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REVIEW

Gut microbiota and childhood malnutrition: Understanding the link and exploring therapeutic interventions

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Abstract

Childhood malnutrition is a metabolic condition that affects the physical and mental well-being of children and leads to resultant disorders in maturity. The development of childhood malnutrition is influenced by a number of physiological and environmental factors including metabolic stress, infections, diet, genetic variables, and gut microbiota. The imbalanced gut microbiota is one of the main environmental risk factors that significantly influence host physiology and childhood malnutrition progression. In this review, we have evaluated the gut microbiota association with undernutrition and overnutrition in children, and then the quantitative and qualitative significance of gut dysbiosis in order to reveal the impact of gut microbiota modification using probiotics, prebiotics, synbiotics, postbiotics, fecal microbiota transplantation, and engineering biology methods as new therapeutic challenges in the management of disturbed energy homeostasis. Understanding the host–microbiota interaction and the remote regulation of other organs and pathways by gut microbiota can improve the effectiveness of new therapeutic approaches and mitigate the negative consequences of childhood malnutrition.

KEYWORDS
dysbiosis, gut microbiota, malnourished children, overnutrition, undernutrition

1 | INTRODUCTION

Childhood malnutrition is one of the major health issues that result from an imbalance between the nutrients consumed and the appropriate requirements for growth and metabolism. Nutritionally speaking, childhood malnutrition includes both under- and overeating, and in the clinical setting, it can present with both chronic and acute symptoms [1]. Malnutrition is the leading cause of

Abbreviations: BMI, body mass index; SAM, sever acute malnutrition; EE, environmental enteropathy; FTO, fat mass and obesity associated; SCFA, short-chain fatty acid; TMAO, trimethylamine N-oxide; GABA, gamma-aminobutyric acid; BA, bile acid; RUTF, ready-to-use therapeutic food; MDCF, microbiota-directed complementary food; FOS, fructo-oligosaccharide; GOS, galacto-oligosaccharide; FMT, fecal microbiota transplantation.

half of all deaths in children under the age of five, the primary target group, and even in the most optimistic survival mode, it has negative physical and neurological impacts [2, 3]. Therefore, malnourished children are vulnerable compared to their healthy peers and aberrant immune responses, mental retardation, invasion of infectious agents, mood instability, cardiac, metabolic, and orthopedic failures can potentially threaten their lives [4, 5]. However, childhood malnutrition has a growing prevalence among low-income and middle-income communities, which highlights the necessity and importance of related studies. According to a study mapping regional patterns of childhood overweight and wasting between 2000 and 2017, childhood overweight risk increased from 5.2% to 6.0% in low- and middle-income countries [6]. Also, global reports on undernourished children under 5 years from 2018 indicate the identification of 144 million stunted children and 47 million wasted children, especially in Asia and Africa [7]. Numerous influencing elements, such as socioeconomic circumstances (particularly in developing nations), food insecurity, illnesses, insufficient prenatal care, gender, and genetic susceptibility, can contribute to the development of malnutrition, but the core reasons go beyond these. According to recent findings, the gut microbiota has been identified as one of the key factors in the etiology of childhood malnutrition [8].

The human gut is the digestive organ with the highest level of microbial specialization. The colonization of early gut microbiota is an important determinant of host clinical safety. The dynamic activity of the gut microbial community improves human health by enhancing the host's metabolic efficiency, immunological resistance to infections, and the development of the sensory and motor functions of the gastrointestinal tract [9]. Although the gut microbiota initiates symbiosis with the host during the fetal, birth, and childhood periods, the unique and normative composition of the microbial population has a potential effect on metabolic pathways and growth patterns in the early life. The significant metabolic activity of Gram-negative bacteria, especially members of the genus Bacteroides, which are the dominant colonizers of the gut microbiota composition of children compared to adults, corresponds to the age-related needs of children, such as the biosynthesis of B vitamins, antibiotic (vancomycin) production, and polysaccharide catabolism [10]. Therefore, any changes that aim to disturb the balance of the gut microbial population may trigger the onset of human physiological and digestive disorders [11].

In this review, we evaluated the association between gut microbiota and childhood malnutrition and investigated the efficacy of microbial therapy on the improvement of childhood malnutrition outcomes.

2 | GUT MICROBIOTA AND CHILDHOOD MALNUTRITION

The intestine has evolved as the preferred habitat for the activity of bacteria throughout the gastrointestinal tract as a result of its ideal circumstances, including a pH range of 5.5–7, slow motility, and accessibility to dietary requirements [12]. Hence, in the human population, the gut is a natural habitat for an average of 600 bacterial species [13], of which Firmicutes and Bacteroidetes are the most common bacterial phyla [14]. Gut microbiota has a changing structure and diversity from infancy to adulthood, which depends on several factors, including mode of delivery, lifestyle, genetics, antibiotics, synthetic chemicals (such as preservatives and flavorings), and nutrition [15]. The critical stage of changing the gut microbiota ecosystem is the transition from breastfeeding to solid food intake; a period known as gut microbiota maturation. According to the pediatric health system, the regular interaction of healthy gut microbiota and feeding cycle is a significant factor for establishing a stable metabolic state in children. As the maturation process targets the development of microorganisms catabolizing complex compounds found in solid foods (especially Firmicutes) along with metabolically compatible bacteria for processing simple compounds in breast milk (such as *Staphylococcus epidermidis*, *Lactobacillus rhamnosus*, *Bifidobacterium dentium*, *Bifidobacterium breve*, and *Bifidobacterium bifidum*). Indeed, this feeding-dependent phase is associated with increased microbial diversity during childhood [16, 17].

Noteworthily, the gut microbiota genome contains 100-fold more coding genes compared to the human genome, which are the main indicator of gut microbiota implication in host physiology [18]. In addition to producing minerals, vitamins, absorbable monomers, and digestion of indigestible polysaccharides, gut microbiota also maintains the integrity of the intestinal barrier and controls immunological responses [10, 19]. However, immunity dysregulation and inflammation persistence related to gut microbiota dysfunction are the common consequences of malnutrition [20]. In a study related to mucosal immunodeficiency in malnourished children, transfer of immunoglobulin A (IgA)-targeted microbiota in a gnotobiotic (germ-free) animal models adversely affected intestinal barrier function, systemic immunity, and weight gain [21]. Also, the gut microbiota has remote modulatory effects on the nervous system of malnourished children through diverse molecular, neuroimmune, and biochemical pathways [22]. The gut–brain axis can mediate the interaction of gut microbiota and neurotransmitters (such as serotonin) or appetite-controlling hormones (such as leptin and ghrelin), which contribute to energy homeostasis

