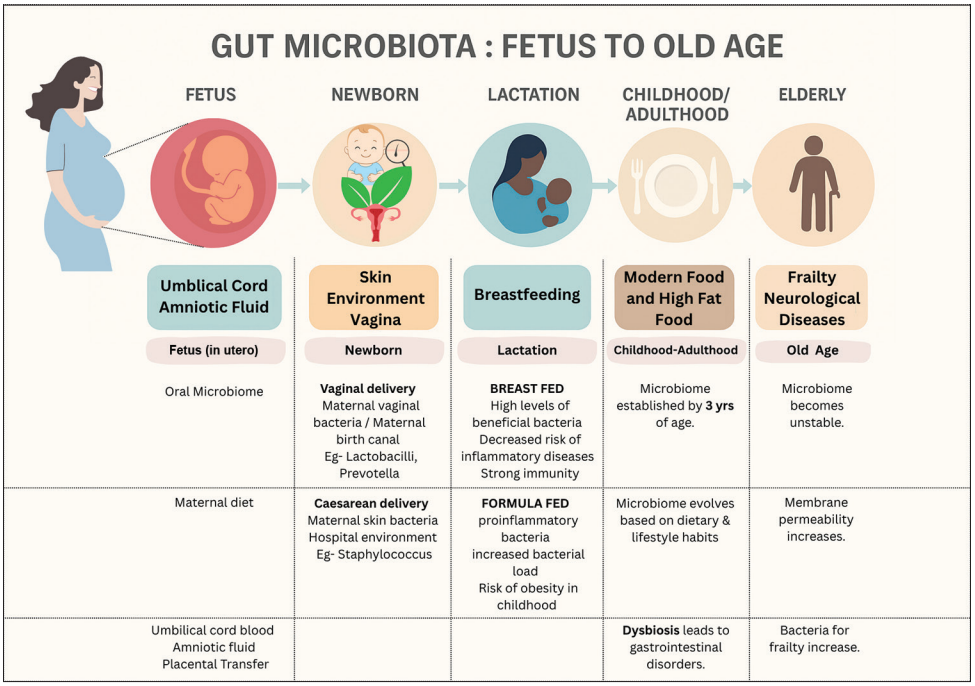

Figure 4: "Seeding" of microbiota and its evolution through life stages.

enlargement and changes in hormonal levels. During pregnancy, there is a significant rise in progesterone, estrogen, and thyroid levels. The alterations in gut microbiota accompany such changes. Though increased intestinal permeability is normal during pregnancy, an unusual rise in permeability may occur due to various pregnancy-related issues. Conditions such as recurrent pregnancy loss, gestational diabetes, overweight, and obesity are some such complications [58]. Moreover, gut inflammation is a significant factor that contributes to an elevated intestinal permeability.

4.1. Route Through the Vagina

The infant gut gets populated *in utero* before delivery, possibly through the consumption of amniotic fluid. Vaginal ascension occurs when microbes move upwards from the vagina into the endometrial uterine tissue, and is responsible for incorporating microbial diversity at the time of placental implantation. Bacteria are also present in uterine sources, for example, cord blood. *Lactobacilli* are present in abundance in the vagina, where they produce lactic acid, giving a pH <4.5. *Lactobacilli* rise during pregnancy due to estrogen levels. Estrogen increases vaginal mucosa thickening and deposition of glycogen for *Lactobacilli* [59]. Vaginal microbiota during pregnancy also contains members of Clostridiales, Bacteroidales, and Actinomycetales, which affect local, systemic, or remote organs. The pregnant women are vulnerable to bacterial vaginosis, which is characterized by the presence of *Ureaplasma urealyticum*, *Treponema pallidum*, *Trichomonas vaginalis*, *Mycoplasma hominis*, *Mycoplasma genitalium*, *Neisseria gonorrhoeae,* and *Chlamydia trachomatis.* As these changes are not seen in non-pregnant women, it is considered a signature of a pregnant woman [60].

5. "SEEDING" OF FETUS GUT MICROBIOTA – THE FIRST MICROBIAL INOCULUM

In a healthy non-pregnant woman, the gut microflora was observed to be rich and diverse in individuals as compared to the beta diversity, which was less diverse among different individuals (inter-individuals) [61]. Furthermore, during the gestation period, the reverse distribution of the gut microbiota was observed, i.e., the beta diversity index was significantly higher than the alpha diversity index. The gut microbiome of a pregnant woman shows similarity to that of a healthy non-pregnant woman during the first trimester. *Firmicutes*, especially those belonging to the order *Clostridiales,* are more abundant than *Bacteroidetes* during this initial phase of pregnancy [62,63]. This is followed by a shift in communities over the long gestation period [64] when significant changes occur during the second and third trimester [65]. Beginning of the second trimester, the levels of lactic-acid-producing bacteria, such as the *Lactobacillus* strains, along with the *Bifidobacteria* and *Proteobacteria,* significantly rise, and in contrast, the butyrate-producing bacteria decline sharply [66]. However, during the last trimester of pregnancy, stark similarities are observed in the gut microbiota with that of the dysbiotic profiles associated with metabolic syndrome as well as obesity [67]. Further, comparable patterns are also observed in metabolic conditions such as elevated blood glucose, reduced insulin sensitivity, increased body fat, and mild inflammation [68]. These modifications are advantageous for the growing fetus, as they support the growth and strengthen immunity by providing energy storage for the lactation process.

