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REVIEW ARTICLE

Harnessing the power of probiotics to enhance neuroplasticity for neurodevelopment and cognitive function in stunting: a comprehensive review

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ABSTRACT

Background: Stunting become a global concern because it's not only affecting physical stature, but also affecting on neurodevelopment and cognitive function. These impacts are resulting in long-term consequences especially for human resources, such as poor-quality labor, decreased productivity due to decreasing of health quality, including immunity and cognitive aspect.

Discussion: This comprehensive review found that based on many studies, there is an altered gut microbiota, or dysbiosis, in stunted children, causing the impairment of brain development through Microbiota-Gut Brain Axis (MGB Axis) mechanism. The administration of probiotics has been known affect MGBA by improving the physical and chemical gut barrier integrity, producing antimicrobial substance to inhibit pathogen, and recovering the healthy gut microbiota. Probiotics, along with healthy gut microbiota, produce SCFAs which have various positive impact on CNS, such as increase neurogenesis, support the development and function of microglia, reduce inflammatory signaling, improve the Blood Brain Barrier's (BBB's) integrity, produce neurotropic factors (e.g. BDNF, GDNF), and promote the formation of new synapse. Probiotics also could induce the production of IGF-1 by intestinal epithelial cells, which functioned as growth factor of multiple body tissues and resulted in improvement of linear growth as well as brain development.

Conclusion: These properties of probiotics made it become the promising and feasible new treatment approach for stunting. But since most of the studies in this field are conducted in animal models, it is necessary to translate animal data into human models and do additional study to identify the numerous components in the MGB axis and the effect of probiotics on human.

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Introduction

Stunting has been a major public health concern especially in under and developing countries since its devastating physical and cognitive impairment on the individuals who are affected as well as socioeconomic decline. The 2020 report by UNICEF-WHO-World Bank Group Joint estimated that 149.2 million children under 5 years old are classified as stunting, and contributes about 22.0% of total population of children under 5 globally. Most of these stunting children live in the lower-middle income countries in Asia and Africa [1]. Although there has been a decrease trend in the number of stunting cases, it did not meet the 2030 target of stunting decline by 50%. The evaluation of this target in 2017 found a required annual average rate of reduction (AARR) of approximately 4% per year. Current global trends suggest that the AARR of 2.3% per year, which indicates insufficient progress [2]. According to the Global Nutrition Report (2020), Indonesia has the third highest prevalence of stunting in the world in children under the age of five [3]. The 2018 Riskesdas data shows that the prevalence of stunting in Indonesia is 30.8%, higher than the prevalence of stunting globally. This indicates that an estimated 1 in 3 children under 5 years in Indonesia is stunting. This number has decreased by 6.4% compared to the number of cases in the previous 5 years (2013), but is not sufficient to meet global criteria [4,5].

Children who are stunting have shorter heights or body lengths than they should. A length or height that is less than minus two standard deviations from the WHO's median child growth standard indicates the presence of this condition [6]. Early childhood or the early years of childhood are frequently referred to as The Golden Age (0–5 years), the time when all

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advantages or privileges enjoyed at the time were not intended to be repeated. Early age periods are considered to be an age of gold during which rapid progress was made in all spheres of human development—physical, intellectual, emotional, linguistic, and social. The development of skills, particularly the development of the motor system, happens very quickly. Children begin to be able to accept skills like the fundamentals for knowledge formation and thought processes in the early years of life, starting at the age of 3 [7]. Stunting can have a negative impact on a person's physical growth, brain development, cognitive function, motor development, and motor activity [6]. According to Probosiwi et al. (2017), it is found that children with and without stunting exhibit different developmental patterns, with a *p*value of 0.033. Following in order, social and interpersonal development (87.5%), language (75%), gross motor skills (25%) and fine motor skills (12.5%) are developmental domains in stunting children that are suspicious [7]. Other study shows that although there is nonsignificant difference on cognitive aspects of stunting children and undernourished children with normal stature, but there is a trend toward lower median score percentiles in the stunting group in the motor (median (range) 1 (0.1–75) vs. 4 (0–79); p 0.183), cognitive (12.5 (0.1–75) vs. 16 (0.1–99.9); p 0.550), and adaptive behavior (7 (0.1–75) vs. 12 (0.1–58); p 0.657) domains [8]. This decline on cognitive function leads to decreased productive capacity and poor health, and an increased risk of degenerative diseases such as diabetes, so that in long term could affect the economic growth [9].