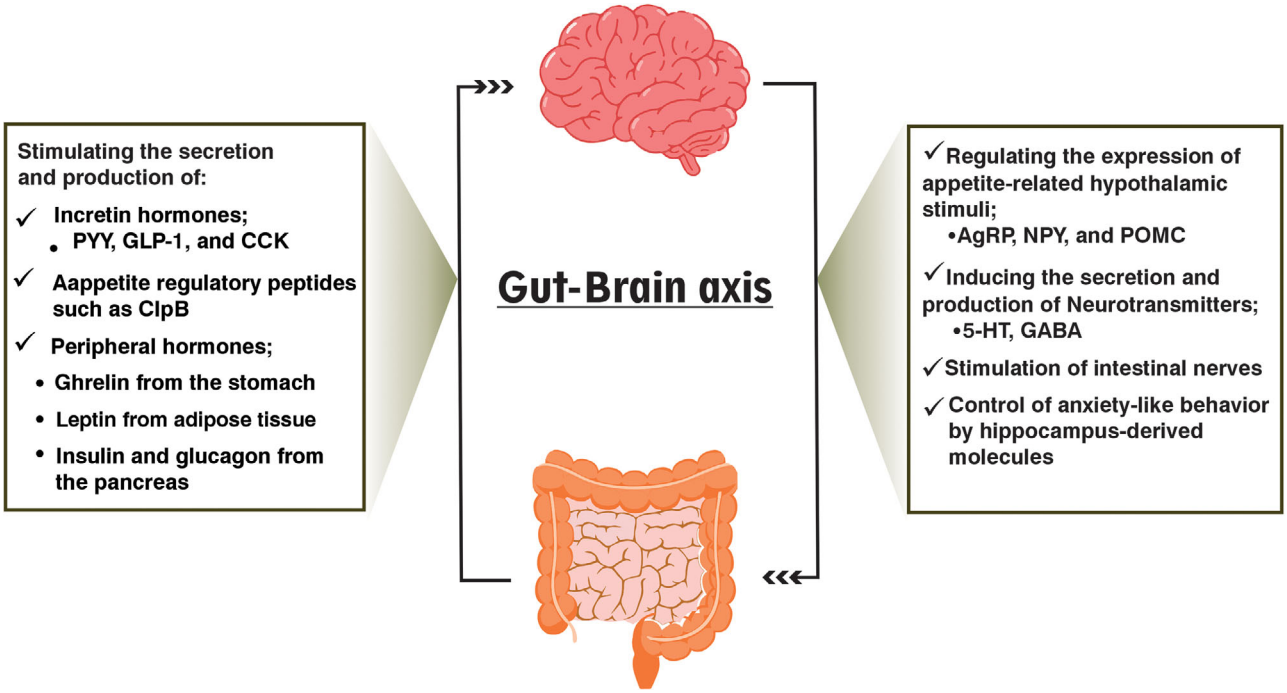

FIGURE 1 Interaction of gut microbiota and neural and hormonal signals in the appetite complex system. The function of the gut microbiota in gut–brain cross-talk affects appetite behavior. Hormonal and neural signals due to microbial metabolism reflect orexigenic and anorexigenic responses in children. Short or long-term effects of PYY, GLP-1, CCK, leptin, and insulin hormones lead to appetite suppression through the AgRP/NPY neural pathway. Conversely, ghrelin induce hunger through the POMC pathway. Also, transmitters, neurons, and peptide stimuli are involved in the development of bilateral communication. AgRP, agouti-related protein; CCK, cholecystokinin; ClpB, caseinolytic protease B; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide 1; 5-HT, serotonin, 5-hydroxytryptamine; NPY, neuropeptide Y; POMC, pro-opiomelanocortin; PYY, peptide YY.

[23]. Indeed, biocompounds derived from metabolically active gut microbiota, or so-called microbial metabolites, can interfere with the function of peripheral appetite hormones such as leptin (satiety hormone) and ghrelin (hunger hormone), which inhibit or induce appetite by affecting specific neurons, respectively (Figure 1). Vehapoğlu et al. studied the correlation of plasma levels of leptin-regulated neuropeptides with weight status in malnourished children. In this trial, a significant decrease in the concentration of alpha-melanocyte-stimulating hormones (anorexia neuropeptide) was reported in obese children. Similarly, agouti-related protein (orexigenic neuropeptide) concentration was low in underweight children [24]. Importantly, the cross-linking between gut, brain, and gut microbiota also leads to the regulation of dietary and behavioral patterns to protect susceptible hosts exposed to infection, inflammation, and antibiotic burden [25].

3 | ETIOLOGY OF CHILDHOOD MALNUTRITION

Childhood malnutrition is a global developmental crisis caused by following inappropriate nutritional patterns in the first years of life. Symptomatically, this clinical phenomenon can have negative effects on children's anthropometric characteristics, especially weight, height, and body mass index (BMI) of same-gender peers. According to the information of the National Center for Health Statistics, BMI at 85th percentile to less than 95th percentile and BMI at or greater than 95th percentile are common indexes to identify children who are overweight or obese, respectively. Meanwhile, nutrient deficiency in a long period (chronic condition) is associated with stunting and in a relatively short period (acute condition) with wasting of undernourished children. Also, underweight children experience a combination of acute and chronic conditions. Importantly, the severity of nutrient deficiency in acute malnutrition may be observed in the clinical forms of marasmus (wasting), kwashiorkor (nutritional edema), or marasmic kwashiorkor (wasting and edema). These forms represent the worst case of malnutrition, severe acute malnutrition (SAM) [26–28]. However, growing evidence supports the involvement of a set of etiopathogenic elements in the development of impaired energy homeostasis as the core of childhood malnutrition. These factors will be discussed in greater detail.

3.1 | Undernutrition

According to converging evidence, immunodeficiency and opportunistic infections are associated with reduced growth potential in children. Mechanistically, enteric pathogens can induce chronic inflammation and a common gastrointestinal disorder or so-called diarrhea by damaging the intestinal mucosa and cell structure. Diarrhea is one of the immediate determinants of undernutrition [29]. Supporting evidence is provided for the cause-consequence relationship of diarrhea disease with childhood undernutrition [30]. Importantly, the alteration of the gut microbiota as a result of vitamin B3 deficiency can in turn lead to inflammation and diarrhea through epithelial damage [31]. This digestive stimulant plays a remarkable role in undernutrition occurrence by increasing the catabolism of essential compounds for growth and reducing the absorption of nutrients. Reducing the efficiency of input energy, height and weight loss are also other manifestations of diarrhea [1, 30]. A systematic review of children with SAM showed that diarrhea caused by intestinal infections led to carbohydrates malabsorption (particularly lactose) which weight loss in children [32]. According to the reanalyzed study of Platts-Mills et al., *Shigella* was introduced as the first potential candidate for the pathogenesis of diarrheal disease in 2-year-old children. While enterotoxigenic *Escherichia coli*, *Campylobacter jejuni*, and typical enteropathogenic *E. coli* were also identified as other bacterial enteropathogens associated with diarrhea in underprivileged children [33].

One of the significant risks of intestinal infections is systemic immune suppression and increased susceptibility of undernourished children to lung infections, which play an important role in clinical exacerbation of condition. Respiratory infections such as pneumonia may have a negative effect on energy homeostasis through increased catabolism, frequent recurrence, occurrence of negative nitrogen balance, immunomodulation, and reduction in intestinal absorption [34]. Martorell et al. [35] and Brown et al. [36] have investigated the impact of respiratory infections on nutritional and growth disorders in children. The results of these investigations on suckling (breast milk) and weaned children during diarrhea showed a low energy intake in children, with the protective role of mother milk against negative consequences of diarrhea [35, 36]. Indeed, breast milk composition and breastfeeding period have a significant correlation with the control of intestinal infections and growth indicators of children, which the interaction of *Bifidobacterium infantis* with milk specific components may be the cause of this beneficial physiological adaptation [37]. Also, in a study in West Africa, acute lower respiratory tract infections resulted in 1/4 of weight loss (equivalent to 14.7 g) in young children on infected days [38].

Moreover, determining the origin of intestinal infections is a key issue in the pathophysiology of undernutrition. Unconfirmed microbial hygiene of food and water due to the intestinal pathogenic contamination can lead to the development of a subclinical condition known as environmental enteropathy (EE) [39]. EE can contribute to childhood stunting by immunomodulation and reducing the capacity of digestion and nutrient uptake as a result of damage to the intestinal epithelium [40]. According to a cohort study among slum populations, altered concentrations of fecal and plasma biomarkers related to local (gut) inflammation, intestinal permeability, and systemic inflammation in children exposed to enteropathogens were associated with growth retardation in the first 2 years of life [41]. Also, examining the mRNA transcripts numbers of immune coding genes as an indicator of EE status in rural Malawian children, revealed an increase in the urinary lactulose percentage and weak integrity in the gut barrier [42]. However, more clinical trials are needed to elucidate the intestinal pathology associated with childhood malnutrition and the differentiation of pathogens involved in EE induction.

It is noteworthy that non-infectious factors, such as high-risk genetic polymorphisms and hypermetabolic stress affected by hormonal and immune reactions, are also linked to the etiology of undernutrition through inducing tissues wasting and rapid consumption of energy reserves [2, 43].

3.2 | Overnutrition

It has been acknowledged that antibiotic consumption (once or repeated) during the prenatal period and in the first years of life especially in the first 6 months, is a threat to overweight and obesity in early life [44]. For example, maternal antibiotic administration is an approved pregnancy protocol to prevent infants at risk of premature infections such as group B *Streptococcus* infection [45]. Alteration of the balanced structure of the gut microbiota due to exposure to antibiotics is implicated in occurrence of childhood weight gain. Indeed, through placental circulation and breastfeeding, antibiotics prescribed for maternal infections from the third month of pregnancy onwards or delivery may have a decisive role on the alteration of early gut microbiota and weight status [46]. This microbial change in the intestinal space is associated with the imbalance of functionally active species, such as the increase of energy-extracting bacteria, the decrease of permeability-controlling bacteria, and dysregulation in metabolic pathways such as the liver axis

[47]. Cho et al. in the investigation of antibiotic-induced weight gain on C57BL/6J mice revealed that with administration of chlortetracycline, penicillin, and/or vancomycin, the abundance of Lachnospiraceae and the ratio of Firmicutes to Bacteroidetes increased compared to the control group, while the total size of the gut microbiota population was constant. Also, the significant effect of altered gut microbiota activity on the increase of fat-catabolizing fermentation products and increased intestinal hormone level promoting weight gain was observed [48]. As another animal study confirmed the role of low-dose penicillin and abnormal gut microbiota composition during the critical prenatal and postnatal periods on metabolic consequences such as fat mass level, hepatic expression of genes involved in adipogenesis, extrauterine fat deposition, and bone area with a change in bone mineral content [49].

