

Gut microbiota in various childhood disorders: Implication and indications

Nermin Kamal Saeed, Mohammed Al-Beltagi, Adel Salah Bediwy, Yasser El-Sawaf, Osama Toema

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Nermin Kamal Saeed, Medical Microbiology Section, Department of Pathology, Salmaniya Medical Complex, Ministry of Health, Manama 12, Bahrain

Nermin Kamal Saeed, Microbiology Section, Department of Pathology, Irish Royal College of Surgeon, Busaiteen 15503, Bahrain

Mohammed Al-Beltagi, Department of Pediatrics, University Medical Center, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Mohammed Al-Beltagi, Osama Toema, Department of Pediatrics, Faculty of Medicine, Tanta University, Tanta 31511, Egypt

Adel Salah Bediwy, Department of Chest Disease, Faculty of Medicine, Tanta University, Tanta 31527, Egypt

Adel Salah Bediwy, Department of Pulmonology, University Medical Center, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, Manama 26671, Bahrain

Yasser El-Sawaf, Department of Tropical Medicine, Faculty of Medicine, Tanta University, Tanta 31527, Egypt

Yasser El-Sawaf, Department of Gastroenterology, University Medical Center, Arabian Gulf University, Dr. Sulaiman Al-Habib Medical Group, Manama 26671, Bahrain

Corresponding author: Mohammed Al-Beltagi, MBChB, MD, MSc, PhD, Chairman, Professor, Department of Pediatrics, University Medical Center, Arabian Gulf University, Dr. Sulaiman Al Habib Medical Group, King Abdulaziz Avenu, Block 328, BLd 61, Manama 26671, Bahrain. mbelrem@hotmail.com

Abstract

Gut microbiota has a significant role in gut development, maturation, and immune system differentiation. It exerts considerable effects on the child's physical and mental development. The gut microbiota composition and structure depend on many host and microbial factors. The host factors include age, genetic pool, general health, dietary factors, medication use, the intestine's pH, peristalsis, and transit time, mucus secretions, mucous immunoglobulin, and tissue oxidation-reduction potentials. The microbial factors include nutrient availability, bacterial cooperation or antagonism, and bacterial adhesion. Each part of the gut has its microbiota due to its specific characteristics. The gut microbiota interacts with different body parts, affecting the pathogenesis of many local and systemic

diseases. Dysbiosis is a common finding in many childhood disorders such as autism, failure to thrive, nutritional disorders, coeliac disease, Necrotizing Enterocolitis, helicobacter pylori infection, functional gastrointestinal disorders of childhood, inflammatory bowel diseases, and many other gastrointestinal disorders. Dysbiosis is also observed in allergic conditions like atopic dermatitis, allergic rhinitis, and asthma. Dysbiosis can also impact the development and the progression of immune disorders and cardiac disorders, including heart failure. Probiotic supplements could provide some help in managing these disorders. However, we are still in need of more studies. In this narrative review, we will shed some light on the role of microbiota in the development and management of common childhood disorders.

Key Words: Gut microbiota; Dysbiosis; Children; Gastrointestinal disorders; Immune disorders; Allergic disorders; Cardiac disorders

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Core Tip: Gut microbiota has an intimate relationship with the various health conditions of the human body. It interacts with different body parts, affecting the pathogenesis of many local and systemic diseases. Gut dysbiosis is observed in many childhood disorders, inside and outside the gastrointestinal tract. Probiotic supplements could provide some help in managing these disorders. However, we are still in need of more studies. In this narrative review, we will shed some light on the role of microbiota in the development and management of common childhood disorders.

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INTRODUCTION

The human has an intimate symbiotic relationship with microbes. The human body harbors about 10-100 trillion microbial cells. Most of these microbes are present mainly in the gut as it provides a warm, stable, and eutrophic environment. There is significant variability in microbial composition at different body sites, with a vast difference between health and disease. Although the term microbiota is sometimes interchangeably used with the term microbiome, microbiota refers to the organisms living in a specific environment, and microbiome refers to the microorganisms and their genome in a particular environment[1]. The microbial microbiome has a set of genes of approximately 3.3 million active genes compared to 22000 human genes. The gut microbiota is the organisms that inhabit the gut, forming about 60% of the dry faces; 99% are anaerobic bacteria. Though bacteria form the main bulk of the microbiome, viruses, archaea, and eukaryotes are present in fewer numbers, but we should not ignore their presence[2].

Microbial colonization with more than 1000 species plays an essential role in gut development and maturation. There is evidence that gut colonization started in utero, and bacteria were detected from the amniotic fluid meconium and placenta in healthy term babies[3]. After delivery, the microbiota of the vaginally delivered neonates resembles those of their mother's vagina, while those delivered by cesarean section resemble those of the mother's skin. Then the infant microbiota changes gradually with every change in the infant diet from the simple neonatal microbiota with a predominance of facultative anaerobic bacteria, such as *Enterobacteria*, *Enterococci*, and *Streptococci*, to the more complex adult-type by the first few years of life with greater diversity and ability to biosynthesize vitamins and digest polysaccharides[4]. However, the child's microbiota continues to develop throughout childhood and adolescence. Despite being like the adult regarding the number of the detected species, the gut microbiota of children and adolescents may differ in genera's relative abundances[5]. Their gut microbiota has more abundances of *Bifidobacterium spp.*, *Faecalibacterium spp.*, and members of the *Lachnospiraceae* than the adults' gut microbiota with more abundances of *Bacteroides spp.* The microbiome also is different in children with more genes involved in amino acid degradation, vitamin synthesis, triggering mucosal inflammation, and oxidative phosphorylation compared with that observed in the adults with more genes associated with inflammation and obesity. So, as expected, the gut microbiota and microbiome go through a continuous and persistent development throughout life[6].

FUNCTION OF GUT MICROBIOTA

Gut microbiota exerts some essential functions in the human body's immunological, metabolic, structural, and neurological landscapes. Gut microbiota also significantly influences an individual's physical and mental health[7]. Gut microbiota significantly impacts normal and physiological gut development and helps gut mucosa maturation and differentiation and its immune system. It restricts the growth of the pathogenic and the potential pathogenic microbes, competes with them, and inhibits their ability to invade and implement the ecosystem. Some microbiota strains can secrete bacteriocins antimicrobial substances to inhibit other bacterial proliferation.

Other microbiota strains can ferment and digest nondigestible carbohydrates, fibers, and endogenous intestinal mucus, producing gases and short-chain fatty acids (SCFAs) such as acetate (the most abundant), propionate, and butyrate. These SCFAs can modulate the various activities in the gastrointestinal tract, including cell proliferation and differentiation, water and electrolytes absorption, hormonal secretion, and immune system activation[8,9]. SCFAs can serve as a food substrate for colonocytes (butyrate) and regulate leukocyte function and immune system activation by producing different eicosanoids, cytokines (IL-2, IL-6, IL-10, and TNF- α), and chemokines production with inducing balance among pro-inflammatory and anti-inflammatory mechanisms. SCFAs may also affect leukocyte chemotaxis, affecting their ability to migrate to the focus of infection or inflammation to destroy the target microbes[10].

Lack of SCFA is one of the causes of leaky gut and local gut inflammation that enhance microbial invasion. Butyrate can also induce colon cancer cells apoptosis and activate intestinal gluconeogenesis to enhance energy balance. It is crucial for glucose homeostasis by regulating hepatic gluconeogenesis and stimulating satiety signaling. The metabolic effects of SCFAs are not limited to the intestine but have extra-intestinal effects. Acetate SCFAs play a crucial role in regulating cholesterol metabolism and lipogenesis[11]. Microbiota also has an essential metabolic function in the biosynthesis of vitamins (vitamin K, biotin, folic acid, vitamin B12, and pantothenic acid) and amino acids from urea or ammonia. It also plays a role in xenobiotics and drug metabolism[12].

Gut microbiota can affect the host's energy balance through different mechanisms. It extracts energy from nondigestible dietary components and impacts gut transit, energy intake, and energy expenditure [13]. It also can modify the available pool of bile acids, affecting their composition and abundance. Gut microbiota-derived enzymes can metabolize the bile acids produced by the liver, a critically crucial process to maintain a healthy gut microbiota, enhance lipid and carbohydrate metabolism, increase insulin sensitivity, and enhance innate immunity[14]. The gut microbiota connects with the brain through several various mechanisms. These mechanisms include neurotransmitters production or modulation of their catabolism, vagus nerve signaling, and the hypothalamus-pituitary axis activation [15]. Gut microbiota produces hundreds of neurochemical substances used by the brain to regulate its basic physiological processes and mental functions such as learning, memory, and mood[16].

FACTORS AFFECTING THE CHILDREN'S GUT MICROBIOTA

The type and the quantities of the gut microbiota show wide individual variability. Many host and bacterial-related factors affect bacterial colonization in the different parts of the human gut. The host factors include the host's age, genetic pool, general health, dietary factors, using medication, pH, peristalsis, and the transit time of the part of the intestine, mucus secretions containing immunoglobulin, and the tissue oxidation-reduction potentials. The microbial factors include nutrient availability, bacterial cooperation or antagonism, and bacterial adhesion[17,18]. Each part of the gut has its microbiota due to its specific characteristics. Table 1 shows the microbiota in the different parts of the gut.

The ability of the host genetics pool to modify the gut microbiome structure is still controversial. There is a strong association between the Lactase gene and the relative abundance of *Bifidobacterium*. However, this association could be related to lactose consumption[19]. The vitamin D receptor gene is associated with some variation in gut microbiota[20]. Other studies proved the association of some host genetic variations with the abundance of certain microbiota species. However, the origin of association is still uncertain[21]. The host diet is crucial in developing gut microbiota as carbohydrate fermentation is one of its core functions. The microbiota of the small intestine adapts quickly to varying nutrient availability in the lumen and can rapidly metabolize the simple carbohydrates. On the other hand, the colon microbiota can degrade complex carbohydrates. A high-fat diet stimulates the proliferation of *Clostridium* and suppresses the proliferation of *Bifidobacterium* and *Bacteroides*[22]. Dietary modification produces rapid alteration of the colonic microbiota within two days and long-term changes[23].