There are multiple attempts in order to reduce the number of stunting cases. The discovery of Microbiota-Gut Brain Axis (MGB Axis) which allows the bi-directional communication between gut and the brain has been bringing the new perspective in order to prevent, diagnose, and treat various health condition [10]. There is a difference of gut microbiota between stunting and healthy children. Even though the amount of food consumed is sufficient, changes in the composition and imbalance of the intestinal microbiota or the loss of one of the non-pathogenic microbiota results in the disruption of the process of food digestion and the production of different vitamins, thus can alter the MGB axis, causing serious problem [11]. One of conditions causing this disruption of healthy gut microbiota in stunting called Environmental Enteric Dysfunction (EED) [12].

The complexity of the relationship between socio-environmental and biomedical elements impacting cognition, especially throughout childhood, highlights the significance of an innovative method and plan to maximize cognitive development [13]. Among biomedical elements (e. g. fatty acids, iron, and iodine), there is rising interest in how probiotics can optimize cognitive development. There are various way how probiotics are able to induce neuroplasticity and improve neurodevelopment and cognitive function. Probiotics supplementation may promote the growth of beneficial bacteria that can boost the production of short chain fatty acids (SCFAs) [14]. SCFAs have a variety of systemic effects, including as anti-inflammatory properties that help maintain the blood-brain barrier's integrity, promotion of brain-derived neurotrophic factor (BDNF) and glial-derived neurotrophic factor (GDNF) production for neuronal and glial growth, neuroprotection, and modification of synaptic connections [15]. Another mechanism how probiotics could promote cognitive function through the activation of NOD2 in intestinal wall cells and production of IGF-1 [16]. IGF-1 has beneficial properties toward neuroplasticity and brain development through re-innervation, inducing potent augmentation of excitatory synaptic transmission, promoting dendritic growth and spine density, enhancing activation of high-voltage-activated calcium channels, and has acute effects on L and N-type calcium channel currents [17]. This article aimed to explore and summarize the effect of probiotics as neuroplasticity agent for neurodevelopment and cognitive function in stunting, highlighting the biomedical mechanisms of this topic.

Impairment of neurodevelopment and cognitive function in stunting

Early cognitive development includes the growth of thinking, attention, memory, and problem-solving skills, all of which aid children in understanding their environment [18]. Different ages mark the development of cognitive abilities, receptive and expressive language, and socioemotional skills. Early childhood is the time when the brain develops most quickly, with many skills continuing to develop in later years [19]. This development supports the acquisition of cognitive, linguistic, and socioemotional skills. Because of the rapid progression of several neurologic processes, such as synapse formation and myelination, the developing brain is especially susceptible to nutrient deficiency between 24 and 42 weeks of gestation. Rapid brain development in the first two years of life in healthy infants is well-documented; this time frame is also essential for long-term neurodevelopment [20]. Some studies demonstrated the negative impact of stunting towards brain development and cognitive function. Arini et al. (2019) found that there is an

association between stunting and disorders of cognitive and motor development. This was demonstrated by the values of the Spearman rho test for children's fine motor development (sig = 0.006) and cognitive development (sig = 0.044) [21]. Another study conducted in Ethiopia which assess the cognitive function of stunting children (5 and 8 year old) shows that stunting children scored 16.1% less in the Peabody Picture Vocabulary Test and 48.8% less in the Quantitative Assessment test at the age of eight, both statistically significant at $p < 0.01$ [22].