In addition, the heritability of BMI is also an internal factor with a significant effect size on nutritional behaviors. Genetic predisposition to obesity is a critical risk factor in determining early life weight status which is affected by lifestyle and environment [50]. In turn, each of these external factors such as physical mobility, gender, high birth weight, parental awareness, strengthening with solid food before 4 months, temporary breastfeeding, and formula feeding can play a determinant role in the occurrence of childhood weight gain [51]. According to genomic studies, the fat mass and obesity associated (*FTO*) gene were suggested as a candidate gene for carrying high-risk obesity alleles with heritable phenotypic effects in sedentary children [52]. In the evidence presented by Tanofsky-Kraff et al., the presence of at least one risk allele related to the *FTO* genotype was associated with an increased risk of obesity and involuntary overeating in children [53]. The worrying issue is the possibility of intensification of the *FTO* gene expression from 4 to 11 years of age [52]. The widespread expression of *FTO* in the brain is closely related to children's positive response to appetitive stimuli and as a result changes in the quantity of energy intake [54].

4 | GUT MICROBIOTA DYSBIOSIS AND DIET

Gut microbiota composition stabilizes during adulthood under healthy conditions but may undergo fundamental changes due to factors disturbing the healthy gut microbiota and leading to imbalanced gut microbiota or dysbiosis. The gut microbiota dysbiosis is an adverse physiological phenomenon that is associated with a decrease in the density of commensal bacteria against the presence of pathogens [55]. Hereof, dysbiosis is implicated in the onset and progression of several metabolic and inflammatory diseases [56]. Since nutrition has a substantial impact on the formation and development of gut microbiota, inadequate or excessive nutritional intake may cause considerable alterations in the microbial balance [57]. Overall, dysbiosis in both undernutrition and overnutrition disorders reflects an irregularity in the density and ratio of gut dominant bacterial phyla and a decrease in gut microbiota biodiversity.

According to the pathophysiological evidence, low plasma levels of the neutral amino acid tryptophan, which are brought on by protein malnutrition or gut malabsorption brought on by angiotensin-converting enzyme 2 deficiency, are one of the main mediators of gut microbiota dysbiosis and the onset of several diseases, including colitis and diarrhea [58]. The De Filippo et al. study showed that African children's high-fiber diets were linked to a decline in the Firmicutes and an enrichment of the Bacteroidetes phylum. Additionally, compared to the European children, the prevalence of *Prevotella* and *Xylanibacter* genera, which include genes for hydrolyzing cellulose and xylan, and a decrease in *Escherichia* and *Shigella* pathogenic genera, showed a favorable impact on improving nutritional value and health [59]. Similarly, another study confirmed a positive relationship between following the Mediterranean diet (rich in starch and fiber), increased fecal level of fermentation product derived from carbohydrate-metabolizing species and higher abundance of Prevotella [60]. Studies have also shown the significant effect of high-fat and high-sugar diets on the disruption of the gut microbiome [61, 62]. According to a study on cecum samples of male mice fed with a high-fat diet enriched with *n*-6 polyunsaturated fatty acids, the low number of Clostridia, Firmicutes, and Lachnospiraceae and increased growth of Deferribacteraceae and Bacteroidetes can be the prelude of metabolic and intestinal inflammatory disorders [63]. Also, the study of Laffin et al. revealed that two-day consumption of a diet enriched with 50% sucrose was associated with a decrease in alpha diversity in adult wild-type mice [64].

5 | GUT MICROBIOTA DYSBIOSIS AND CHILDHOOD UNDERNUTRITION

Undernutrition is defined as not consuming enough nutrients and energy to meet individual needs for maintaining good health [65]. According to practical reports, the energy efficiency of less than 70% is disproportionate to child growth criteria [66]. Inadequate intake of protein energy or micronutrients like iron, vitamin A, and iodine, which are the most prevalent types of deficits in undernutrition, can lead to clinical signs of undernutrition [27]. Due to insecure nutritional conditions in developing countries, weaning and introducing solid foods in turn can be a

risk indicator for gut microbial balance of undernourished children [67]. Recent findings have shown that the gut microbiota of malnourished children is less diverse and mature than that of their healthy peers [68]. As Gatya et al., by comparing the gut microbiota of undernourished children with normal children aged 8–12 years, reported a decrease in bacterial diversity and an increase in the ratio of Firmicutes to Bacteroidetes. Interestingly, *Akkermansia*, a gut health promoting colonizer, was identified as an indicator species in the gut microbiota composition of the undernourished group [66]. Conversely, the study conducted by Hidalgo-Villeda et al on SAM mice, indicated a lower concentration of mucin degrader *Akkermansia*, an increase in bacteria attached to the terminal ileum, and altered mucosal layer morphology. Also, in the previous study, the reduction of T helper 17 (Th17)-inducing bacteria, *Candidatus arthromitus*, and as a result the imbalance of Th17 to regulatory T cells ratio was related to the physiology of SAM mice [67]. Another diligent study reported that *Ruminococcus gnavus* and *Clostridium symbiosum* can be able to prevent the growth-restraining effects of immature gut microbiota of undernourished children in germ-free mice [69]. Children who are undernourished lack the beneficial microbial communities and metabolizing genes required for the development of gut microbiota [70]. A study by Smith et al. proved that gnotobiotic mice receiving the gut microbiota of children with kwashiorkor experienced considerable weight loss and disruptions in their amino acid and carbohydrate metabolism [71]. While in the study reported from Mexico, a significant concentration of Lachnospiraceae family with high metabolic function related to food energy extraction was observed in stunted children compared to normal individuals. Indeed, this microbial alteration can protect children with stunting conditions who do not reach their full physical and intellectual potential [72]. According to a study by Schwarzer et al., *Lactobacillus plantarum* can activate signaling pathways in the liver to counteract the inhibitory effect of undernutrition on growth hormones [73]. Table 1 shows more human clinical trials on investigation of gut microbiota in malnourished children.

6 | GUT MICROBIOTA DYSBIOSIS AND CHILDHOOD OVERNUTRITION

Malnutrition or imbalanced nutrition in the form of overnutrition results from an excessive consumption of nutrients, which builds up body fat and harms health [53]. This form of absence of energy homeostasis is also characterized by overweight or obesity and the weight-for-height screening index namely BMI is defined as greater than or equal to 25 kg/m^2 (85th $\leq$ BMI $<$ 95th percentile) for overweight and greater than or equal to 30 kg/m^2 (BMI $\geq$ 95th percentile) for obesity. Due to the rapid change of anthropometric characteristics in children, BMI percentiles are used to appropriate assessment of children's weight with other age-matched and same gender peers [86]. According to the recent evidence, BMI status has a significant link with quantitative, genetic and metabolic changes of the gut microbiota (Table 1), which may often be indicated by the decline in the dominance of Bacteroidetes phyla and increased abundance of Firmicutes [87]. The significant concentration of Firmicutes in hosts with high BMI is proportional to the ability of members of this phylum in harvesting energy from complex compounds such as indigestible polysaccharides [88]. Therefore, overnutrition may be significantly influenced by how the gut microbiota interactions with other metabolic pathways, including glucose homeostasis and the metabolic activity of peripheral tissue [89]. Furthermore, intestinal and systemic function of diet-dependent gut microbiota is related to the regulation of fat metabolism. The secretion of a number of cytokine biomarkers from fat tissue leads to mild inflammation and as a result underlying disorders related to overweight and obesity such as high hypertension. In the first related study designed by Orbe-Orihuela et al., a positive relationship was reported between the serum level of tumor necrosis factor-α and the high density of Firmicutes in overweight and obese children [90]. Also, endotoxemia (the presence of LPS in the bloodstream) causing by leaky tight junctions and the disruption of catabolism of lipopolysaccharide can lead to one of the most common metabolic complications associated with obesity known as insulin resistance [91]. Studies in recent decades have reported the association of low diversity of gut microbiota with increased insulin resistance [92]. In Yuan et al. study on obese Chinese children with insulin resistance, a decrease in the Firmicutes to Bacteroidetes ratio and a remarkable increase in the Peptococcaceae members were observed compared to insulin-sensitive counterparts [93]. Moreover, weight gain may be associated with dysbiosis of specific genus and species in gut microbiota. For instance, *Staphylococcus aureus* with special increase in the stool samples of overweight children has identified as a candidate for the development of obesity in early childhood [94].

7 | METABOLOMICS AND CHILDHOOD MALNUTRITION

The gut microbiota has evolved with humans, acquiring traits, and properties that are essential for the maintenance of host physiology [26]. One of the microbial adaptations in response to the metabolic status is the production of

TABLE 1 Human trials on the role of the gut microbiota in the childhood malnutrition.