Infants born through vaginal delivery (VD) get bacteria resembling the maternal vaginal microbiome (e.g., *Lactobacilli* and *Prevotella*). Infants born through cesarean delivery (CD), show a microbiome, that resembles the maternal skin microbiome [69]. In general, the gut microbiota of CD infants exhibits decreased diversity and richness. There is a decreased population of *Bifidobacterium*, *Bacteroides*, and *Lactobacillus* [66,70] while a high colonization of opportunistic pathogens (*Enterococcus, Staphylococcus, Streptococcus, Enterobacter,* and *Clostridioides*) is observed [71]. Many species contain antibiotic resistance genes [72]. This difference is associated with the increased disease risks in CD infants, besides the slow rate of development as compared to VD. The microbiota difference subsequently diminishes between CD and VD infants in the first 6

months of birth. It is important to understand that following birth, maternal control continues in the form of lactation. The breast milk provides the best neonatal diet in terms of optimal nutrition and gut microbial community [73,74].

By the end of the second year, both microbiomes are at parity, dominated by *Lactobacilli* and *Prevotella.* Researches indicate that only a subset (if any) of the microbes of the newborn will permanently colonize the GIT when the child grows into an adult [75]. Differences also exist in the gut virome, with a higher diversity present in VD infants at 1 year of age [76]. Whether the gut differences between CD and VD are significant or not, and even if the differences are confined to a short period of infancy, the effect of disrupting the microbiome remains lifelong. Exemplifying it further, the disrupted gut microbiota manifests in adults as psychological vulnerability to stress exposures. This research as supported by the documentation indicates that the gut and the brain microbiome undergo parallel development starting from birth onwards till 36 months of growth period [77]. Due to dysbiosis created by caesarean section birth, Vaginal Microbiota Transfer, a high-profile medication may be resorted for reversing C-section-related microbiome disturbances in the newborns [78].

6. FINE TUNING GUT HEALTH

Research has indicated that the first microbial inoculum which the fetus acquires *in utero* evolves in diversity and complexity till about the age of 3–4 years, after which it becomes similar to that of the adult [79]. Following this, the microbial communities remain almost stabilized for most of adulthood, only to become unstable again during the elderly phase of life. This change may become progressive during the twilight years of life, manifesting in diseases such as Alzheimer's disease. Variables such as the dietary patterns, lifestyle changes, medication, and anxiety are the causative factors that accelerate the change of microbiota in the gut, especially during late adulthood to the elderly life phase [80,81]. In older adults, there is reduced diversity, and dominant species are replaced. Observed changes include a surge in the growth of facultative anaerobic bacteria while the beneficial organisms show a downward trend with simultaneous reduction in SCFAs [82]. These changes and alterations in the gut microbiota have been observed to be associated with physical frailty [83]. Unlike pregnancy, where an imbalance in microbial population is beneficial as it prepares the body for the growth of the fetus [84], the changes in the elderly are generally neurodegenerative. Likewise, certain other factors affecting health such as obesity, celiac disease, colitis, gastritis, and diabetes, may occur at any stage of life, and are due to lifestyle factors and lack of exercise. It is therefore important that one becomes mindful of the gut status and takes necessary preventive and precautionary measures. The simplest way to restore gut microbiota is to make better food choices and to include prebiotics and probiotics in the diet. The idea that we can either add bacteria to the gut or add food items to our diet to help bacteria grow on their own, is picking up across the globe [85].

7. "CONTROVERSIES AND FUTURE PERSPECTIVES"

Almost more than 100 years have passed, and still the controversy and the debate related to womb sterility lingers on [45]. The bacterial DNA present in the placenta and the birth of a preterm infant has been found to be related, as the studies suggest [44]. The contamination of the placenta by the bacteria or their DNA occurs during various stages. *Lactobacillus* contaminates during the delivery process, *Deinococcus geothermalis* contaminates the placenta during the collection of the sample, and during sample processing, *Paraburkholderia silvatlantica* and *Thellungiella halophila* affect the placenta. Further contaminations have also been observed to occur during sequencing or the library preparations being carried out at the facility. *Vibrio cholera* used in metagenomic sequencing has been shown to have an effect on the placenta. These studies substantiate that the microbiome maybe absent from the human placenta. At the same time placenta serves as the ground for the perinatal acquisition of the causative organism for neonatal sepsis, i.e., *Streptococcus agalactiae* [44].