Stunting is one of the major risk factors for not reaching full developmental potential, along with inadequate cognitive stimulation, iodine deficiency, and iron-deficiency anemia. Stunting children have delayed behavioral maturation in infancy, are less likely to enroll in school or enroll later, tend to achieve lower academic standards, and have less cognitive ability than non-stunting children. Additionally, children who are stunting are less exploratory, more apathetic, and have altered physiological arousal [23]. Nutritional deficiency is linked to structural and functional brain dysfunction, as well as a wide range of cognitive deficiencies. Chronic malnutrition, specifically protein malnutrition, in the CNS can cause tissue damage, disordered differentiation, a decrease in synapses and synaptic neurotransmitters, a delay in myelination, and a general slowing of dendritic arborization development in the growing brain [24]. There are anomalies in the temporal sequences of brain growth, which disrupt the creation of neural networks. Long-term changes in brain function have been described, which may be related to long-term cognitive impairments caused by malnutrition [25].

In the perspective of neuroimaging studies, it has been found that there are some differences between the healthy and malnourished children. The study using EEG by Taboada-Crispi and colleagues, found that when comparing the same previously malnourished children to controls, there is significant differences in the z spectra. Increased theta (3.51, 4.68, and 5.07 Hz), alpha 2 (13.28 Hz), and beta (13.67-18.36 Hz), as well as a decrease in alpha 1 (8.98 Hz) wave, were among these differences [26]. One of the few controlled studies employing MRI to examine the neurological effects of early childhood malnutrition in Chilean high school students found that both genders had substantial cerebral atrophy, or decreased brain volume, that persisted up to 18 years after malnutrition exposure [26]. In an RCT study in Guinea-Bissau, the cerebral blood flow of children with malnutrition was assessed using functional Near-Infrared Spectroscopy (fNIRS) as a biological sign of cognitive function impairment. The cerebral blood flow was significantly correlated with cognitive performance, and children with malnutrition showing lower cerebral blood flow compared to control group [27].

The microbiota-gut brain axis

The huge population of bacteria (10–100 trillion) that inhabit the human body is referred as the microbiota. These bacteria commonly found in the gastrointestinal (GI) tract which contains the bulk of microbial colonies, and also can be found in skin, upper respiratory tract, genitourinary tract, and other mucosal surfaces of the body [28]. The number of these bacteria exceeds the quantity of eukaryotic cells in the human body, roughly 10–100 times more [29]. Mammals' gut become colonized by microbes very early in life, right after birth, primarily through the vaginal canal [30]. The microbiota in the human gut is balanced, with two main phyla, Bacteroidetes (including Bacteroides) and Firmicutes (e.g. Lactobacillus, Clostridium, and Enterococcus), composing 70–75% of the total phyla [31]. Less common phyla include Proteobacteria, Actinobacteria, Fusobacteria, and Verrucomicrobia. Several conditions early in life (especially the channel for delivery and as we mature) can have an impact on the composition of these bacteria. The host's health, including the host's food, genetics, environment, exposure to medications and antibiotics, and other lifestyle factors, affects the gut microbiota [32]. The gastrointestinal microbiota plays a dynamic role in a variety of biological processes that take place inside the human body, including regulating the host's neuroimmune system's development and operation as well as strengthening the gastrointestinal epithelial barrier and preventing pathogen invasion [33]. Since the host and gut microbiota interact in a complicated way, if this interaction were to be disrupted, microbiota might either cause or contribute to disease [29].

Recent studies demonstrated the relationship of microbiota in GI tract and human brain, known as the Microbiota-Gut Brain Axis (MGB Axis), a mechanism of bidirectional neurohormonal communication, connects the host's brain and gut functions [34]. The gut-brain axis' bidirectional relationship principally reveals how signals from the gut microbiota affect brain activity and how signals from the brain alter GI tract physiology and gut bacteria activity [35]. Gut microbiota could affect central nervous system (CNS) through various pathways. Gut microbiota produces various byproducts and metabolites such as lipopolysaccharide (LPS), peptidoglycan, and flagellin, are recognized

by pattern-recognition receptors (PRRs), such as Toll-like receptors (TLRs), NOD-like receptors (NLRs), or RIG-1-like receptors (RLRs), inducing production of cytokines and hormones by gut epithelial and immune cells and acting as a neurotransmitter in the CNS [36]. Traditionally, the recognized channels of communication include the neural pathway made up of intrinsic branches of the enteric nervous system (ENS), the extrinsic parasympathetic (primarily represented by the vagus nerve) and sympathetic branches of the autonomic nervous system (ANS), as well as the immune, endocrine, and humoral pathways [33].