	Study	Study size	Study location	Main findings (malnourished versus control)
Undernutrition				
1	Monira et al. [74]	14 Subjects: 7 Malnourished, 7 Healthy controls	Bangladesh	↑ 9 Times *Escherichia* genus, ↑ 174 Times *Klebsiella* genus, ↑ Phylum Proteobacteria, ↓ Phylum Bacteroidetes
2	Gupta et al. [75]	2 Subjects: 1 Malnourished, 1 Apparently healthy	Kolkata	Families Campylobacteraceae and Helicobacteraceae were 35 and 12 folds higher
3	Tidjani Alou et al. [76]	15 Subjects: 10 Children with kwashiorkor, 5 Healthy controls	Nige and Senegal	↓ Diversity and lack of 45 bacterial species, ↓ Anaerobic species, ↑ *Streptococcus gallolyticus, Proteobacteria*, and *Fusobacteria*
4	Kristensen et al. [77]	87 Hospitalized subjects with symptomatic SAM	Uganda	↓ microbial α -diversity in non-edematous patients Predominance of Proteobacteria phylum with high abundance for Enterobacteriaceae in both SAM groups
5	Million et al. [78]	184 Subjects for meta-analysis: 107 Children with SAM 77 controls	Africa and Asia	↓ Ruminococcaceae, Erysipelotrichaceae), ↓ Actinobacteria (Eggerthella, Coriobacteriaceae) ↓ Firmicutes (Eubacteriaceae, Lachnospiraceae, ↓ Bacteroidetes (Bacteroidaceae), ↑ *Enterococcus fecalis, E. coli*, and *Staphylococcus aureus*
6	Ghosh et al. [79]	20 Children with different severity of SAM	India	↑ *Shigella, Enterobacter, Veillonella, Streptococcus, Faecalibacterium*, and *Escherichia* is a diagnostic criterion of gut microbiota in severe malnutrition
7	Dinh et al. [80]	20 Subjects: 10 Stunted children, 10 Controls	South india	↑ Bacteroidetes at 12 months of age, Enrichment of inflammogenic taxa: *Desulfovibrio* genus and Campylobacterales order
8	Campbell et al. [81]	72 Children with enteropathy related to growth failure	Gambia	Fecal neopterin concentration as a potential marker of gut inflammation is inversely related to growth
Overnutrition				
1	Karlsson et al. [82]	40 Children: 20 Overweight or obese, 20 Normal weight	Sweden	↑ level of Enterobacteriaceae, ↓ levels of *Desulfovibrio* and *Akkermansia muciniphilalike bacteria*, No significant differences for levels of *Lactobacillus, Bifidobacterium* or *Bacteroides fragilis*, Less bacterial diversity but with non-significant difference
2	Gao et al. [83]	126 Children: 63 Obese, 63 Normal non-obese	China	↑ *E. coli* ↓ *Bifidobacteria* ↓ *Bifidobacteria*/*E. coli* ratio
3	Seidell et al. [84]	84 Children: 30 Lean 24 Overweight, 30 Obese	Brazil	↑ *Lactobacillus* spp. and *B. fragilis* group and positive correlation with BMI in obese children
4	Borgo et al. [85]	61 Children: 28 Obese, 33 Normal weight	Italy	↓ *Faecalibacterium prausnitzii*, *Akermansia muciniphyla*, *Bacteroides/Prevotella* and significant positive correlation with BMI Z-score in obese group

biomolecules known as metabolites [95]. Since altered gut microbiota can lead to the onset or development of childhood malnutrition, their derived metabolites may also be closely linked to energy homeostasis. Metabolites derived from the dysbiotic species involved in many metabolic disorders and childhood malnutrition, such as short-chain fatty acids (SCFAs), trimethylamine *N*-oxide (TMAO), gamma-aminobutyric acid (GABA), bile acids (BAs), and glycine have the main role in the remote interaction of gut microbiota with other organs and biological path-

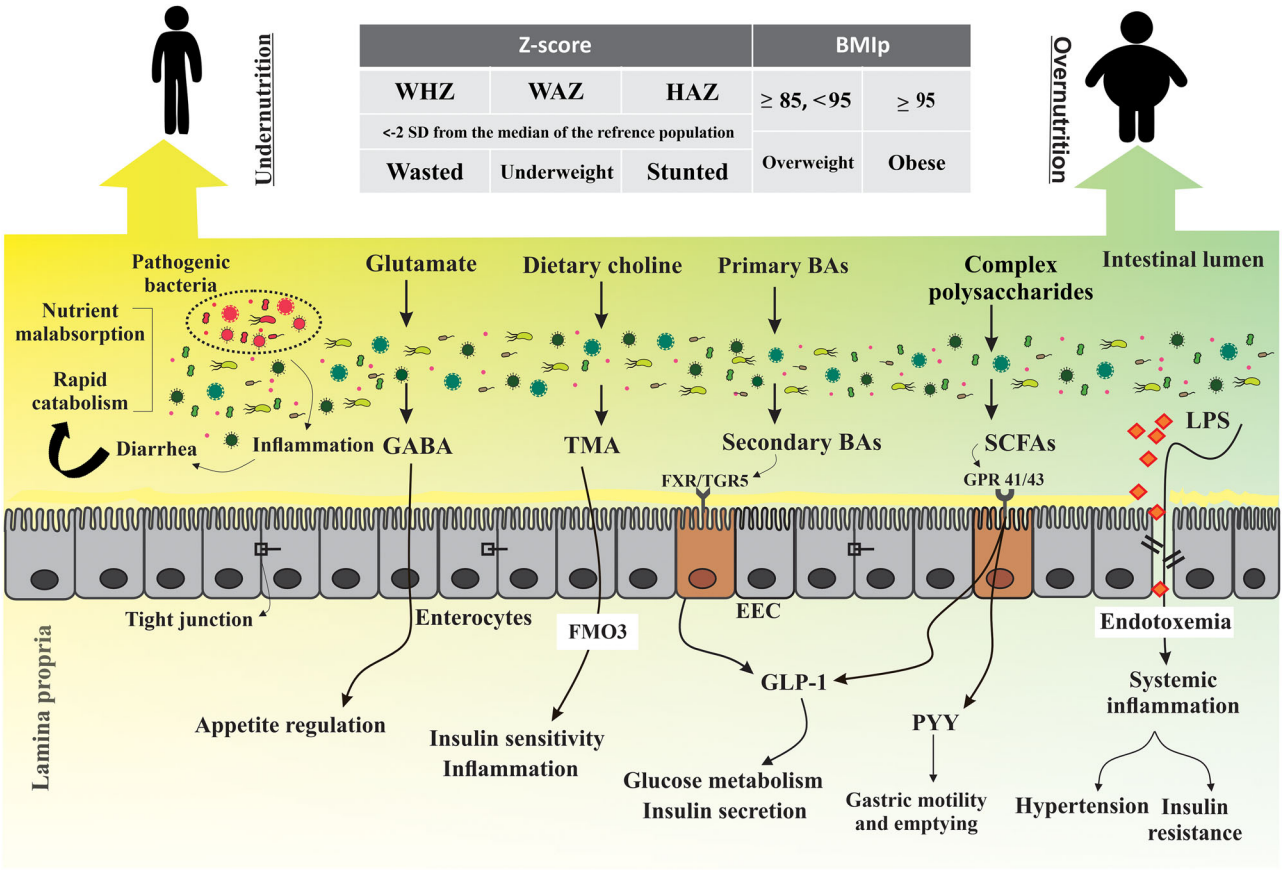

FIGURE 2 A schematic view of gut microbial products associated mechanisms involved in childhood malnutrition. The production level of microbial metabolites regulates their main function in undernutrition or protection against overnutrition. SCFAs derived from complex carbohydrates such as fiber lead to the regulation of glucose homeostasis, insulin sensitivity, and appetite through the hormones GLP-1 and PYY. Secondary BAs are produced by microbial removal of glycine or taurine amino acids from the structure of primary BAs, which have the similar mediates pathway and metabolic function as SCFA/GLP-1 through the FXR/TGR5 receptors. GABA, metabolized from glutamic acid, is an important factor in controlling appetite-related neural patterns. TMAO, as the final microbial metabolite produced from dietary choline, reflects important effects by controlling the inflammatory responses and insulin secretion. Bacterial LPS as a component of the outer membrane is associated with immune modulation and increased inflammatory responses (overnutrition). The indicators of weight-for-age Z-score (WAZ), weight-for-height Z-score (WHZ), height-for-age Z-score (HAZ), and weight-for-height percentile (BMIp) are used to evaluate the age-appropriate growth status of children. Z-score is deviations in attained growth from a reference population median. BAs, bile acids; EEC, enteroendocrine cell; FMO3, flavin monooxygenase 3; FXR, farnesoid X receptor; GABA, gamma-aminobutyric acid; GLP-1, glucagon-like peptide 1; GPR, G-protein coupled receptor; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids; TGR5, takeda G-protein receptor-5; TMA, trimethylamine; TMAO, trimethylamine *N*-oxide; PYY, peptide YY.

ways. The intermediary role of the mentioned metabolites explains the active function of the gut microbiota in the pathogenesis cycle of childhood malnutrition (Figure 2).