The type of delivery can early-life microbiome. However, this effect may differ upon intrapartum antibiotic exposure. The gut microbiota of vaginally delivered infants shows enrichment of *Bifidobacterium spp.* and reduction of *Enterococcus* and *Klebsiella spp.* Over the first year of life, the gut microbiota in infants born with caesarean section appears less stable with a predominance of pathogenic bacteria such as *Klebsiella* and *Enterococcus* and delayed acquisition of the beneficial *Bifidobacterium*[24]. Breast or

Table 1 The microbiota in the different parts of the gut

Site	pH	Predominant microbiota	Bacterial load (CFU/gram content)	Other factors
Mouth	6.5-7	Bacteria (esp <i>Fusobacterium nucleatum</i>), fungi, viruses and protozoa	700 species	Ideal warm environment
Stomach	Strongly acidic	<i>Lactobacilli</i> , <i>streptococci</i> , <i>Lactobacillus</i> , <i>Peptostreptococcus</i> , <i>Helicobacter pylori</i> , and yeasts	Low (10^2)	Gastric acidity, Acid suppressive therapy, <i>H. pylori</i> colonization, the reflux of bile, mucus thickness and gastric peristalsis
Duodenum	4-5	<i>Lactobacilli</i> and <i>Streptococci</i>	More than (10^2 - 10^4)	Age, diet, antibiotic, and proton pump inhibitor use
Jejunum-ileum	6-7.4	<i>Firmicutes</i> and <i>Proteobacteria</i>	More than duodenum (10^6 - 10^8)	Nutrient rich environment faster transit time, bile acids, and antimicrobial peptide exposure
Colon	Left colon 6.1-7.5; Cecum 5.7; Rectum 6.7	<i>Bacteroidetes</i> (especially the genera <i>Bacteroides</i> and <i>Prevotella</i>) and <i>Firmicutes</i> (especially members of the genus <i>Clostridium</i>). Methanogenic archaea and fungi; Cecum: Aerobic bacteria; Rectum: <i>Bacteroides</i> and <i>Prevotella</i> .	10^{10} - 10^{12}	High diversity and density, no digestive secretions, nutrient-poor environment, & slow transit time (30 h)

H. pylori: *Helicobacter pylori*.

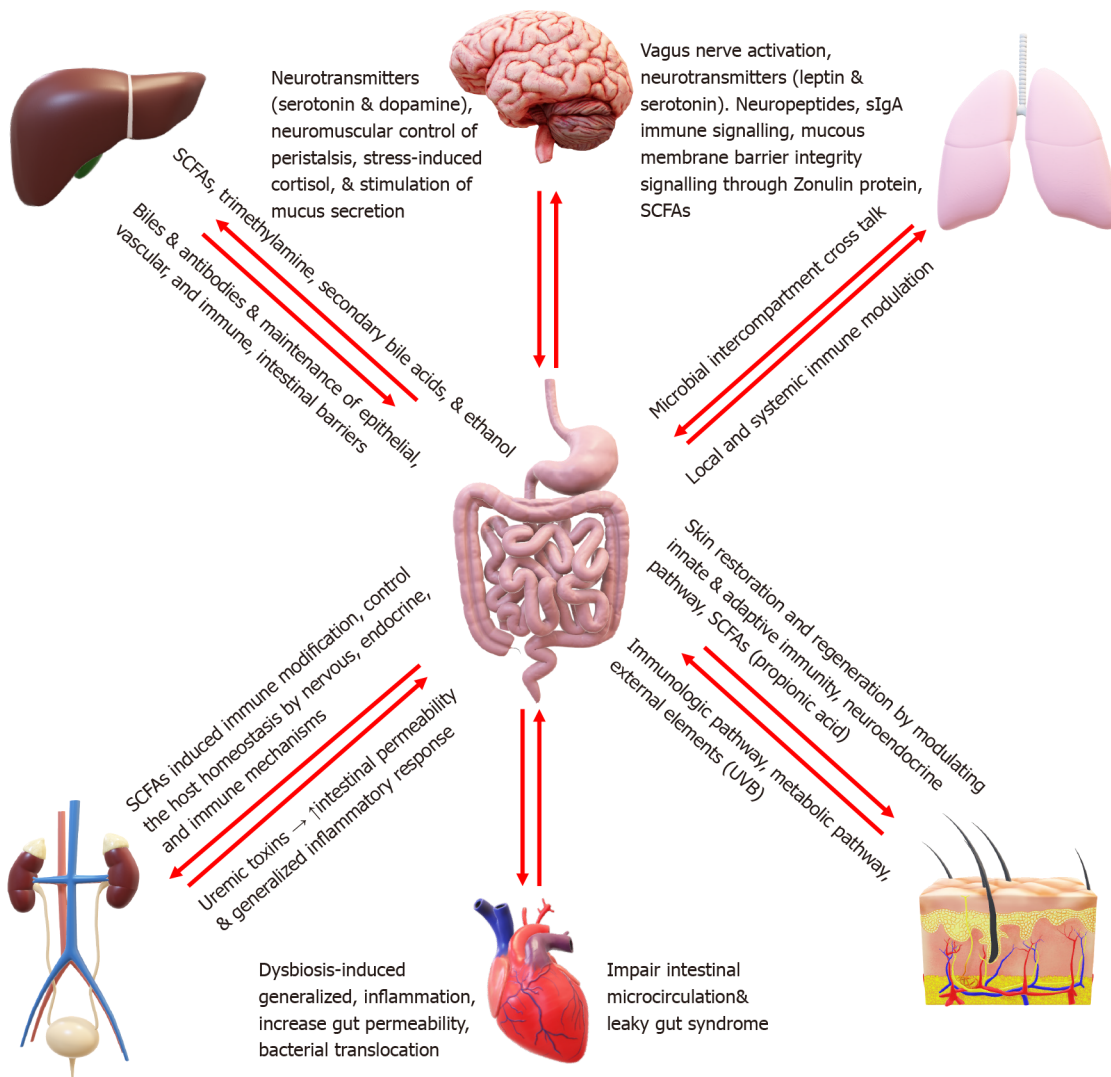
bottle feeding also significantly impacts the gut microbiota. Exclusively breastfed infants have lower microbial diversity with a predominance of infant-type *Bifidobacteria* than formula-fed babies whose gut microbiota is more diverse and like older children. The predominance of infant-type *Bifidobacteria* significantly impacts the immune system's maturation and development, which may help decrease the incidence of childhood infections[25].

The gut microbiota develops throughout human life in predictable patterns, with fast change from the neonatal pattern to the age of three, reaching the adult pattern. Then the microbiota goes into a stable phase until middle age, and then it goes into accelerated changes in late adulthood. These changes could be related to aging itself, underlying diseases, and the use of medications. At the same time, changes in the microbiota pattern can predict decreased longevity[26]. The use of the proton pump inhibitors is associated with decreased bacterial richness and predominance of an unhealthy gut microbiome which predisposes to *Clostridium difficile* enteric infections[27]. Antibiotics negatively impact the gut microbiota by reducing the species diversity, altering the metabolic activity, and favoring the predominance of antibiotic-resistant microbial strains, which sequentially can cause antibiotic-associated diarrhea and recurrent *Clostridium difficile* infections[28].

Microbial cooperation is a characteristic feature of microbial communities. An example of bacterial cooperation appears clearly in *Bacteroidales*, the predominant Gram-negative bacteria in the human gut. *Bacteroides ovatus* and *Bacteroides vulgatus* showed a mutual relation where *Bacteroides ovatus* can digest the dietary complex polysaccharide inulin producing energy and food source for other *Bacteroides*, including *Bacteroides vulgatus*. In return, *Bacteroides vulgatus* benefits *Bacteroides ovatus* by detoxifying inhibitory substances and the secretion of a depleted or growth-promoting factor. This bacterial cooperation is vital to stabilize the gut ecosystem[29]. Bacterial antagonism is common in microbial communities and contributes to specific bacterial strains' different compositions and relative abundance. It also helps for the long-term stability of the microbial community. This antagonism can occur by interference competition with the secretion of specific molecules such as antibacterial peptides and proteins that inhibit other strains. These antimicrobial toxins perform a significant role in microbiota-mediated colonization resistance by inhibiting the invasive pathogens[30]. Bacterial adhesion to gut epithelial surfaces affects their retention time and, therefore, considerably impacts interactions between the microbiota and their hosts. This adhesion ability of some bacteria could help their transient colonization in the gut and help to boost their immunomodulatory effects and enhance the gut barrier and metabolic functions[31].

GUT-MICROBIOTA AXES

The intestinal microbiota is considered an organ of the human body, with its features making it crucial in various body functioning. There is a mutual bidirectional relation of the gut, microbiota, and the other body systems, forming different systemic axes, *e.g.*, Brain-gut-microbiota axis, liver- gut-microbiota axis, skin- gut-microbiota axis, kidney- gut-microbiota axis, lung- gut-microbiota axis (Figure 1).



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Figure 1 The different gut-microbiota-axes (brain-gut-microbiota axis, liver- gut-microbiota axis, skin- gut-microbiota axis, kidney- gut-microbiota axis, lung- gut-microbiota axis).

BRAIN-GUT-MICROBIOTA AXIS

The brain and the gut interact together through the central and the enteric nervous system. The brain interacts with the gut through several mechanisms, including neurocrine and endocrine pathways, which may be involved in gut microbiota-to-brain signaling, and the brain can, in turn, alter gut microbiota composition. The brain controls the gut and gut microbiota through neurotransmitters such as serotonin and dopamine, neuromuscular control of peristalsis, stress-induced cortisol, and stimulation of mucus secretion[32]. On the other hand, the gut affects the brain through vagus nerve activation, neuropeptides, and neurotransmitters such as leptin and serotonin, immune signaling through secretory IgA, mucous membrane barrier integrity signaling through Zonulin protein, and SCFAs such as butyrate[15,33]. Alternatively, the microbiota affects the brain through different mechanisms. Some strains of *Lactobacillus* and *Bifidobacterium* can produce gamma-aminobutyric acid (GABA), which is the dominant brain inhibitory neurotransmitter. Other bacterial species such as *Enterococcus* and *Escherichia* and some candida strains can produce serotonin. Some bacillus species can produce dopamine neurotransmitters. Bacteria can also affect the brain by making SCFAs (such as butyric acid, propionic acid, and acetic acid), stimulating the sympathetic nervous system, and inducing mucosal serotonin release sequentially, impacting the memory and learning process in the brain[34].