The human brain has a remarkable ability to rearrange itself, a mechanism called neuroplasticity. The ability of the nervous system to alter its activity in response to intrinsic or external stimuli by changing its structure, functions, or connections is known as neural plasticity, also known as neuroplasticity or brain plasticity [37]. Neurogenesis, cell migration, adjustments to neuronal excitability, and alterations to existing connections are only a few of the basic mechanisms that contribute to neural plasticity [38]. Long-term potentiation, or LTP, is an example of Hebbian plasticity in synaptic plasticity, which involves a change in synaptic strength mediated by changing neuronal activity after the start of stimulation. Homeostatic plasticity, on the other hand, is a negative feedback loop in response to increased neuronal activity. Homeostatic plasticity involves mechanisms like the control of neuronal excitability or the stabilization of the total synaptic strength, whereas Hebbian plasticity involves lifetime modifications [39]. By training and rehabilitation, which can alter and improve these neural plasticity processes, brain plasticity can result in an extremely high degree of recovery. This neuroplasticity properties could also be promoted *via* MGB axis, in which the modification or restoration of healthy gut microbiota as the approach to improve various condition related to CNS disorder, including cognitive function [10].

EED in stunting cases

Stunting is a condition resulted from complicated interaction of multiple factors. It divided into 3 factors, 1) basic factors (family income, parents' education), 2) direct factors (maternal fertility, birth spacing, mother's height, baby's weight at birth, diversity of foods consumed, and infectious diseases), as well as 3) indirect factors (poor sanitation, clean water, vaccination coverage, maternal antenatal visits, and suboptimal breastfeeding) [11]. Poor sanitation is one theory for why this might be happening, as prolonged pathogen exposure causes a subclinical change in gut structure and function. Environmental enteropathy, tropical enteropathy, or more recently environmental enteric dysfunction are terms used to describe the ensuing condition (EED). EED commonly defined as disturbance marked by increased permeability, crypt hyperplasia, villous atrophy, and inflammatory cell infiltration in the gut [40]. The gut immune system is thought to be driven by T-cell-mediated hyperstimulation through a process that keeps it in an inflammatory, hyperimmune state after continuous exposure to enteric pathogens [41]. This normal immune response causes the structural changes in the gut discussed above as well as increased intestinal inflammation and permeability, which disrupt the gut immune response, limit nutrient delivery, absorption, and utilization, and ultimately result in nutritional deficiencies [12].

The pathophysiology of EED consisted by five highly interconnected mechanism: increased intestinal permeability with the translocation of bacteria or antigens, malabsorption, gut inflammation, hormonal disturbance, and disruption of the gut microbiome [42]. The gut lumen and the systemic circulation are physically separated from one another by a healthy intestine. It is possible for bacteria or their metabolites to enter the systemic circulation when the gut architecture is disrupted in EED and tight connections between cells are broken down [43]. This could result in a systemic inflammatory state and subsequent immunological activation, both of which could have negative implications on one's health [44]. The damaged of intestinal architecture also results in shorter and blunted villi and crypt hyperplasia, both of which reduce the absorptive intestinal surface area. A mismatch between the availability and consumption of micronutrients and macronutrients could emerge from deficiencies in the absorption of vital nutrients caused by this reduction of surface area [45]. High C-reactive protein levels are linked to small intestinal inflammation in EED, which may also be accompanied by the release of cytokines that suppress appetite and food intake and prevent the generation and activity of chondrocyte growth factors [46]. EED may also be associated with the alteration of healthy gut microbiota, also known as enteric microbiome dysbiosis. EED results in reduce of the surface area of the gut and causes severe enteric inflammation, which affects the ecological niches that support particular bacterial taxa. The prolonged exposure of pathogenic bacteria also contributes to this enteric dysbiosis [47]. Maintaining a balanced gut microbiota is essential for the proper operation of gut physiology and the intricate signalling of the MGB axis, which affects the host's general health. Dysbiosis could negatively affect CNS function,

neurodevelopment and cognitive function, which in turn, making the stunting children have a worse prognosis [10].