7.1 | Short-chain fatty acids

Through the fermentation process, saccharolytic bacteria can produce SCFAs, which are fast-absorbing metabolites with several beneficial bioactive properties. Due to bacteria's fermentation preference for indigestible complex carbohydrates over protein macromolecules, SCFA concentration is superior to hazardous chemical concentration in the human colon [14]. SCFAs (acetate, propionate, and butyrate) can regulate the intestinal permeability and the effectiveness of anti-inflammatory responses, as well as support the growth of beneficial bacteria like *Bifidobacteria* and *Lactobacilli* affected by lowering luminal colonic pH [11]. The SCFA concentration is an indicator of the amount of energy derived from macronutrients [26]. In a study conducted on undernourished and healthy Indonesian children, the concentration of dominant SCFAs such as acetate, propionate, and butyrate was low in undernourished children compared to the control group [96]. Additionally, one of the four main causes of children's mortality in SAM-affected children (the other three being diarrhea,

upper intestine inflammation, and systemic inflammation) was reported to be a low concentration of fecal SCFAs [97]. Also, based on a study on Indian children with SAM, the quantitative changes of *Roseburia* and *Butyrivibrio* due to insufficient level of SCFAs was related with impaired energy production. Therefore, the change in the level of SCFAs as a result of the gut microbiota dysbiosis affect the energy availability of children [79]. Although researchers have confirmed the increase of microbial SCFAs due to the extraction of excess energy from nutrient compounds in overweight and obese individuals [87], another physiological hypothesis is the possibility of a protective function of SCFAs against the metabolic consequences of overeating in children with high BMI [98]. Mechanistically, the intervention of SCFAs absorbed from the lumen in the metabolism of glucose and lipid and the consequences associated with malnutrition can be explained through different pathways: (I) substrate role for hepatic and intestinal gluconeogenesis and lipogenesis, (II) activating AMP-activated protein kinase (AMPK) in liver and muscle tissue, chained stimulator of catabolic metabolism (activation of peroxisome proliferator-activated receptor-γ coactivator 1-α [PGC1α] and activation of several transcription factors), and (III) stimulation of enteroendocrine hormone secretion through G-protein-coupled receptor (GPR)-41 or GPR-43 [26]. Interestingly, disturbances in the genetic pathways of the gut microbiome can also be the cause of inefficient energy extraction from indigestible food components, including glycans and phytates, which has been reported in animal models suffering from protein energy undernutrition [99].

7.2 | Trimethylamine *N*-oxide

TMAO is a microbial metabolite derived from choline, betaine, and carnitine. Basically, this metabolite is the final product of the catalytic activity of hepatic flavin monooxygenase 3 (FMO3) on the trimethylamine namely primary metabolic product of some gut species and phyla, for example, *Anaerococcus hydrogenalis*, *Clostridium sporogenes*, *Clostridium hathewayi*, *Clostridium asparagiforme*, *Desulfovibrio desulfuricans*, *Escherichia fergusonii*, *Edwardsiella tarda*, Firmicutes, *Proteus penneri*, *Providencia rettgeri*, and *Proteobacteria* [56]. Diet, gut microbiota, and FMO3 activity are main determinants of TMAO plasma level [100]. Based on various tissue studies, TMAO is a potential biomarker for metabolic disorders. A high level of TMAO were positively correlated with increased risk of obesity (visceral obesity), BMI, insulin resistance, and adipocyte inflammation [101]. In a 6-month intervention on the lifestyle (adherence to the Mediterranean diet and WHO recommendations) of prepubertal obese children, while introducing TMAO as the strongest metabolic classifier among the studied groups, its significant urinary reduction was noted [102]. Also, a study on insulin-resistant high-fat diet-fed mice revealed the positive effect of deletion or genetically inhibition of FMO3 on obesity [103].

In addition, it has been reported that in protein undernutrition associated with *Cryptosporidium* infection, disturbance in gut microbiota metabolism and increased urinary excretion of TMAO were among the infectious outcomes [104] Similarly, Komatsu et al. showed that casein deficiency in animal models had a positive correlation with increased expression of FMO and hepatic and urinary levels of TMAO [105]. Choline is also an important promoter in bone formation, fat transfer, cell structure, cell signaling, and neurotransmission. The relationship between serum choline and its derivative with growth and stunting status was investigated on Malawian children. In this study, a significant relationship was observed between the relative increase of betaine to choline, TMAO to choline, and low serum choline concentration with growth failure [106]. However, it has been reported that high intake of choline and increased TMAO resulting from the metabolic activity of the gut microbiota can counteract one of the consequences of kwashiorkor, called hepatosteatosis [107].

7.3 | Gamma-aminobutyric acids

GABA is an inhibitory neurotransmitter with stress management capability that is obtained from glutamate as a result of the decarboxylation reaction under the regulatory function of *Lactobacilli* and *Bifidobacteria* strains [108]. GABA is a key metabolite in the control of energy intake through activation of central neurons and induction of enteroendocrine cells. Hence, disruption in the GABA signaling pathways can prevent several metabolic functions such as hunger-induced appetite, neuropeptide tyrosine-induced hyperphagia, and post-weaning feeding [109]. In the study of Patel et al, it was proven that undernutrition was a factor for delaying (but reversible delay with aging) the development and functional growth of glutamate decarboxylase, an effective bio-transformer in glutamate fermentation [110].

Undoubtedly, changes in glutamate-fermenting microbial species are related to the level of circulating metabolites. For example, it has been reported that the reduction of *Bacteroides thetaiotaomicron* in obesity as well as weight loss (bariatric surgery) and serum glutamate concentration were negatively correlated [111]. Furthermore, in a study on transgenic mice, the association between GABA transporter overexpression, the significant development of hereditary obesity, and fat deposition were an unanticipated result despite normal growth [112]. However, the

possibility of GABA entering the central nervous system and the details of how appetite can be regulated by affecting the central nervous system, are questions that require more studies to answer [109].

7.4 | Bile acids

Primary BAs are cholesterol-derived products that are produced in the liver under the catalytic reactions of at least 17 enzymes. The regulation of the expression of some of these enzymes is also in the control of the gut microbiota. The amphipathic structure of conjugated primary BAs is the main and effective factor in the absorption of lipid-based nutrients from the intestine. Five percent of primary BAs remaining from ileum absorption made by deconjugation of bacteria with bile salt hydrolase activity (microbial resistance factor against bile toxicity, e.g., members of *Lactobacilli*, *Bifidobacteria*, *Clostridium*, and *Bacteroide)* enter the colon and then through a complex reaction directed by bacteria containing BA-inducible genes (*Clostridium*, *Eubacterium*, and Firmicutes) are converted into secondary BAs [113]. Zhang et al. investigated the alteration of BAs homeostasis in children with SAM. In this study, an increase in secondary BAs was reported in SAM children as a result of microbial activity and further deconjugation of primary BAs, and ultimately the possibility of damage to the human gut and liver [114].

Ileum damage and abnormal gut mucosa resulting in impaired enterohepatic circulation of BAs in young children with EE is one of the main reasons for the low level of total serum BAs ([12% ↓] a balance biomarker between gut input and hepatic extraction) and lack of liver disease [40]. Also, deficiency of BAs metabolism and the resultant malabsorption of lipid nutrients in undernourished children was consistent with reduced growth and severity of EE [115]. Conversely, supportive evidence confirms that homeostasis changes caused by alteration in the synthesis or transport of BAs by interfering with various metabolic pathways can lead to the development of obesity [116]. A transcription factor activated mainly by primary BAs and regulated by PGC1α (an activated receptor in the mentioned AMPK chain pathway) known as farnesoid X receptor (FXR) controls the synthesis of BAs by the rate-limiting enzyme (cholesterol 7 α-hydroxylase) [113]. The gut microbiota influence the lipid and glucose metabolism of the host through influencing FXR signaling [26]. According to a study by Parséus et al. on germ-free and normal mice, gut microbiota improved obesity caused by high-fat diet through FXR signaling [117]. In addition, TGR5 (membrane-bound GPR) mainly activated by secondary BAs is a leading factor in the activation of hormonal signals regulating metabolism [118]. For example, prevention of diet-induced obesity is the result of TGR5 function through control of the glucagon-like peptide-1 secretory response from intestinal L cells [119].