LIVER-GUT-MICROBIOTA AXIS

The liver-gut-microbiota axis is a bidirectional relationship between the liver and the gut and its

microbiota on the other side. The gut-derived products are transported directly to the liver through the portal veins, and the liver manufactures the bile and antibodies to be transported back to the intestine. The gut microbiota is essential for preserving the immune homeostasis of the liver-gut-microbiota axis. Microbe-derived metabolites, such as SCFAs, trimethylamine, secondary bile acids, and ethanol, may play a role in non-alcoholic fatty liver disease pathogenesis. On the other hand, liver cirrhosis induces intense changes in gut microbiota and impairment of the intestinal epithelial, vascular, and immune barriers[35]. A change in gut microbiota structure can activate the mucosal immune response triggering homeostasis imbalance. This imbalance results in bacterial transport and immune cells migrating to the liver, inducing inflammation-mediated liver injury and tumor progression[36,37].

HEART-GUT-MICROBIOTA AXIS

The heart-gut axis is relatively newly described based on intestinal microbiota's ability to affect the cardiovascular status and vice versa. Gut dysbiosis is linked to the state of generalized inflammation associated with increased risk of obesity and type II diabetes mellitus, which are important cardiovascular risk factors, especially for atherosclerosis and heart failure. At the same time, the diet that can cause dysbiosis, *e.g.*, a high fatty diet, can also cause metabolic syndrome. On the other side, Most cardiovascular disease (CVD) risk factors, such as aging, dietary patterns, obesity, and a sedentary lifestyle, can induce gut dysbiosis. Dysbiosis can also increase gut permeability, leaky gut syndrome, and bacterial translocation and are considered risk factors for CVD. Meanwhile, congestive heart failure will impair intestinal microcirculation aggravating the leaky gut syndrome and causing more bacterial translocation worsening the heart failure with a vicious cycle[38-40].

KIDNEY-GUT-MICROBIOTA AXIS

The gut microbiota has critical roles in various diseases involving hypertension and chronic kidney disease. The gut microbiota connects with the nervous, endocrine, and immune systems to control the host homeostasis, involving blood pressure and renal functions. The gut-kidney axis is conducted through metabolism-dependent mechanisms and immune pathways[41]. SCFAs produced by commensal gut microbiota can affect the kidneys through a wide range of mechanisms, including immune system modification and interactions with the renal cognate receptors and transporters[42]. On the other side, kidney injury causes uremic toxins accumulation in the intestine with increased intestinal permeability and generalized inflammatory response[43]. Uraemia increases bacterial translocation and impairs immunity by decreasing T and B cell responses from vaccination and decreasing the memory of T and B cells. Increased nitrogen waste products in uremia promote the overgrowth of proteolytic bacteria[44].

LUNG-GUT-MICROBIOTA AXIS

Despite the clear anatomical distinction between the gut and the lung, recent evidence showed that the gut and lung microbiota affect each other, significantly impacting respiratory diseases[45]. The lung microbiome is much lower than the gut microbiota. Its composition depends on the oropharynx and upper respiratory tract microbial colonization through salivary micro-inhalations, the host abilities for microbial elimination, primarily through cough and mucociliary clearance, the interactions with the host immune system, and on local conditions that control the microbial proliferation, such as oxygen concentration and local pH[46]. The lung microbiota composition is also strongly correlated with the gut microbiota composition. The gut microbiota enriches the lung bacteria, impacting the gut microbiota composition. For example, inhalation of gastroesophageal content (through gastroesophageal reflux) and sputum swallowing may explain this inter-organ connection. The lung-gut-microbiota axis may also involve indirect communications through the host immune modulation either by gut microbiota's local or systemic immune impact, especially on the pulmonary immune system[47].

SKIN-GUT-MICROBIOTA AXIS

Skin and gut play crucial immune and neuro-endocrine roles and are distinctively related in function. The gut microbiota affects the skin microbiome through the skin-gut-microbiota axis. SCFAs produced from fiber fermentation by gut microbiota have a significant role in skin microbiota composition and immune defense mechanisms[44]. Propionic acid has a powerful antimicrobial effect against the community-acquired methicillin-resistant *Staphylococcus aureus*[49]. Gut microbiota also helps skin

restoration and regeneration by modulating innate and adaptive immunity. It enhances the skin barrier through modulation of T cell differentiation in response to different immune stimuli[50]. Several environmental factors, *e.g.*, diet and psychological stress, can impact the gut microbiome, directly or indirectly influencing skin health.

GUT MICROBIOTA IN COMMON PEDIATRIC DISORDERS

Table 2 summarizes the disease-associated dysbiosis and the proposed probiotics.

GUT MICROBIOTA AND CHILD NEURODEVELOPMENT

Gut microbiota exerts a considerable effect on the child's physical and mental development. The human brain has a rapid growth rate throughout the perinatal period, matching the remarkable maternal and infant microbiota changes[51]. The microbiota plays an essential role during brain development through its effects on gamma-aminobutyric acid and serotonin synthesis from tryptophan and altered neurotransmitters such as noradrenaline and dopamine. Serotonin is crucial to brain development. Decreased brain serotonin impair synaptogenesis and the brain wiring, causing long-term neurodevelopmental impairment[52]. About 95% of the body's serotonin is formed by the gut microbiota, affecting mood and gastrointestinal activity. However, scientists found that serotonin cannot cross the blood-brain barrier. So, it works mainly on the peripheral enteric nervous system and works as a hormone affecting different tissues, including those regulating metabolic homeostasis[53]. However, the beneficial role of probiotics in alleviating the manifestation of many psychiatric disorders such as depression and anxiety could be related to their ability to secrete serotonin, a significant player in many psychiatric disorders[54]. Meanwhile, animal studies showed that probiotic use might cause rising plasma tryptophan levels, decreased serotonin concentrations in the frontal cortex, and decreased cortical dopamine metabolites, thus improving depressive symptoms[55].

SCFAs, a product from the fermenting effects of the colonic bacteria, regulate microglial homeostasis. The effects of SCFAs are markedly observed during the early phases of brain development during the early postnatal stage, while brain plasticity is still preserved[56]. Two interesting studies showed that gut microbiota is crucial to maintain healthy microglia functions, vital to preventing neurodevelopmental and neurodegenerative disorders[57,58]. Tamana *et al*[59] showed that boys who have a higher *Bacteroidetes* ratio in the gut microbiota at one year have higher cognitive functions and advanced linguistic skills after one year of follow-up. They also observed that girls have cognitive and linguistic scores than boys at the same age. They also noted a higher *Bacteroidetes* ratio in girls than boys. They related this increase in cognitive function due to the sphingolipid production by *Bacteroidetes*, which is an essential substrate for brain structures and functions. Factors that deplete *Bacteroidetes*, *e.g.*, caesarean section or flourish *Bacteroidetes* such as normal vaginal delivery, breastfeeding, high-fiber diet, exposure to pets, and outdoor nature with green spaces can negatively or positively impact child cognitive functions[60].

Investigating the underlying mechanisms of neural development and neuropsychiatric disorders proved that the intestinal microbiota could affect brain physiology and behavior through the humoral and neural pathways of gut-brain communication, suggesting that the gut microbiota has a vital role in many neuropsychiatric disorders[61]. Autism is a multifactorial disease in which the gut microbiota plays an important role. The gut microbiota in children with autism showed plenty of *Bacteroidetes* and a lesser amount of *Firmicutes* than controls with characteristic mucosal microbiota signatures. This dysbiosis observed in children with autism correlates with cytokine quantities and tryptophan homeostasis. However, we do not know whether the observed dysbiosis is a cause or a result of the associated behavior problem observed in children with autism[62,63]. The effect of the gut microbiota is not limited to the child's gut but is also related to the maternal gut microbiota. A study by Li *et al*[64] found significant differences in the gut microbiota composition between the mothers and children with autism spectrum disorder (ASD) compared to healthy children and their mothers. They found that mothers of children with ASD had more *Alphaproteobacteria*, *Proteobacteria*, *Acinetobacter*, and *Moraxellaceae* than mothers of healthy children. Children with late-onset (regressive) autism have more colony numbers of fecal clostridial species and non-spore-forming anaerobes and microaerophilic bacteria, which are absent in the typically developed children, which could be related to the frequent use of antibiotics, disrupting the microbiota with more colonization by these types of autism-promoting microbiota species[65]. According to this hypothesis, the use of minimally absorbed oral vancomycin can induce temporary improvement in autistic symptoms[66]. However, a meta-analysis that included 28 studies done on children with autism by Bezawada *et al*[67] showed the inconsistency of the data due to heterogeneity of the included populations and the used methods. They suggested that despite several reasons to consider the role of gut microbiota and their product in the pathogenesis of autism, we need more studies to understand better and confirm their effects. The developing hypothesis of a microbiota-gut-brain axis proposes that gut microbiota modulation may be an amenable strategy to developing a