Park *et al*. (2023) in a study refuted the concept of "sterile womb." A cohort of 178 neonates and 141 pregnant women was analyzed, and they demonstrated a relation between the GIT of the fetus and the sterile environment of the uterus. It was these parts that harbored the microbial communities. The newborns meconium had bacteria whose composition was diverse, and this supported the fact that during a healthy pregnancy, the colonization of microbes occurred. Further, the neonatal gastric liquid contained the microbiome, which was similar, yet not identical to the amniotic fluid of the mother. The swallowing of the amniotic fluid by the fetus and the recycling of the urine to the fluid contributed to this similarity.

In recent literature, the gut referred to as the "metabolic organ" has received increased attention due to its application in the prevention and cure of diseases. Through the gnotobiotic studies, it has become possible to understand the gut-related diseases and administer microbial therapies against immune and neural diseases. Furthermore, the intensive studies on analyses of gut microbiota in relation to the immune system, if carried out, would help to understand the interaction and co-development of the two systems. The malfunction or disruption in the coordination of the microbiome and immune system triggers an abnormal immune response, leading to severe inflammation and disease occurrence. Hence, it is equally important to detect such disruptive coordination during the critical period of infancy which might help in early detection of gut-related disorders. Due to the impact of the microbial communities present in the gut, the latter qualified as a "supra-organ." However, due to our present insight into this organ and the "microbial communities in gut" it is now better understood as a "microbial organ." It is important to know that these communities are not static but grow and develop as any other organ or system of the body. Equally essential is to maintain a non-leaky gut with an effective blood–brain barrier, which would restrict the beneficial resident bacteria from invading other parts of the body where they may get eliminated by the immune cell attack [86].

The personalized therapy, which can modulate the gut microbiome and deal with gut dysbiosis, holds great promise. The treatments, such as targeted microbial therapy comprising the use of next-generation probiotics and synthetic consortia, lead to the production of specific metabolites that have a healing effect [87]. Such insights into the gut microbiome-immune system axis and their correlation with other body organs have opened up several new therapeutic strategies that aim at providing relief to humankind.

8. CONCLUSION

As the gut holds the key to the well-being of individuals, it is important that the microbial ecosystem in this 'supra-organ' and the underlying metabolic processes are well understood. The gut microbiome as a science has just started to unravel the power of the trillions of microbes and the biological conversation inside our body. The high-throughput tools have enabled us to understand the process of symbiosis at the gut brain–barrier. The breakdown of this barrier leads to a role reversal of the microbiome. Once the modern tools are applied in deciphering

the several metabolic processes that occur in the gut microbiome, it will be a breakthrough in personalized or precision medicine. The gut microbiome may be improved by either or both generalized or specified (also known as personalized) dietary interventions. The generalized diet caters to the broad health benefits, which are less potent when compared to the personalized interventions, which are superior as they address targeted and individualized therapeutic outcomes.

The gut microbiome would then no longer be rated as a forgotten organ, and chronic disorders would find a corrective treatment through "a keystone consortium" for the gut. This is rated to be a better choice for chronic diseases as the consortium offers greater therapeutic utility than a single microbial strain. The consortia when engineered are anticipated to perform better as they can be manipulated to produce safer and higher yields of bioactive products. The interaction of gut microbiota with other physiological functions has started to surface and if investigated further would help to promote well-being in patients that suffer from lifestyle diseases such as obesity and mental health. Microbes of five body parts, namely gut, nasal, oral, skin, and vaginal environments, signify the ecological community of commensal, symbiotic, and pathogenic microorganisms that literally share our body space". It is not just enough to study disease occurrence and prevention/cure by analyzing the genome of the patient but the gut microbiome must also be analyzed. Since such therapy also involves one's lifestyle and environment, it is clear that microbial interfaces be discussed. Hence, the microbiota in the gut plays a significant role in the overall health of the individual, including the immune, endocrine, and metabolic systems of the body. If an individual is cautious with the gut microbial diversity, a lot of health issues can be kept at bay.

9. AUTHORS' CONTRIBUTIONS

All authors made substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work. All the authors are eligible to be author as per the International Committee of Medical Journal Editors (ICMJE) requirements/guidelines.

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11. CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

12. ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

13. DATA AVAILABILITY

All the data are available with the authors and shall be provided upon request.

14. PUBLISHER'S NOTE

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15. USE OF ARTIFICIAL INTELLIGENCE (AI)-ASSISTED TECHNOLOGY

The authors declare that they have not used artificial intelligence (AI)-tools for writing and editing of the manuscript, and no images were manipulated using AI.

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