7.5 | Glycine

Glycine is a multi-role amino acid with the functions of regulating the secretion of immune biomolecules, facilitating the metabolism of fat-soluble nutrients, and controlling the response to nutritional stimuli. This nonessential amino acid in significantly low concentrations can cause metabolic crises and disrupted energy homeostasis by affecting the immune and digestive pathways [120]. Due to the microbial fermentation capacity, the gut bacteria use peptides and amino acids released from proteases or peptidases activity on proteins for their growth and metabolism [121]. The importance of this metabolite has increased since the days when lack of dietary protein was thought to be the main cause of severe malnutrition, especially the edematous type, and it was thought that alterations could be identified by checking the plasma level of amino acids [122]. The glycine is one of the three amino acids involved in the synthesis of glutathione (glycine, cysteine, and glutamic acid) that abundantly found in Gram-positive and negative gut bacteria such as *E. coli*, *Clostridium difficile*, *Clostridium perfringens*, and *Acidaminococcus fermentans* [121]. In a study on severely malnourished children, a significant decrease in glutathione concentration was observed in the subgroups of edematous, kwashiorkor, and marasmic kwashiorkor, but the failure of children's growth was not affected by this variable [123]. Low plasma level of glycine due to gut microbiota dysbiosis is associated with impaired signaling of obesity-related metabolic pathways. Also, the bioavailability of this protein building block in the liver may be reduced by the gut microbiota [124]. Interestingly, glycine is the major amino acid that participates in the conjugation of BAs before entering the bile and transferring to the duodenum [113].

8 | CHILDHOOD MALNUTRITION TREATMENT

8.1 | Engineered bacterial therapy

The metabolic programming and energy balance of the malnourished human can be improved by applying genetic alterations to the gut microbiota, which is thought of as the second human genome. Therefore, metagenomics or analysis of the entire genomic information of the gut microbiota becomes a specific preliminary step to target the framework of genetic techniques used to produce

biotherapeutic products [125]. Microbiome engineering aims to design candidate probiotics with the ability to signal to the immune system and providing index elements involved in many physiological disorders such as nutrients, antioxidants, and enzymes [126]. For instance, some strains of *E. coli* Nissle are known to be efficient probiotics for genetic innovations. The determined genomic map, analyzed gene interactions, immunity of strains, and short-term symbiosis are reasons for the priority of *E. coli* Nissle in genetically modified bacterial treatments. *E. coli* Nissle 1917 as an engineered bacterial model can have therapeutic activity in gut metabolic disorders [127]. Its recombinant strains by overexpressing satiety factor *N*-acylphosphatidylethanolamine can suppress obesity caused by high-fat diet, insulin resistance, and hepatosteatosis [127, 128]. Prevention of pathogen colonization (e.g., Enterococcal species and *Salmonella typhimurium*) and production of antimicrobial peptides are some of the functions using this engineered bioproduct in the improvement of gut microbiota [127]. In addition, *E. coli* Nissle SYNB1618 is another engineered strain to regulate the catabolism of the amino acid phenylalanine related to phenylketonuria disorder. In this genetic defect, adherence to a low-protein nutritional habits to maintain low brain or serum concentrations of phenylalanine may be associated with growth failure. Whereas, modified *E. coli* Nissle SYNB1618 responds to phenylalanine increase signals by simulating the metabolizing function of phenylalanine hydroxylase [129]. Importantly, recent trials have reported a positive correlation between phenylketonuria and increased BMI as a result of the children's tendency to follow carbohydrate-based diets [130]. Hence, engineered microbiota can be promising bioproducts to control the prevalence of childhood malnutrition.

8.2 | Diet therapy

The first stage in the treatment of childhood undernutrition is based on two main therapeutic diets; F-75 (low protein, low energy) and F-100 (high protein, high energy) or ready-to-use therapeutic food (RUTF; based on lipid) [131]. Due to the severe clinical condition of hospitalized children, ready therapeutic foods are prescribed in a planned manner. According to nutrition science, reductive adaptation, downregulation of metabolic-dependent functions, is one of the causes of high energy density intolerance at the beginning of diet therapy in children [132]. Hence, initially F-75 therapeutic milk is suggested for the relative stability of metabolic homeostasis, and then F-100 or RUTF which have a similar formula base, are substituted to compensate for growth failures [131]. The transition from F-75 to F-100 or RUTF is a critical and gradual period with significant physiological effects [133]. In a randomized controlled study on Bangladeshi children with SAM, observance of principles of the structured diet (F-75 to F-100) led to appetite regulation, edema clearance, and weight gain [134]. The base composition of therapeutic diets contains several mineral and vitamin (such as vitamin A), but targeted supplementation can help to improve the consequences of micronutrient malnutrition [135]. In a prospective review, the addition of formulated thiamine to the RUTF diet was concluded to promote immunity of critically ill patients with malnutrition [136]. Also, the cost of commercial products is a reason for the substitution of local formulas instead of standard samples in low-income countries [137]. In the study conducted by Hendrixson et al., oat-based RUTF compared to standard RUTF, resulted in improved anthropometric characteristics, increased growth rate, reduced probability of mortality and SAM persistence and hospitalization in African children [138]. Importantly, the timely access of outpatients (SAM without complications) to RUTF is one of the main factors in controlling nosocomial infections and management of malnutrition process [139].

However, if symptoms returned and the expected recovery did not occur, modifying treatment regimens by adding antibiotics or shifting focus to microbiota-based therapies may be needed. Investigating dietary habits and processing of microbial metagenomics and metabolomics data for targeted design a diet based on the specific characteristics of the altered gut microbiota in malnourished children is a progression step in diet therapy. Microbiota-directed complementary foods (MDCF) are regulated diets to normalize the abundance and function of the immature gut microbiota and treatment of malnutrition [140]. According to a double-blind trial conducted in Bangladesh, administration of affordable formulated foods in gnotobiotic mice and piglets carrying the gut microbiota of children with acute malnutrition resulted in the development of species involved in growth and several types of MDCF. The human part of this study also revealed that MDCF-2 type led to the gut microbiota restoration and the increase of physiological health-inducing plasma biomarkers [141]. It has also been reported that compared to RUTF, the introduction of MDCF to moderately malnourished children was associated with greater promotion of physical, neurological, and immune development and modulation of the gut microbiota [142].

8.3 | Antibiotics and childhood malnutrition

Antibiotics are the treatment priority of 10%–15% of children with severe malnutrition who did not respond favor-

ably to the ready and outpatient therapeutic diet [143]. The most effective solution introduced recently for children with severe malnutrition is β-lactam antibiotics, especially third generation cephalosporins, such as cefdinir [144]. In a study on children with SAM, the administration of amoxicillin or cefdinir was associated with recovery and reduced mortality as well as weight gain in recovered children [145]. The combined effect of two antibiotics, ampicillin and gentamicin, was to increase the chance of survival of SAM patients [146]. Although, the spread of clinical infections in hospitalized patients with severe malnutrition led to the routine prescription of antibiotics even for outpatients. This action aimed at prevention or facing suspicious cases is not an effective strategy because it results in the creation of resistant strains and worsens the treatment path [143, 144]. In addition, a wide range of conflicting studies have confirmed the relationship between the use of antibiotics and increased risk of overweight and obesity or the ineffectiveness of antibiotics on BMI change [44, 147]. However, it has been reported that the synergy of penicillin and oligofructose by modulating the gut microbiota had protected rats and their offspring against obesity effects [148].

8.4 | Novel pharmacological approaches to modify gut microbiota

A deeper comprehension of cutting-edge and treatment modalities is required since the incidence of childhood malnutrition is rising and has the potential to become epidemic. Microbiome-based pharmacological interventions of the gut microbiota with the goal of reprogramming is a promising method in contemporary medicine to alleviate the symptoms of malnutrition and prevent its long-term effects in adulthood.

8.4.1 | Probiotics

Probiotics, which are living, non-pathogenic microorganisms, can alter the gut microbiota. This has benefits for the host when used as directed, including improved immune and nervous responses, epithelial resistance against pathogens, and maintenance of gut barrier functions [149]. Foremost, probiotics are recommended supplements to restore disturbed metabolic stability in various forms of malnutrition [65]. There are several ongoing or completed clinical trials related to the effectiveness of probiotics on childhood malnutrition (Table 2). Underweight is one of the common clinical manifestations in severely malnourished children, which can be resolved by the effects of probiotics such as *B. breve* [65]. In a study by Camara et al., absence of *Methanobrevibacter smithii* in SAM children questioned the hypothesis of "gut microbiota immaturity". Indeed, *M. smithii* that has a strong potential in energy metabolism and weight homeostasis was reported in a lower percentage of children with SAM than in the control group, and decreased with age. According to this study, dysbiosis of gut microbiota in SAM does not correspond to immaturity but means the absence of *M. smithii* and the probiotic role of *M. smithii* in the treatment of childhood undernutrition was strengthened [150]. In addition, an in vitro study has reported that the probiotic strains *B. animalis* subsp. *lactis* INL1 and *L. plantarum* 73a (derived from mother milk) were able to modulate inflammation related adiposity and insulin resistance caused by *Escherichia* and *Shigella* genera, regulate the number of *Proteobacteria*, and increase the alpha diversity of gut microbiota in obese children [151]. The results of an animal study also supported the effectiveness of probiotic combination (*L. plantarum* KY1032 and *Lactobacillus curvatus* HY7601) compared to a single probiotic in diet-induced obesity. Based on this study, cooperation of both strains contribute to the host health by regulating the metabolic function of adipose tissue and liver and reducing or inhibiting the expression of fatty acid synthesis genes [152]. Probiotic therapy can show promising results in improving growth and height status as well as promoting mental reasoning in undernourished children with persistent diarrhea who suffer from zinc, vitamin A, and iron deficiency [1, 153].