Table 2 The diseases-associated dysbiosis and the proposed probiotics

The disease	Encountered dysbiosis	The proposed probiotics
Autism[57,58]	Mother have abundance of <i>Alphaproteobacteria</i> , <i>Proteobacteria</i> , <i>Acinetobacter</i> , & <i>Moraxellaceae</i> . Children have more clostridial species, non-spore-forming anaerobes, and microaerophilic bacteria	No suggested type yet
Malnutrition[60]	Less Bifidobacteria. More pathogenic microbes (<i>Escherichia coli</i> , <i>Fusobacterium mortiferum</i> , & <i>Streptococcus</i> spp.)	The lack of strong evidence for specific types of probiotics
Obesity[75-78]	Less <i>bifidobacteria</i> . More <i>Bacteroides</i> & <i>Staphylococcus</i> spp.	Bifidobacterium lactis and Lactobacillus GG
Infant colic[85-87]	More abundance of <i>Proteobacteria</i> . Less abundance of the genera <i>Lactobacillus</i> & <i>Bifidobacterium</i> . Reduced gut bacterial diversity	Lactobacillus reuteri DSM17938 in breastfeeding infants
Functional abdominal pain[90,91]	More <i>Prevotella</i> , <i>Lactobacillus</i> , <i>Veillonella</i> , & <i>Parasporo</i> bacterium. Less <i>Verrucomicrobium</i> & <i>Bifidobacterium</i>	Sporobacter & Subdoligranulum
Functional constipation[94,95]	More <i>Prevotella</i> . More butyrate-producing bacteria as <i>Roseburia</i> , <i>Coprococcus</i> , & <i>Faecalibacterium</i>	Still investigational
Necrotizing enterocolitis[98,99]	More <i>Citrobacter koseri</i> and/or <i>Klebsiella pneumoniae</i> . Reduced diversity. Less <i>Lactobacillus</i> abundance	<i>Bifidobacteria</i> and <i>Lactobacillus</i>
<i>Helicobacter pylori</i> infection[102,106,107]	<i>Prevotella</i> , <i>Clostridium</i> , <i>Proteobacteria</i> , and <i>Firmicutes</i> . Less <i>Bacteroides</i>	<i>Saccharomyces boulardii</i> , <i>L. acidophilus</i> , <i>L. casei</i> DN-114001, <i>L. gasseri</i> , and <i>Bifidobacterium infantis</i> 2036 and <i>Lactobacillus reuteri</i> Gastrus
Celiac disease[109, 114-116]	Reduced Gram-positive/Gram-negative bacteria ratio. Less <i>Bifidobacterium</i> , <i>Clostridium histolyticum</i> , <i>Clostridium. lituseburensis</i> and <i>Faecalibacterium prausnitzii</i> . More <i>Bacteroides-Prevotella</i> group. Less IgA coating the <i>Bacteroides-Prevotella</i> group	<i>Lactobacillus rhamnosus</i> , <i>Bifidobacteria breve</i> & <i>Longum</i> , and <i>Lactobacilli</i> strains (<i>L. ruminis</i> , <i>L. Johndoni</i> , <i>L. amylovorus</i> , <i>L. salivaris</i>)
Inflammatory bowel diseases[122,126-128]	Less abundance of the healthy commensal (such as <i>Clostridium IXa</i> and <i>IV</i> groups, <i>Bacteroides</i> , <i>Bifidobacteria</i>). More abundance of the pathogenic bacteria as sulphate-reducing <i>Escherichia coli</i>	Still controversial. <i>Saccharomyces boulardii</i> . <i>Escherichia coli</i> Nissle1917, <i>Bifidobacterium breve</i> , <i>Bifidobacterium bifidum</i> , <i>Lactobacillus acidophilus</i>
Cystic fibrosis[135-137]	Aberrant colonization of gut and respiratory microbiota due to altered intestinal & airway microenvironment	<i>Lactobacillus rhamnosus</i> GG & <i>Lactobacillus reuteri</i>
Allergic rhinitis[140, 142-144]	Decrease gut bacterial diversity	<i>Lactobacillus paracasei</i> . <i>Bifidobacteria</i> mixture
Bronchial asthma[147]	Relative abundance of the bacterial genera <i>Rothia</i> , <i>Veillonella</i> , <i>Lachnospira</i> , & <i>Faecalibacterium</i> . Low total & gut microbial diversity	Still controversial
Atopic dermatitis[154-157]	Reduced microbial diversity. More abundance of pathogenic <i>Staphylococcus aureus</i> and <i>Malassezia</i> . Presence of <i>Clostridioides difficile</i> . More <i>Bifidobacteria</i> abundance. Lower <i>lactobacilli</i> abundance	Topical <i>Roseomonas mucosa</i>
Psoriasis[160,161,163, 164]	More bacterial diversity & heterogeneity. More <i>Staphylococcus aureus</i> . Less <i>Staphylococcus epidermidis</i> & <i>Propionibacterium acnes</i> . Reduced microbiota stability. Variable topographic dysbiosis	Still controversial. Oral <i>Lactobacillus</i> , one sachet thrice daily with biotin
Systemic lupus erythematosus[166, 168]	Less microbiota abundance and diversity	Animal studies showed <i>Lactobacillus fermentum</i> CECT5716 (LC40)
Juvenile idiopathic arthritis[172,174]	Less <i>Faecalibacterium prausnitzii</i> abundance. More <i>Bifidobacterium</i> abundance, mostly <i>B. adolescentis</i>	Not conclusive. Trial with <i>Lactobacillus acidophilus</i> , <i>Lactobacillus casei</i> , <i>Lactobacillus bulgaricus</i> , <i>Lactobacillus rhamnosus</i> , <i>Bifidobacterium breve</i> , <i>Streptococcus thermophilus</i> & <i>Bifidobacterium longum</i>
Dental caries[176,178, 179]	More abundance of <i>Prevotella melaninogenica</i> , <i>Leptotrichia shahii</i> , <i>Leptotrichia HOT 498</i> , <i>Veillonella dispar</i> , and <i>Streptococcus mutans</i>	Insufficient evidence. <i>Lactobacillus rhamnosus</i> may help
Chronic congestive heart failure[180,184, 187,189]	Decreased gut microbiota diversity. More pathogenic Microbes as <i>Campylobacter</i> , <i>Yersinia enterocolitica</i> , <i>Salmonella</i> , <i>Shigella</i> & <i>Candida</i> . Low <i>Coriobacteriaceae</i> , <i>Erysipelotrichaceae</i> and <i>Ruminococcaceae</i>	<i>Bifidobacteria</i> , yeasts, and lactic acid-producing bacteria such as <i>Lactobacillus rhamnosus</i> GR-1. <i>Saccharomyces boulardii</i>

new therapeutic approach for complex central nervous system disorders[68].

Epilepsy is a common childhood disorder. There is a close relation between epilepsy and autoimmune diseases and between gut microbiota and autoimmune disease; a suggested association arises between epilepsy and gut microbiota. An exciting study by Huang *et al*[69] presented forty children who developed benign infantile convulsions after mild gastroenteritis, linking changing the gut microbiota and the epileptogenesis. Şafak *et al*[70] tried to elaborate on the relationship between gut microbiota and epileptogenesis. They studied the intestinal microbiota composition in patients with idiopathic focal epilepsy and compared them to a healthy volunteer group. They found an increased prevalence of *Fusobacteria species* in patients with epilepsy (10.6%) but not in the healthy volunteer

group. This significant taxonomic drift and variations in the intestinal microbiota and the resulting gut dysbiosis may be associated with certain forms of epilepsy.

Meanwhile, some anticonvulsants can be metabolized by the gut microbiota, affecting their efficacy. For example, the intestinal microbiota can metabolize Zonisamide to 2-sulfamoyl-acetyl-phenol, which is pharmacologically not active[71]. In addition, the anti-epileptic effects of the ketogenic diet used in drug-resistance epilepsy (although its exact mechanism of action is unclear) could be related to the ketogenic diet-induced changes in the gut microbiome composition and function of patients with epilepsy. The gut microbes modify the seizure vulnerability through mechanisms different from just alterations of beta-hydroxybutyrate levels (a measure of ketosis). The anti-seizure protective effects of diet and microbiota are associated with elevating hippocampal GABA relative to glutamate content[72]. The probiotics supplement could provide additional benefits to the anti-epileptics, especially in drug-resistant epilepsy. Gómez-Eguilaz *et al*[73] supplied patients with drug-resistant epilepsy with a probiotic mixture for four months. The patients showed a significant reduction in seizures frequency and improved quality of their life. Consequently, reformation of the gut microbiota through fecal microbiota transplantation, probiotic supplement, and the ketogenic diet has potential favorable impacts on drug-resistant epilepsy[74].

GUT MICROBIOTA AND CHILD PHYSICAL DEVELOPMENT AND NUTRITION

The gut microbiota typically develops hand in hand with the child's growth. The prenatal microbial communities affect fetal and postnatal development. Maternal microbiota is a crucial element for intrauterine growth. An exciting study by Sato *et al*[75] showed that the maternal gut microbiota correlates with the neonatal anthropometrics measures. In male neonates, the head circumference and weight are negatively correlated with genus *Eggerthella* and *Parabacteroides*. In female neonates, a high ratio of *Streptococcus* correlates with low anthropometric measures. Neonates with very low birth weight and restricted extrauterine growth had a predominance of *Proteobacteria* of their intestinal microbiota [76]. The gut microbiota affects growth by affecting growth hormone and insulin-like growth factor 1 production and regulation through its effects on the hypothalamic-pituitary-somatotropic axis. Delayed maturation and colonization of the gut microbiota may result from underlying food insecurity, malnutrition, and infections and could negatively impact the child's nutritional status[77]. The malnutrition-associated dysbiosis of the gut microbiota starts with depletion of the *Bifidobacteria* followed by the establishment of potentially pathogenic microbes (*Escherichia coli*, *Fusobacterium mortiferum*, and *Streptococcus spp.*), causing diarrhea and essential nutrients malabsorption[78]. Dysbiosis may result in a generalized inflammatory state and enteropathy that may precipitate growth faltering. The effects of these microbiota changes are significant in the first 1000 d. It provides a window of opportunity for modifying the gut microbiota through different interventions such as diet, antibiotic use, supplementary probiotics, prebiotics, symbiotics, postbiotics, or fecal microbiota transplantation to restore the proper growth and development[79].

Dysbiosis may explain why malnourished children may miss up the desired weight compared to their well-fed counterparts, despite gaining some weight and growing better with nutrient-rich supplements. Subramanian *et al*[80] showed significant differences in the proportions and species of gut microbiota in children up to two years of age with and without malnutrition. Children with malnutrition showed the immaturity of their gut microbiota, resembling their healthy counterparts but at a younger age. This malnutrition-induced microbiota imbalance fails to recover even after correcting the malnutrition. Oral probiotic supplements with beneficial gut bacteria and fecal transplantation from healthy children can restore the malnutrition-induced dysbiosis, and the malnourished children thrive. Probiotic supplements can improve a child's growth by preventing infections and micronutrient deficiency. They have been shown to improve the absorption of specific nutrients (vitamin B12, calcium, and zinc) and decrease the possibility of anemia[81]. However, there is no clear evidence to use them in the treatment of malnutrition. This lack of evidence is also augmented by the difficulty of modifying the gut microbiota. It resists long-term change and is affected by other factors such as diet and sleep pattern [82].

The cause of malnutrition also impacts the composition of gut microbiota. For example, moderate-to-severe diarrhea in children reduces bacterial diversity and changes gut microbiota composition[83]. Diarrhea can also affect weight, height, and the child's mental development, especially for diarrhea occurring below the age of 2 years[84]. The diarrhea-induced changes in gut microbiota increase the risk of persistent diarrhea, which causes stunted growth and decreases the affected children's mental abilities. Interventions to restore the gut microbiota as prebiotic and probiotic supplementation could help to combat the risk of diarrhea and the resulting malnutrition[85].

Meanwhile, subclinical changes in the gut microbiota may result in stunting even in the absence of clinically evident infections such as diarrhea. For example, poor hygiene may cause persistent exposure to environmental pathogens inducing subclinical alteration in the gut microbiota structure and function and consequently cause stunting[86]. For instance, poor sanitary conditions with chronic exposure to environmental pathogens resulting in subclinical alteration in the gut microbiota structure and function

initiate a condition known as environmental enteric dysfunction. This environmental enteric dysfunction induces a cell-mediated inflammation that ends in stunting[87].