Notably, only the tested dose exhibits the probiotics' features associated to effectiveness in various trials. The comparable conclusion for varied doses may not be applicable, despite no change in strain [154]. A number of other studies conducted to evaluate the effect of probiotics on early life malnutrition are listed in Table 3.

8.4.2 | Prebiotics

Prebiotics as a treatment solution of childhood malnutrition are selectively degradable nutrients by the gut microbiota that provide energy for the survival of the gut microbiota and the systemic health of the host. Nutritional supplements, fructo-oligosaccharides (FOSs), galacto-oligosaccharides (GOSs), and trans-GOSs are the principal type of prebiotics [170]. One of the effects of prebiotics' functional processes is to direct the undernutrition-induced disruption of the microbial balance toward a desirable combination with adequate metabolic capabilities. For instance, prebiotics-enriched lipid-based nutritional supplement can lead to a nine-fold increase in the relative abundance of *Bifidobacterium*, reducing pathogenic species such as *Enterobacteriaceae* and *Bilophila* and a

TABLE 2 Clinical trials on childhood malnutrition with probiotics and prebiotics (completed or ongoing).

Title	Conditions	Interventions	Primary outcomes	Country	Trial identifier
Probiotics					
Improvement of nutrition status, digestive conditions, and upper respiratory infections by using oral nutritional supplementation on children in Vietnam	Wasting, undernutrition, malnourished, malnutrition	Colos Gain	Improvement of anthropometric indicators (height, weight) and nutrient status (wasting)	Vietnam	NCT05570045
Improvement of nutrition status and digestive conditions by using oral nutritional supplementation on children in Vietnam	Undernutrition, wasting, malnourished	Kazu Gain Gold	Improvement of anthropometric indicatorsm (weight, height) and nutrient status (wasting), Improvement of digestive disorders and anorexia nervosa	Vietnam	NCT05551637
Effect of a three combined probiotics supplementation on weight loss in obese/overweight children	Childhood obesity	*L. salivarius* AP-32, *B. animalis* subsp. *lactis* CP-9, *L. rhamnosus* bv-77, mix probiotics powder, placebo	Change in waist circumference, body fat, BMI, blood pressure and sugar and lipids, liver function	Taiwan	NCT03883191
BIFI-OBESE: clinical trial in pediatric obesity	Childhood obesity	*Bifidobacterium breve* B632 and *Bifidobacterium breve* BR03, placebos	Change in glucose level and HOMA-IR index	Italy	NCT03261466
Prebiotics					
Comparing several strategies to manage moderate acute malnutrition among children from 6 to 24 months old	MAM	Inulin, FOS, fortified blended flour, azithromycin, albendazole	Recovery at 3 months due to the weight/size Z-score ≥−1.5 SD	Niger, Madagascar, Senegal, Bangui	NCT03474276
Nutritional intervention for the treatment of uncomplicated SAM	Child nutrition disorders	Nutritional intervention with RUTF and prebiotic GOS in combination, RUTF and Starch (placebo)	Nutritional cure	Pakistan	NCT05390437
Fruit and vegetable products enriched with fiber from potato starch with prebiotic properties for children and youth	Overweight and obesity, hypertension, NAFLD	Vegetable and fruit mousse (enriched with fiber from potato starch), dietary advice, and physical activity	BMI Z-score change	Poland	NCT05140070

HOMA-IR, homeostatic model assessment for insulin resistance; MAM, moderate acute malnutrition; NAFLD, non-alcoholic fatty liver disease; RUTF, ready to use therapeutic food. (Data from https://clinicaltrials.gov/).

TABLE 3 Some studies on childhood malnutrition using probiotics, prebiotics and synbiotics.

Compounds	Subjects	Duration	Main outcome	Reference
Probiotics				
Enterococcus faecium IS-27526	79 Underweight and normal pre-school children: 39 Probiotic recipients 40 Placebo recipients	90 days	↑ Salivary sIgA concentration, improving the humoral immune respons, ↑ Bodyweight in probiotic group	[155]
Bifidobacterium animalis subsp. *lactis*, *Lactobacillus rhamnosus*	400 SAM children: 200 Probiotic recipients 200 placebo recipients	8–12 weeks	↓ Number of days of with diarrhea in the outpatient treatment period (not during hospitalization) in the probiotic group	[156]
Lactobacillus reuteri DSM 17938, *Lactobacillus casei* CRL 431	494 Indonesian children from low socio-economic urban: 124 *L. reuteri* recipients 120 *L. casei* recipients 250 calcium milk recipients (in two groups)	6 months	↑ Significantly of weight gain and monthly weight and height velocities in *L. reuteri* group, Changes of WAZ in *L. reuteri* group, ↑ Significantly of monthly weight velocity in *L. casei* group	[157]
Lactobacillus rhamnosus GG	71 Undernourished children: 38 Probiotic recipients 33 Controls	3 months	↑ BMI and BMI Z-score, Prevention and reduction of most infections e.g., upper respiratory, urinary tract infections and gastroenteritis in probiotic group	[158]
Bifidobacterium pseudocatenulatum CECT 7765	48 Obese children with insulin resistance: 23 Probiotic recipients 25 Controls	13 weeks	↓ Body fat, ↑ Bacterial groups associated with the lean phenotype, Intervening in inflammatory markers	[159]
Lactobacillus salivarius Ls-33	50 Obese patients: 27 Probiotic recipients 23 Placebo recipients	12 weeks	↑ *Prevotella, Porphyromonas*, *Bacteroides* group/Firmicutes belonging bacteria in probiotic group	[160]
Prebiotics				
Galacto-oligosaccharides (Oligomate)	30 Children with SAM	48 days	Improvement of gastrointestinal symptoms and most blood parameters in the two-phase interval including hemoglobin level, levels of hematocrit and white blood cells, number of vomiting per day, etc. and as a result, reducing the risk of infection	[161]
Oligofructose-enriched inulin	24 Children with overweight or obesity: 12 Prebiotic recipients 12 Placebo recipients	16 weeks	Prebiotic group: ↓ Body and trunk fat percentage, ↓ Body weight Z-score, ↓ IL-6 and triglycerides serum concentration, ↑ Significantly of *Bifidobacterium* spp. ↓ *Bacteroides vulgatus*	[162]

(Continues)

TABLE 3 (Continued)

Compounds	Subjects	Duration	Main outcome	Reference
Oligofructose-enriched inulin	42 Children with overweight or obesity: 22 Prebiotic recipients 20 Placebo recipients	16 weeks	↓ Appetite, prospective food consumption and BMI Z-score in prebiotic group, ↓ Energy intake in older children in prebiotic group, ↑ Fasting adiponectin and ghrelin in prebiotic group	[163]
Oligofructose	79 Children with overweight or obesity: 40 Prebiotic recipients 39 Placebo recipients	12 weeks	Absence of remarkable difference in BMI, weight loss, and total body fat between the two groups	[164]
Synbiotics				
Bifidobacterium breve, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus*, + FOS	56 Children and adolescents with high BMI: 29 Synbiotic recipients 27 Placebo recipients	8 weeks	in synbiotic group: ↓ Rate of waist/hip, BMI Z-score, waist size ↓ Serum triglyceride, TC and LDL-C concentration	[165]
Bifidobacterium bifidum, *Bifidobacterium longum*, *Enterococcus faecium*, *Lactobacillus acidophilus*, *Lactobacillus rhamnosus*, + FOS	107 Children: 77 Synbiotic recipients (obese chidren) 40 Controls	1 month	in synbiotic group: ↓ BMI and weight ↓ Serum concentrations of TC, LDL-C and total oxidative stress Significant changes in anthropometric measurements	[166]
Bifidobacterium lactis HN019 + Oligosaccharide	624 Children: 312 Synbiotic recipients 312 Controls	1 year	↓ The risk of iron deficiency and anemia by 45% ↑ Weight gain	[167]
Leuconostoc mesenteroides, *Lactobacillus paracasei* ssp. *paracasei*, *Lactobacillus plantarum*, *Pediococcus pentosaceus* +inulin, oat bran, pectin, and resistant starch	795 SAM children: 399 Synbiotic recipients 396 Controls	33 days	No changes were observed in the recovery process of children with SAM including nutritional status and weight	[168]
Bifidobacterium breve, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei*, *Lactobacillus rhamnosus*, *Streptococcus thermophilus* + FOS	69 Mild to moderate undernourished children: 37 Synbiotic recipients 32 Placebo recipients	30 days	↑ Mean weight in synbiotic group, ↑ Significantly of BMI	[169]

FOS, fructo-oligosaccharide; LDL-C, low-density lipoprotein cholesterol; sIgA, secretory IgA; TC, total cholesterol.

remarkable increase in SCFAs dominates [171]. Meanwhile, some clinical trials that are currently underway clarify the other impacts of functional processes of prebiotics on childhood malnutrition (Table 2). Human milk oligosaccharides (HMO) are a complete and rich source of prebiotics fermentable by gut *Bifidobacterium* and *Bacteroides* spp. [172]. According to a cohort study of Malawian severely stunted children, the increase of anabolic output in nutrient utilization namely weight gain, bone morphology change, and liver, muscle and brain metabolism change has a direct correlation with the amount of sialylated HMO. Indeed, the growth of undernourished children is influenced by sialylated HMO with the management of gut microbiota [173]. Interestingly, prebiotics usually reach the distal parts of the colon before the metabolization processes and inulin-type prebiotics are able to increase the absorption of minerals, for example, calcium, magnesium, zinc, and iron from the colon [68]. Also, oligofructose supplement is able to increase satiety by affecting appetite regulating hormones and conversely decrease energy intake which is very important in overweight and obesity [174]. Prebiotics that are related to obesity have a prospective therapeutic role; because they can improve glucose tolerance and insulin resistance, reduce body weight and fat accumulation, and moderate intestinal permeability, endotoxemia, and inflammation [61]. In addition, prebiotics combined with zinc is an effective combination for shortening the period of acute diarrhea [175]. This therapeutic option has been examined previously for the recovery of Bangladeshi children with poor economic condition [176]. Table 3 presents other researches on the effect of prebiotics in childhood under- and overnutrition.

8.4.3 | Synbiotics

Synbiotic is a unique combination with probiotic and prebiotic properties in which the synergy of the selected prebiotic and probiotic component improve the growth of microorganisms and outcomes of gastrointestinal disorders and childhood malnutrition [154]. Many clinical evidences have confirmed the role of synbiotics in modulating the anthropometric features of malnourished children (as can be seen in Table 3). In a trial conducted on stunted children, the administration of synbiotic powder with *L. plantarum* Dad-13 and FOS showed the increased abundance of *Lactiplantibacillus plantarum* and *Bifidobacterium* and the decrease of *Enterobacteriaceae* which targeted the protein intake and carbohydrate and increased the weight and height in the under five groups [177]. According to a trial by Xuan et al., synbiotic containing *Lactobacillus paracasei* NCC2461, *Bifidobacterium longum* NCC3001, and inulin and FOSs by promoting the immune function and IgA level plays a significant role in prevention of common infectious diseases and improvement of nutritional status (level of vitamins and minerals) and growth (weight and height) [178]. Another possible therapeutic mechanism of the synbiotic supplement is to increase the amount of SCFA and regulate digestive, immunity, and appetite pathways [177]. Symbiotic-target obese children may also experience anti-obesity effects such as changes in anthropometric characteristics (waist circumference and BMI Z-score) and body fat [179].

A mixture of prebiotics and probiotics are thought to elicit more potent clinical responses compared to their single biofunction [55]. Notably, the generalization of this idea to childhood malnutrition requires more investigations. Recently, Nuzhat et al. have shown that infants supplemented with *B. infantis* EVC001 gained more body weight than recipients of synbiotic combination of lacto-*N*-neotetraose and *B. infantis* EVC001 [37]. Hence, the priority of research on the formulation of potential synbiotics is identification of functional probiotic strains, prebiotic composition, optimal dosage, and the possibility of therapeutic product effectiveness under in vivo conditions with maintaining the host health [154].

8.4.4 | Postbiotics and paraprobiotics

Biofactors released or produced with structural diversity as a result of the metabolic activity of probiotics are extracted by various mechanical and chemical methods. These derivatives are known as postbiotics. Since postbiotics do not contain any living bacteria and hence do not pose any significant risks to human life, they may either directly or indirectly have probiotic-like effects on the host health [180]. Rocha-Ramírez et al. have reported that heat-killed *Lactobacillus casei* IMAU60214 promoted the immune response of macrophages derived from monocytes of target groups including malnourished infected children [181]. Postbiotics are also able to prevent obesity by reducing hepatic insulin resistance and activating transcription factors that regulate glucose intolerance and adipose tissue inflammation [182].

In addition, paraprobiotics are microbial extracts of intact non-viable cells which along with postbiotics show the therapeutic role of probiotics even in non-living form [183]. According to the animal study reported by Schwarzer et al., the peptidoglycans of *L. plantarum* LpWJL strain can activate anti-stunting and growth promoting responses by inducing the biological function of the intestinal nucleotide-binding oligomerization domain 2 receptor [184]. Another animal study in immunocompromised malnourished mice, demonstrated for the first

time that nonviable *L. rhamnosus* CRL1505 and its cell wall and peptidoglycan can resist pneumococcal respiratory infection by modulating lung and systemic immunity [185]. According to animal and human evidence, passive microbial treatment is often effective in improving the disorders by appropriate modulation of immune responses such as regulating the expression and production of cytokines, anti-inflammatory, and antimicrobial functions. However, in order to be certain that postbiotics and paraprobiotics are helpful, further confirmatory studies are required due to the paucity of clinical data on pediatric malnutrition.

8.4.5 | Fecal microbiota transplantation

Fecal microbiota transplantation (FMT) is the transmission of healthy filtered fecal solution to improve the gut microbiota in recipient patients [186]. The ability to transfer the complete gut microbiota and metabolites produced to the patient makes this therapeutic method unique [187]. FMT basically exhibits positive effects in the management of recurrent *C. difficile* infections (three or more times) [186]. Meanwhile, differences in the fecal microbiota of healthy and undernourished or overnourished children support the potential of FMT in the treatment of malnutrition. For example, in transplantation the fecal microbiota from obese children to germ-free male Swiss Webster mice, an increase in average body weight and total feeding efficiency with low levels of butyric acid and isobutyric acid in the cecum were reported [188]. According to the methodology of many clinical trials, gnotobiotic mice are index models for receiving the fecal sample of malnourished children to investigate the metabolic consequences of disrupted gut microbiota. The assessment of these animal models have indicated that the fecal transmission of gut microbiota from malnourished children is associated with (I) the effect of the age of the donor child on the growth rate, (II) maintaining the nature of the discriminatory species associated with growth after transfer, (III) widespread systemic effects of growth-discriminatory species, and (VI) the potential to cause EE conditions under special diet by IgA-targeted microbes especially *Enterobacteriaceae* members [189]. In addition to modifying the gut microbiota, FMT can improve the intestinal barrier, inhibits pathogens translocation, and modulates immunity accordingly [190]. Based on a study conducted on children with SAM (kwashiorkor), 12 identified species from the phyla Firmicutes, Bacteroidetes, and Actinobacteria with probiotic competence, that is, production of SCFAs, antioxidant metabolism, and antibacterial potential were introduced for safe fecal transplantation in healthy children [76]. Nevertheless, human studies on the therapeutic effect of FMT on childhood malnutrition are rare.

9 | CONCLUSIONS

The active biological function of the gut microbiota is the basis of clinical interventions associated with nutritional status and growth phenotype in children. This function is closely related to microbial components and metabolites, the response of vital body systems, and the participation of multiple environmental and physiological factors. Childhood malnutrition and gut microbiota interactions have shown that an unbalanced microbial environment is crucial to the development of the disease. Therefore, restoring gut microbial homeostasis is the key to treating this condition. We concluded that emerging microbiome-based approaches are possible therapy choices for childhood malnutrition due to their promise of therapeutic benefits for children, who are the most vulnerable members of society, despite some contradicting findings and the need for additional research.

AUTHOR CONTRIBUTIONS

Conceptualization: Sevda Zoghi, Fatemah Sadeghpour Heravi, and Hamed Ebrahimzadeh Leylabadlo; *Writing of original draft preparation*: Sevda Zoghi; *Writing—review and editing*: Fatemah Sadeghpour Heravi; *Reviewed the manuscript*: Zeinab Nikniaz, Masoud Shirmohamadi, and Seyed Yaghoub Moaddab; *Conceived the idea for this manuscript and edited subsequent drafts and supervision*: Hamed Ebrahimzadeh Leylabadlo.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data sharing not applicable to this article as no datasets were generated during the current study.

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