CHILDHOOD OBESITY

The link between gut microbiota and obesity was evident in the adult population but not yet well documented in childhood. Obesity correlates with altered gut microbiota distinguished by raised *Firmicutes* and reduced *Bacteroidetes* abundance. This correlation is believed to be through the powerful effects of the gut microbiota on the human metabolic and immune status. Higher levels of SCFAs, a fermentation product by the gut microbiota, were found in children with obesity which tightened the relationship between the gut microbiota and the development of obesity[88]. The maturation patterns of gut microbiota in infancy can impact the relative chance of developing overweight and obesity in later childhood. Pregnant women with a high body mass index (BMI) have a higher load of *Bacteroides* than those with normal BMI[89].

Consequently, the maternal microbiota during pregnancy and breastfeeding significantly affects the newborn microbiota. The presence of *Bacteroides spp.* or their relatives and the relative lower abundances of *Bifidobacteria* in early infancy are related to developing childhood overweight and obesity. *Staphylococcus* species may also serve as a predictive but inconsistent tool for childhood BMI[90]. Children with an average BMI at seven years have more *Bifidobacterium spp.* in their gut during their first year of life than children with high BMI[91]. Gut microbiota could modify obesity through its role in metabolic regulation, food availability, and digestion. Gut microbiota has extra-intestinal effects involving the brain, liver, and adipose tissue, possibly linked to obesity, insulin resistance, diabetes mellitus type-II, and related cardiovascular disorders. Gut microbiota might also impact food intake and satiation through gut peptide signaling[92].

Consequently, gut microbiota can modify energy regulation and systemic inflammation, two crucial pillars for obesity development. Early modification and restoration of gut microbiota may be an encouraging tool to counteract the increasing childhood metabolic disorders, including overweight and obesity, providing the specific anti-obesity microbiota[93]. Despite the evidence of the beneficial effects of probiotics on glucose tolerance, insulin sensitivity, and inflammatory markers, there is no substantial evidence to recommend the use of probiotics in obesity[94]. Antenatal supplement with *Bifidobacterium lactis* and *Lactobacillus GG* decreases the risk of gestational diabetes mellitus and consequently reduces the risk of macrosomia and large baby size at birth, an effect that could last up to six months after birth [95,96].

GUT MICROBIOTA AND FUNCTIONAL GASTROINTESTINAL DISORDERS IN INFANCY AND CHILDHOOD

Gut microbiota can modulate various types of chronic pain through direct modulation of neuronal excitability dorsal root ganglia and neuroinflammation regulation in the central and peripheral nervous systems[97]. Numerous studies reported a strong association between the human gut microbiota and the development of functional gastrointestinal disorders, especially for infant colic, functional constipation, and irritable bowel disease. Randomized controlled trials showed that probiotics could be helpful in a variety of functional gastrointestinal disorders, including infant colic and irritable bowel syndrome. Probiotics may induce gut microbiota diversity with strain-specific effects on colonization resistance, the integrity of the epithelial barrier, signal transduction modulation, with a significant impact on both innate and adaptive immune responses, and notable effects on visceral hyperalgesia[98, 99].

Infant colic

About 20% of infants developed infant colic, with prolonged crying without apparent cause. The exact etiology of infant colic is unknown, but many factors are proposed to have a role, such as gastrointestinal, psychosocial, and neurodevelopmental factors[100]. Several studies addressed the role of the gut microbiota in developing infant colic. Gut dysbiosis was described in infant colic in the form of more abundance of *Proteobacteria* and less abundance of the genera *Lactobacillus* and *Bifidobacterium* with reduced gut bacterial diversity[101]. A meta-analysis done by Sung *et al*[102] showed that *Lactobacillus reuteri* DSM17938 was an effective treatment for infant colic in breastfed infants. Still, they cannot generalize this recommendation to formula-fed infants with colic, which needs further research. The unique effect of *Lactobacillus reuteri* DSM17938 in the breastfed infant may be related to the distinctive structure of breast milk or probably the direct effects of *Lactobacillus reuteri* or human milk oligosaccharides in breast milk[103]. How probiotics improve infant colic is not yet determined but may be mediated *via* modifying the activity of the colonic intrinsic sensory neurons with improving the gut motility. In addition, they have positive impacts on function and visceral pain[104].

Functional abdominal pain

About one-third of the school-aged children suffer from abdominal pain weekly, which causes school absenteeism and limitation of their social activities in about 20% of them. In children, functional abdominal pain is defined as when it persists for two or more months without an evident organic cause [105]. Functional abdominal pain is further subclassified into four conditions: irritable bowel syndrome (IBS), functional dyspepsia, abdominal migraine, and functional abdominal pain not otherwise specified [106]. Despite the high prevalence of dysfunctional abdominal pain, the exact pathogenesis is not well-defined. However, many risk factors increase the rate of dysfunctional abdominal pain, including the winter season, sleep, school stress, and diet. Many studies relate dysbiosis of the gut microbiota to dysfunctional abdominal pain such as irritable bowel syndrome. Rigsbee *et al* [107] showed that children with irritable bowel syndrome had more abundance of *Prevotella*, *Lactobacillus*, *Veillonella*, and *Parasporo* bacterium and less quantity of *Verrucomicrobium* and *Bifidobacterium*.

On the other hand, a low fermentable substrate diet decreased the abdominal pain frequency in children with irritable bowel syndrome by increasing the abundance of bacterial taxa belonging to the genera *Sporobacter* and *Subdoligranulum* and reduced the abundance of taxa belonging to *Bacteroides* [108]. Probiotic use might change the gut microbiota composition and decrease inflammation. It could also promote the physiology of the gut and improve functional symptoms. Some probiotics may impact colonic motility by increasing stool fluidity through modifying water and electrolytes secretion and absorption, smooth muscle cell contractions modification, increasing the production of lactate and SCFAs, and reducing intraluminal pH [109].

Functional constipation

Functional constipation is a common childhood disorder characterized by reduced gut movements and/or hard stools without organic causes. Functional constipation affects about 18% of infants and 3% of children and adolescents worldwide, with considerable influence on the child's and family's quality of life [110]. The pathophysiology of functional constipation is multifactorial, with a complex interaction between gastrointestinal dysmotility, psychological factors, and gut microbiota. Disturbances in gut microbiota may promote development and affect the outcome of functional constipation in children [111]. Zhu *et al* [112] showed that obese children suffering from constipation had a low-fiber diet and lower prevalence of gut *Prevotella* with an increased ratio of butyrate-producing bacteria such as *Roseburia*, *Coprococcus*, and *Faecalibacterium* than the control, which could be related to the low fiber intake. Probiotics can enhance intestinal transit time, stool frequency, and consistency [113]. Data about the efficacy of probiotic use to treat functional constipation are conflicting. A meta-analysis by Gomes *et al* [114] showed that "despite the probiotics' positive effects on certain characteristics of the intestinal habitat, there is still no evidence to recommend it in the treatment of constipation in pediatrics". So, the use of probiotics to treat functional constipation is still investigational.

GUT MICROBIOTA AND GASTROINTESTINAL DISEASES IN INFANCY AND CHILDHOOD

Necrotizing enterocolitis

Necrotizing enterocolitis (NEC) is a significant danger to neonatal life, especially preterm neonates. Prematurity is associated with many risk factors that alter the infant microbiome. These factors include mode of delivery, maternal microbiome diversity, feeding pattern, antibiotic use, environmental exposure to pathogenic and commensal bacteria in the neonatal intensive care unit [115]. Dysbiosis, alterations in the gut microbiome, and low microbial diversity of the preterm neonate significantly correlate with a higher risk and raised rate of complication of necrotizing enterocolitis and, consequently, the development of late-onset sepsis. Low microbiota diversity may provoke pathogenic bacteria overgrowth, a significant risk factor that promotes NEC development [116]. Dobbler *et al* [117] found powerful domination of *Citrobacter koseri* and/or *Klebsiella pneumoniae*, reduced diversity, less *Lactobacillus* abundance, and an altered microbial-network structure during the first days of life, correlate with NEC risk in preterm infants.

Oral administration of probiotics shows a significant reduction of NEC incidence. However, their safety still needs to be proven as preterm babies have immature immune systems with possible vulnerability even to the commensal bacteria [115]. Probiotic supplementation allows restoration of the normal commensal bacteria with the transition to the beneficial bacteria through enhancement of mucosal barrier function competitive inhibition of the pathogenic bacteria. It induces an anti-inflammatory effect on mucosal signaling [118]. Probiotics upregulate the cytoprotective genes of the gut and down-regulate the pro-inflammatory gene expression. They also enhance butyrate and other SCFAs productions to nourish colonocytes. Some probiotics decrease the pH and lower the oxygen tension in the intestinal lumen, thus inhibiting the growth of pathogenic bacteria, especially *Enterobacteriaceae*. Other probiotics can support the maturation intestinal barrier and functions and regulate cellular immunity through balancing the Th1:Th2 ratio [119].

Helicobacter pylori infection

Helicobacter pylori (*H. pylori*) is a flagellated, spiral-shaped, Gram-negative bacillus that colonizes the human gastric mucosa causing gastric mucosa inflammatory response, gastric and/or duodenal ulcers, intestinal metaplasia, or even gastric cancer[120]. *H. pylori* infection in children differs from the adults in the prevalence, rate of complications, difficulties in diagnosis, and the higher rate of antibiotic resistance. The prevalence of *H. pylori* in children is higher in developing countries (20%) than in developed countries (0.5%)[121]. *H. pylori* infection in children increases the risk of gut colonization with *Prevotella*, *Clostridium*, *Proteobacteria*, and *Firmicutes* compared to children without infection who have more *Bacteroides*. These changes in the gut microbiota associated with *H. pylori* infection could be related to the development of chronic gastrointestinal diseases and drug resistance[122]. Eradication of *H. pylori* has a positive and negative impact on the host. It may restore the gut microbiota with decreased abundance of *Bacteroidetes* and increase *Firmicutes*, producing plenty of SCFAs with positive and negative effects[123]. While supplements with probiotic strain can improve infection conditions, it is not enough to eradicate *H. pylori* infection[124]. Adding probiotics to the traditional triple therapy to eliminate *H. pylori* increases the chance of successful treatment and decreases the therapy-related side effects compared to treatment without probiotics[125]. The addition of *Saccharomyces boulardii* to the standard treatment of *H. pylori* increases the eradication rate and reduces the therapy-related side effects [126]. Addition of *Lactobacillus*- and *Bifidobacterium*-containing probiotics such as *L. acidophilus*, *L. casei* DN-114001, *L. gasseri*, *Bifidobacterium infantis* 2036, and *Lactobacillus reuteri* Gastrus had the same beneficial effects during *H. pylori* therapy[127]. Various studies reported that certain probiotic strains could demonstrate an inhibitory activity against *H. pylori* bacteria. In contrast, other strains can ease the side effects of antibiotic therapy and subsequently improve the *H. pylori* eradication rate[128].

Coeliac disease

Coeliac disease (CD) is a life-long chronic autoimmune inflammatory systemic disorder but mainly affects the small intestine due to a deviated immune response to dietary gluten proteins (glutenins and gliadins) in genetically susceptible individuals. Several risk factors increase the risk of CD, including a family history of CD or dermatitis herpetiformis, delivery with caesarean section, type-1 diabetes mellitus, chromosomal abnormalities (Down syndrome or Turner syndrome), Addison's disease, and presence of other autoimmune disorders as autoimmune thyroiditis, or microscopic colitis[129]. As mucosal immune response *via* IgA secretion is among the first defense lines accountable for neutralizing harmful antigens and pathogens, patients with CD have significantly lower levels of IgA-coated fecal bacteria than in healthy controls. De Palma *et al*[130] found a significant reduction of the Gram-positive/Gram-negative bacteria ratio in patients with CD than in healthy controls. They also found less predominance of *Bifidobacterium*, *Clostridium histolyticum*, *Clostridium lituseburense* and *Faecalibacterium prausnitzii*, more abundance of *Bacteroides-Prevotella* group, and reduced IgA coating the *Bacteroides-Prevotella* group. Dysbiosis and predominance of the bacteria associated with the development of CD can be a risk factor for CD, either by its direct effects on the mucosal immune responses or by increasing the inflammatory reactions to gluten[131]. Fasano *et al*[132] found increased Zonulin expression in the intestinal tissues during flaring of celiac disease. Zonulin is a human protein like a toxin derived from *Vibrio cholera* called Zonula occludens toxin. Both Zonulin and Zonula occludens toxin increase intestinal permeability by decreasing the mucosal epithelium's tight intercellular junction.

Meanwhile, dysbiosis may result in a complication of the strict gluten-free diet, which reduces the beneficial bacteria, especially *Bifidobacterium* and *Lactobacillus*, and abundance of gram-negative bacteria such as *Bacteroides* and *Escherichia coli*[133]. The gluten-free diet-induced dysbiosis results from excluding crucial dietary carbohydrate resources, the primary resources for the energy required by the beneficial bacteria[134]. Despite being the only available treatment for CD, compliance with the gluten-free diet is complex. Consequently, there is a strong need for alternative therapy. Probiotics could supplement a gluten-free diet in patients refractory to the gluten-free diet. Probiotics can help to support the gluten-free diet through different mechanisms: improving the intestinal barrier function by *Lactobacillus rhamnosus* containing probiotics[135], anti-inflammatory modulation by *Bifidobacterium breve* and *Bifidobacterium longum*[136], and gluten degradation, lysing the proline/ glutamine-rich gluten peptides, and reduction of the gluten concentration and toxicity by *Lactobacilli* strains (*L. ruminis*, *L. Johndoni*, *L. amylovorus*, *L. salivaris*)[137]. The use of probiotics enriched with *Lactobacilli* species may relieve the effects of accidental or contaminant gluten exposure by chopping up gluten proteins into smaller portions, not triggering an immune reaction or damaging the patients[138]. However, we need more studies and effort to evaluate probiotics in CD management.

Inflammatory bowel diseases

Inflammatory bowel diseases (IBD, Crohn's disease, ulcerative colitis, and unclassified) are a group of chronic, relapsing, and remitting inflammatory diseases of the gastrointestinal tract in a genetically predisposed person due to an aberrant immune response against gut microbiota, causing intestinal damage[139]. About 25% of the patients develop the disease before the age of 20 years, 18% before the age of 10 years, and 4% before the age of 5 years, and still on the rise[140]. Crohn's disease and ulcerative colitis affect the terminal ileum and colon, where there is heavy bacterial colonization. The

presence of IgG antibodies and hyperactive presentation of T-lymphocytes in the intestinal mucosa indicates a decrease in the local tolerance mechanisms[141]. In normal situations, the commensal bacteria cannot invade the intestinal mucosal barrier. Even when succeeded to pass through it, it is rapidly phagocytosed and eliminated by the mucosal macrophage. Under unusual conditions, these commensal bacteria can cross the mucosal barrier and induce the inflammatory cascade[142]. Fava *et al* [143] found that patients with IBDs have different microbiota composition than that observed in the healthy controls, with decreased abundance of the healthy commensal (such as *Clostridium* IXa and IV groups, *Bacteroides*, *Bifidobacteria*) and increased the pathogenic bacteria as sulfate-reducing *Escherichia coli* reaching up to 40% of the dominant bacteria and consequently decreasing the microbiota diversity. The observed dysbiosis coupled with defective innate immunity and reduced bacterial killing ability due to impaired phagocytosis, decreased mucosal IgA and defensins, and over destructive adaptive immunity with ineffective regulatory T cells and antigen-presenting cells initiate the process of the pathogenesis of IBDs[144].

Treatment of pediatric IBDs is one of the fundamental challenges to pediatricians with frequent treatment failure and numerous therapy-associated side effects. Gut microbiota modification is one of the promising therapies for IBDs but is still controversial. Probiotics supplementation can restore the metabolic activity of the intestinal microbiota and modify their relative components by inhibiting the pathogenic bacterial overgrowth, decomposing their antigen, secreting antimicrobial substances, and increasing mucosal IgA. Probiotics also help to improve mucosal barrier function and preserve their integrity by tightening the epithelial junction and stabilizing the intestinal permeability. They also modulate intestinal epithelial and mucosal cells' immune response and induce T-cell apoptosis. Consequently, probiotics regulate the immune response and decrease the production of pro-inflammatory factors[145,146].

However, probiotic treatment for IBDs is still controversial. Vilela *et al*[147] showed that administering *Saccharomyces boulardii* helped maintain remission, improve intestinal permeability, and bowel sealing in patients with Crohn's disease. Kato *et al*[148] and Kruis *et al*[149] showed that *Escherichia coli* Nissle1917, *Bifidobacterium breve*, *Bifidobacterium bifidum*, and *Lactobacillus acidophilus* showed a promising effect on in maintaining the remission phase in patients with ulcerative colitis as effective as the standard mesalazine therapy but with high safety and tolerability profiles. However, Bousvaros *et al* [150] showed that the addition of probiotic *Lactobacillus rhamnosus* strain GG (LGG) to the standard therapy showed no significant differences compared to placebo in prolonging remission in children with Crohn's disease. Moreover, we need more randomized controlled studies to evaluate the effectiveness of *Lactobacillus* GG and other probiotic strains in children with IBDs.

GUT MICROBIOTA AND RESPIRATORY DISORDERS IN INFANCY AND CHILDHOOD

The gastrointestinal microbiota plays a crucial role in future lung development and future health status. Perinatal antibiotic use induces highly selective alterations on the resident gut microbiota, leading to precise modifications in susceptibility to TH2- or TH1-/TH17- determined lung inflammatory disorders [151].

The coronavirus disease 2019 infections in childhood

The coronavirus disease 2019 (COVID-19) is a real worldwide threat for all individuals of different ages, including children. Despite being mainly a respiratory disease, the gastrointestinal tract is a significant target, especially children. The virus can actively infect the gastrointestinal tract cells and replicate in the epithelium of the small and large intestine, stimulating an excessive immunological reaction in the host [152]. Angiotensin-converting enzyme-2 (ACE2) receptors are highly expressed in the upper esophagus and absorptive enterocytes from the ileum till the colon. The ACE2 receptor is an essential receptor for the virus entry to the cell membrane of host cells, with the interaction between the S protein of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). This interaction induces a state of an inflammatory cascade that ends with dysbiosis and leaky gut syndrome. The degree of expression of ACE2 throughout the gut is an essential factor that aggravates or alleviates the resulting gut dysbiosis and gastrointestinal leakage[153]. Meanwhile, SARS-CoV-2 infection causes many plasma cells and lymphocytes infiltration. It possibly provokes interstitial edema and the deterioration of the intestinal-blood barrier, causing the spread of endotoxins, viruses, bacteria, and microbial metabolites into the systemic circulation, impairing the host's response to SARS-CoV-2 infection and causing multisystem dysfunction and even septic shock[154].

The resulting dysbiosis lasts for a long time after clearance of SARS-CoV-2 virus from the body, indicating the presence of a more long-long-term harmful effect on the gut microbiome, in the form of reduced beneficial bacteria such as *Lactobacillus*, *Bifidobacterium*, and *Faecalibacterium prausnitzii* and more abundance of *Clostridium hathewayi*, *Clostridium ramosum*, *Coprobacillus*, *Candida* and *Aspergillus*. The presence of comorbidities such as diabetes mellitus, hypertension, and old age, and antibiotics, antivirals, antifungal, and steroid use increase dysbiosis severity[155]. Diversity of the gut microbiota and the gut predominance of beneficial bacteria share in determining the course of COVID-19 infection.

Restoring the gut microbiota diversity could help improve the severity of the disease. Dietary supplements with specialized pre/probiotics such as fructooligosaccharide, galactooligosaccharide could improve gut dysbiosis, especially in patients presenting with gastrointestinal manifestations such as diarrhea and thus improving the overall immune response in these patients[156]. Probiotics can produce bioactive peptides capable of inhibiting the ACE receptors by blocking the active sites, preventing the entry of SARS-CoV-2 from attacking the enterocytes. We can use prebiotics, probiotics, or symbiotics to protect the high-risk groups, such as healthy contacts with a suspected case or the front-line caregivers[157]. However, microbiota modulation as a treatment method of patients with COVID-19 disease is based on indirect evidence and needs further studies.

Cystic fibrosis

Cystic fibrosis is an inherited systemic disease that produces severe injury to the lungs, digestive system, and other body organs and might lead to death. The relation between the microbiota and cystic fibrosis is bidirectional. Loss of the function of cystic fibrosis transmembrane conductance regulator results in aberrant colonization of gut and respiratory microbiota due to altered intestinal and airway microenvironment even in the absence of antibiotic use[158,159]. Homozygous cystic fibrosis is associated with more significant changes in the gut microbiome and the severity of the disease. The resulting changes in the gut microbiota associated with cystic fibrosis induce changes in the airway microbiota due to the dynamic interaction between gut and airway microbiota[160].

On the other hand, the gut microbiota could impact the disease severity and progression. Restoration of the gut microbiota in cystic fibrosis either by adding oral probiotics, prebiotics, or even postbiotics by adding certain bacterial strains, indigestible fibers, or SCFAs; namely, butyrate improves the gut and the systemic inflammation, energy intake, nutritional status, and the respiratory function of the patients [161]. Oral probiotic intake, especially with LGG and *Lactobacillus reuteri*, can reduce inflammation, improve body weight, reduce pulmonary exacerbations, and upper respiratory infections and improve the pulmonary functions in children with cystic fibrosis with mild-to-moderate lung disease. These effects are related to the probiotics' anti-inflammatory and immunomodulatory properties and their impact on the intestinal barrier[162-164]. However, a recent multicentre study by Bruzzese *et al*[165] showed that LGG supplementation had no significant effect on the respiratory and nutritional outcomes in a large group of children with cystic fibrosis. This study's failure to show a beneficial effect for LGG supplementation could be related to the lower dose of probiotics. They used 109 colony-forming units instead of 10¹⁰ in the previous two studies. Meanwhile, we remain in need of more studies to confirm these effects.

Allergic rhinitis

Allergic rhinitis in children has a significant impact on the child's health with many comorbidities, impaired quality of life, and poor educational performance. It may progress to asthma or complicate the control of existing asthma[166]. Many factors that cause decreased microbial diversity (*e.g.*, delivery by caesarean section) are associated with an increased risk of allergic rhinitis and other atopic diseases such as atopic dermatitis and asthma. Bisgaard *et al*[167] found that the bacterial diversity in the early gut microbiota at one and twelve months after birth was negatively associated with the increased risk of allergic sensitization, peripheral blood eosinophilia, and allergic rhinitis. As the gut microbiome shows significant development during the first year of life, it is highly susceptible to disruption during that time. Early antibiotic use has a significant adverse effect on the gut microbiota by modifying the relative abundance of the bacterial composition and initiating dysbiosis, with increasing the risk for childhood allergic diseases[168].

Oral Probiotic supplementation can alter the gut microbiota in children with notable positive immunomodulatory effects help prevention of allergic diseases, including allergic rhinitis. Lin *et al*[169] examined the effects of *Lactobacillus paracasei* supplementation on the treatment of perennial allergic rhinitis in children between 6-13 years. They found significant improvement in individual parameters in the rhino-conjunctivitis quality of life questionnaires, including sneezing, nasal itching, and swollen puffy eyes in the supplemented group, but without significant effects on total symptom score and the nasal total symptoms score. Miraglia Del Giudice *et al*[170] found that children supplemented with probiotic *Bifidobacteria* mixture for four weeks achieved a significant improvement of allergic rhinitis symptoms than the control without probiotic supplementation. A meta-analysis by Güvenç *et al*[171] showed the evident beneficial immunologic and clinical effects of probiotics, especially for *Lactobacillus paracasei*-33 strains in managing patients with allergic rhinitis despite the high heterogeneity among the included studies. However, despite the beneficial effects of probiotics in improving allergic rhinitis symptoms and the patient quality of life, there is limited evidence for the primary preventive role of probiotics supplementations in children with a high risk of allergic rhinitis[172,173].

Bronchial asthma

Asthma is a prevalent childhood disease. More than 300 million children and adults are affected by asthma worldwide. The development of asthma is multifactorial and is affected by environmental and other exogenous factors and genetic predisposition. Shaping the lung microbiota, especially during birth

and very early life, plays a crucial role in asthma development. Arrieta *et al*[174] found a significant decrease in the relative abundance of the bacterial genera *Rothia*, *Veillonella*, *Lachnospira*, and *Faecalibacterium*, in children at risk of asthma. The noticed abundance of these bacteria decreases the fecal acetate levels and consequently induces dysregulation of enterohepatic metabolites. In the same context, Abrahamsson *et al*[175] showed that children who developed asthma at the age of 7 years had a reduced total and gut microbial diversity in the first month of life than healthy children.

On the other hand, more abundance of the good bacteria as *Bifidobacterium longum* and less quantity of *bacteroid fragilis* in the gut microbiota early in life reduces the risk of asthma[176]. The recent decrease in pediatric asthma incidence, noted in some parts of Europe and North America, could be related to judicious antibiotic use during early infancy and childhood that preserve the gut microbiota community [177]. The use of oral probiotics, prebiotics, or synbiotics (combination of pro and prebiotics) could modify the airway microbiota directly through microaspiration of the probiotic strain from the gastrointestinal tract to the airway or indirectly through their metabolic products[178]. Probiotics might generate local effects, such as reducing mucosal permeability and thus decreasing systemic antigens penetration, enhancing local IgA production, and tolerance induction. Their systemic anti-inflammatory effects are mediated through Toll-like receptors, stimulating Th1 response to allergens, enhancing tolerogenic dendritic cells, and the production of Treg[179]. Probiotic supplementation could restore the airway microbiota dysbiosis, promoting the healthy microbiota, which could modify the course of the pulmonary disorders. However, there are not enough studies concerned with the effects of probiotic supplementation on childhood asthma. A systemic review by Lin *et al*[180] failed to confirm the beneficial role of probiotic supplementation on the disease course in children with bronchial asthma.

GUT MICROBIOTA AND SKIN DISORDERS IN INFANCY AND CHILDHOOD

Atopic dermatitis

Atopic dermatitis (AD) is a common chronic, recurrent inflammatory skin disease in children, affecting about 20% worldwide and on the rise, especially in developed countries. Skin microbiota can reflect general human health. The quantitative and qualitative skin and gut microbiota composition alteration can trigger various diseases, including allergic dermatoses[181]. The skin microbiota of children with AD shows significant dysbiosis, with reduced microbial diversity and more abundance of pathogenic *Staphylococcus aureus* and *Malassezia*[182]. Melli *et al*[183] showed an association between the presence of *Clostridioides difficile*, more quantity of *Bifidobacteria*, and a lower abundance of lactobacilli in the gut microbiota of children with atopic dermatitis. Bacterial strains such as *Staphylococcus epidermidis*, *Staphylococcus cohnii*, Gram-negative *Roseomonas mucosa*, and *Cutibacterium* strains that inhibit *Staphylococcus aureus* can serve as potential probiotics in children with atopic dermatitis[184]. Myles *et al*[185] showed that the local application of *Roseomonas mucosa* to the skin of 10 adults and five children with atopic dermatitis was associated with significant improvement of atopic dermatitis severity, a decrease in topical steroid requirement, and *Staphylococcus aureus* burden with no adverse events or treatment complications. Probiotics can decrease the severity and progression of atopic dermatitis by reducing inflammation through modulating T-cell immune response and improving the Th1/Th2 ratio; inhibiting Th2 cell response, and decreasing cytokines production such as IL-4, IL-5, IL-6, IL-13, and INF, enhance phagocytosis, increase serum IgA is increased[186]. Probiotics also inhibit the differentiation of mature dendritic cells and naive T cells' transformation into Th2[158]. Probiotics also can regulate brain function involving stress response on the gut-brain axis[187].

Psoriasis

Psoriasis is a chronic, complex, immune-mediated, inflammatory disease characterized by keratinocytes hyperproliferation. Unlike atopic dermatitis, patients with psoriasis have more bacterial diversity and heterogeneity with increased *Staphylococcus aureus* and decreased *Staphylococcus epidermidis* and *Propionibacterium acnes* and reduced microbiota stability than in healthy controls. *Staphylococcus aureus* colonization of the skin triggers Th17-induced inflammation with impaired community stability and accumulation of pathogenic bacteria[188]. The bacterial dysbiosis in psoriasis shows topographic changes. An exciting study by Fahlén *et al*[189] showed a significant decrease in the ratio of *Staphylococci* and *Propionibacteria* in psoriasis limb skin and enriched *Proteobacteria* in the trunk skin in patients with psoriasis than in controls. Gut dysbiosis also plays a significant role in psoriasis. There is a decrease in gut *Bifidobacterium* and *Firmicutes* and an increase in *Bacteroidetes* in patients with psoriasis than in healthy children. This gut dysbiosis also correlates with the severity of the disease[190]. Probiotics use in the treatment of psoriasis is promising *via* immune modifying response through restoring the gut microbiome. Vijayashankar *et al*[191] described the successful use of oral *Lactobacillus* strain with biotin to treat pustular psoriasis. However, a systematic review and meta-analysis by Zeng *et al*[192] showed that prebiotics might positively impact relieving the clinical symptoms of psoriasis with a low incidence of side effects. The probiotics exert their effects through their immunomodulatory effect on the skin and repair the skin barrier by decreasing the bacterial load and restoring the skin microbiota.

GUT MICROBIOTA AND IMMUNE DISORDERS

The relation between adaptive immunity and gut microbiota is well documented. Systemic lupus erythematosus (SLE) is a chronic systemic severe autoimmune disease that affects connective tissues. Pathogenesis of SLE results from the interaction between genetic and environmental factors[193]. Gut microbiota dysbiosis with disturbed composition and activity plays a role in many autoimmune diseases, including SLE and rheumatoid arthritis. A study done by Ma *et al*[194] found that the fecal microbiota of SLE mice had lesser community abundance and diversity than healthy mice. They can also induce anti-double-stranded DNA (anti-dsDNA) antibodies production in germ-free mice, promote the inflammatory response resembling SLE inflammation, and modify the SLE susceptibility genes expression in these mice by fecal microbiota transplantation. Another interesting experimental study by Ma *et al*[195] performed fecal microbiota transplantation from healthy controls and patients with active untreated SLE to germ-free mice. The Germ-free mice developed a series of lupus-like phenotypic and laboratory features that confirm the contributing role of abnormal gut microbiota in promoting SLE development.

On the other hand, Toral *et al*[196] found that *Lactobacillus fermentum* CECT5716 (LC40) ameliorates disease activity and cardiovascular complications in female mice models by improving gut barrier integrity. At the same time, de la Visitación *et al*[197] showed that *Lactobacillus fermentum* CECT5716 (LC40) prevented renal damage in a female mouse model of SLE. Long-standing use of probiotics is supposed to counteract the imbalance in the gut microbiota that causes reduced antibody production and attenuated inflammatory response, resulting in reduced severity and improving the signs and the manifestation of SLE[198]. However, we need more human-based studies on patients with SLE, as most animal-based studies confirmed the potential beneficial role for oral probiotics intake, which can alter the gut microbiome's composition and prevent SLE progression.

Gut dysbiosis is also a potential pathogenic factor for developing juvenile idiopathic arthritis (JIA). Wu *et al*[199] were able to induce autoimmune arthritis in mice using segmented filamentous bacteria, which could elaborate the potential role of the microbiota and development of autoimmune arthritis. On the other hand, some degree of intestinal inflammation is observed in about two-thirds of children with spondyloarthritis arthritis which may indicate that gut microbiota in children with spondyloarthritis is both modified and unusually affected by the deviated immune system[200]. Meanwhile, Stoll *et al*[201] found less abundance of *Faecalibacterium Prausnitzii* and a more abundance of *Bifidobacterium*, mostly *B. adolescentis*, in children with enthesitis-related arthritis than in healthy control. However, Öman *et al* [202] found no significant variations in microbiota α -diversity or composition between children with JIA, their healthy siblings, or unrelated healthy controls. Trials to modify gut microbiota using probiotics, exclusive enteral nutrition, or other modalities have variable success. Esmaeili *et al*[203] found no significant differences in the improvement criteria of rheumatoid arthritis in patients supplemented with synbiotic (500 mg capsule containing a prebiotic (fructooligosaccharides) and probiotics including 10^9 CFU/mL of *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus bulgaricus*, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, *Streptococcus thermophile*, and *Bifidobacterium longum*.) for three months and placebo groups. They suggested that lack of response is probably related to the short duration of the treatment, but we think that the dose also was suboptimal. However, we need more studies with different probiotic strains and concentrations.

GUT MICROBIOTA AND DENTAL DISORDERS

Dental caries is a common pediatric disorder, especially in children with special needs. Understanding the association between specific bacterial strains in dental biofilms and different health conditions is crucial to preventing and combating dental caries. Richard *et al*[204] found that the microbiomes of supragingival dental plaque vary considerably between tooth surfaces and in children with different caries activities. Qudeimat *et al*[205] found that children with active caries have a significantly higher abundance of *Prevotella melaninogenica*, *Leptotrichia shahii*, *Leptotrichia* HOT 498, *Veillonella dispar*, and *Streptococcus mutans*. In comparison, children without active caries had a significantly higher abundance of *Lautropia mirabilis*, *Corynebacterium durum*, *Corynebacterium matruchotii*, and *Neisseria elongata*. Kanasi *et al*[206] also confirmed the presence of diverse microbiota that varied in children with severe caries from caries-free children. Probiotics might be helpful to inhibit or treat dental caries, periodontitis, or gingivitis. Certain probiotic bacterial strains have variable effects on the gut microbiome. Each probiotic bacterial strain has specific abilities to inhibit the growth of particular strains, particularly cariogenic bacterial strains and yeast[207].

Probiotic dairy products have a naturally occurring buffer to acid. When combined with calcium and calcium lactate effects, it produces anti-cariogenic properties that benefit the oral cavity. In the short term, probiotic products can hamper the development of harmful strains, but the long-term effects have not been thoroughly studied. Lee *et al*[208] showed that *Lactobacillus* species strongly inhibited the growth of oral *streptococci*. They also showed that *Lactobacillus rhamnosus* might inhibit oral biofilm formation by decreasing the glucan production of *Streptococcus mutans*. Systematic review and meta-

analysis by Gruner *et al*[209] showed insufficient current evidence to recommend probiotics in managing dental caries but support using probiotics to manage gingivitis or periodontitis. Future studies are needed to confirm the role of probiotics in the management of dental caries.

GUT MICROBIOTA AND CARDIAC DISORDERS

Recent evidence revealed that modifications of the gut microbiota composition and function could accelerate the progression of CVDs. The gut microbiota has a crucial effect in inducing inflammatory and immune responses that could link the gut microflora to heart failure. The gut microbiota of patients with chronic heart failure has more pathogenic bacteria such as *Campylobacter* and *Shigella* and more candida than the healthy controls. The ratios of these pathogenic bacteria and candida positively correlated with the severity of heart failure[210]. Increased intestinal permeability is observed in a significant portion of patients with congestive or right-sided heart failure, which correlates with right atrial pressure[211]. This observation could explain the increased serum endotoxin levels in patients with chronic heart failure. Reduced cardiac output and systemic congestion observed in heart failure cause intestinal mucosal ischemia and/or edema, which increases the bacterial translocation and the circulating endotoxins that can promote the underlying inflammation observed in patients with heart failure[212]. These mucosal changes also cause enhanced bacterial growth, which is reflected by the increase in serum levels of immunoglobulin A-antilipopolysaccharide[213]. In heart failure, there is a decreased gut microbiota diversity with an increased ratio of the pathogenic bacteria such as *Shigella*, *Campylobacter*, *Yersinia enterocolitica*, *Salmonella*, and *Candida* species[214]. Luedde *et al*[215] also observed significant downregulation of key intestinal bacterial groups such as *Coriobacteriaceae*, *Erysipelotrichaceae*, and *Ruminococcaceae*.

Probiotics may have significant beneficial effects on cardiovascular health. The effects are strain-specific and target specific cardiovascular risk factors. For example, *Lactobacillus rhamnosus* can significantly reduce body weight while *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, and *Bifidobacterium bifidum* can dramatically lower blood glucose levels by 38% in patients with DM type II. At the same time, *Lactobacillus acidophilus* and *Bifidobacterium lactis Bb12* significantly lower fasting blood glucose, hemoglobin A1c, and malondialdehyde and raise erythrocyte glutathione peroxidase and superoxide dismutase activities and improve total antioxidant states. Meanwhile, *Lactobacillus acidophilus*, *Lactobacillus reuteri*, and *Bifidobacterium longum* improve dyslipidemia, increase high-density lipoprotein (HDL) cholesterol level, and reduce low-density lipoprotein (LDL)/HDL cholesterol ratio. *Lactobacillus curvatus* and *Lactobacillus Plantarum* increase apolipoprotein AV and LDL particles size. *Streptococcus thermophiles* can significantly decrease systolic blood pressure[92,216-219].

Probiotics may have a role in managing heart failure, primarily those containing *Bifidobacteria*, yeasts, and lactic acid-producing bacteria, as they can reduce inflammation, repair, protect the intestinal mucosal barrier, and improve its function[220]. Gan *et al*[221] showed that six weeks of supplementation with *Lactobacillus rhamnosus* GR-1-containing probiotic could significantly improve left ventricular hypertrophy and increase its ejection fraction in rates with induced myocardial infarction due to coronary artery occlusion. Animal studies also showed that probiotics could decrease myocardial cell apoptosis and alleviate ventricular remodeling in rat models of spontaneous hypertension[222]. There are very few studies of the effects of probiotics in human patients with heart failure. Costanza *et al*[223] studied the impact of three months of supplementation with *S. boulardii* (1000 mg per day) on outpatients with heart failure with NYHA class II or III and left ventricular ejection fraction (LVEF) < 50%. The supplemented patients showed a significant reduction of left atrium diameter and improvement of LVEF compared to the patients supplemented with placebo. Children with heart failure may have underlying cardiac conditions that increase the risk of infective endocarditis. Probiotics in such patients are not entirely safe, and there is a risk of bacterial translocation with a possible occurrence of sepsis and infective endocarditis. Their safety in such vulnerable patients requires additional studies.

LIMITATIONS FOR PROBIOTIC USE

Despite probiotics being part of the body's good microbiota and are safe in most cases, there are some limitations to their use. The side effects of probiotics lie in four categories: excessive immune stimulation, adverse metabolic activities, generalized infections, and gene transfer[224]. They may occasionally trigger allergic reactions, especially with *Saccharomyces boulardii* in those with a history of yeast allergy, and should be used judiciously. Abdominal discomfort could happen in the first few days of therapy, occasionally with diarrhea and bloating. Probiotics are safe to be used by children, especially those containing *Bifidobacteria* or *Lactobacillus*, which can be used for up to one year without any safety issues[225]. Bacteriemia and infective endocarditis have been recorded in a few patients taking probiotics containing *Bifidobacteria* or *Lactobacillus* probiotics, especially among patients with central lines or impaired immunity, *e.g.*, who are suffering from tuberculosis or acquired immune deficiency

syndrome[226]. Probiotics containing *Lactobacilli* can cause mural and valvular infective endocarditis. Although this is extremely rare, patients with valvular heart disease may be more prone to this complication. Before dental or surgical procedures, patients with valvular or congenital heart disease with high-pressure shunt should discontinue probiotic use[227]. Some probiotics may transmit antibiotic resistance genes, such as enterococci. Other probiotic strains such as the *Bacillus cereus* group can produce enterotoxins and emetic toxins[228]. Another limitation is the lack of international regulatory measures that control probiotics production and prescription. Another limitation is the need to elucidate the mechanism of action of each probiotic, the ideal strain and its effect for each medical condition, and which health benefits can be gained[229]. We need to do more clinical and mechanistic studies to understand better the interaction between the microbes and host cells, including the mucus and immune defenses, and produce effective interventions.

CONCLUSION

There is an intimate relationship between the human and his body microbes. The gut is the primary residence for this microbiota, as it provides the bacteria with a convenient environment for thriving. The microbiota plays a significant role in gut development, maturation, and immune system differentiation. It exerts a considerable effect on the child's physical and mental development. Gut dysbiosis is also a potential pathogenic factor for developing various childhood disorders inside and outside the gastrointestinal tract. Probiotics may have a role in managing these disorders with variable degrees. Even though probiotics could help address these disorders, we need more studies to prove the efficacy, select the proper probiotic for each disease, the appropriate dose, and ensure its safety.

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Country/Territory of origin: Bahrain

ORCID number: Nermin Kamal Saeed [0000-0001-7875-8207](https://orcid.org/0000-0001-7875-8207); Mohammed Al-Beltagi [0000-0002-7761-9536](https://orcid.org/0000-0002-7761-9536); Adel Salah Bediwy [0000-0002-0281-0010](https://orcid.org/0000-0002-0281-0010); Yasser El-Sawaf [0000-0001-8083-3042](https://orcid.org/0000-0001-8083-3042); Osama Toema [0000-0003-2408-1573](https://orcid.org/0000-0003-2408-1573).

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