The therapy of EED is riddled with problems. First, it is challenging to diagnose EED in a specific child since the lack of reliable point-of-care biomarkers. Furthermore, there isn't strong proof from clinical trials that certain therapies can cure or lessen the symptoms and signs of EED [12]. The mainstay of preventing EED is to 'clean' the environment because the disorder has environmental roots. Several large interventional trials have focused on ways to reduce environmental contamination through water, sanitation, and hygiene (WASH) program [48]. Community-wide improvements in water and sanitation facilities are likely to lower the burden of EED. However, these findings imply that individual or household-level WASH interventions may not provide sufficient protection against environmental contamination to prevent or treat EED [49]. The inadequate resource in lower and middle income countries (LMICs) resulted in greater challenge in making a large scale community environmental program, thus more feasible approach is needed in order to solve it. Due to the fact that obtaining 90% coverage with the top 10 nutrition-specific treatments will only result in a 20% reduction in stunting, current interventions, such as exclusive breastfeeding (EBF), have little effect on growth [50]. Since there is gut microbiome dysbiosis in EED, and microbiota colonization happens in childhood, focused intervention at this crucial moment may have an impact on linear growth [51]. Aside from linear growth, the dynamics of MGB axis also allows the restoration of healthy microbiota to have a positive implication toward short- and long-term neurodevelopment. The administration of probiotics as the robust intervention has been explored in several studies, resulting in promising effect for both linear growth and neurodevelopment [52].

Probiotics: new approach to promote neuroplasticity

Probiotics are living microorganisms that, when given in sufficient quantities, boost the host's health [53]. Probiotics, which are mostly found in human intestines, can benefit the host by preserving the balance of intestinal microorganisms [54]. The initial probiotics that were readily available only contained one type of bacterium, often one from the *Saccharomyces* or *Lactobacillus* genera. The type and quantity of microbes in later probiotic formulations increased, ranging from 10^8 to more than 10^{10} organisms [55].

Probiotics is a new promising approach for management of stunting which focused on impact to neuroplasticity for neurodevelopment and cognitive function. This comprehensive review has shown that administration of probiotic is beneficial for neurodevelopment and cognitive function through several mechanisms following the principle of MGB axis and neuroplasticity [10, 15]. There are several mechanisms how probiotics exert beneficial effect to their host's body. The intestinal epithelium, which is made up of a single layer of intestinal epithelial cells, arranged into villi and crypts, is the biggest mucosal surface on the human body [56]. Establishing a physical and chemical barrier between the external environment and the host immune system is one of the tasks of the intestinal epithelium [57]. The mucosal barrier is made up of the mucus layer, the epithelium lining of the mucosal tissues, and the immune cells in the subepithelial layer. The study established that probiotics can improve the function of the barrier by encouraging mucus secretion [58]. Probiotic *L. plantarum* BMCM12, for instance, can release extracellular proteins, reduce pathogen adherence, and shield the gut barrier [59]. It also has been discovered that the probiotic metabolite butyric acid encourages the intestinal epithelium to consume oxygen, enhancing the expression of barrier-protective hypoxia-inducible factor (HIF) target genes and preserving HIF stability [60]. Another study by Monteguade-Mera et al. (2019) showed goblet cells can generate mucin when exposed to probiotics, preventing pathogen adhesion [61]. Probiotics have been shown to protect the digestive tract by suppressing harmful bacteria in previous research. Probiotics can inhibit pathogenic microbes through a variety of ways, including the activation of epithelial barrier function, the production of antimicrobial compounds, preventing access to nutritional resources, and competitive exclusion through competition for binding sites [62]. On the other hand, probiotics also play a crucial role in the secretion of antimicrobial substances. Probiotics can release organic acids including butyric acid, acetic acid, and propionic acid during the fermentation of carbohydrates [63]. The primary antimicrobial substances thought to be in charge of their inhibitory activity against infections have been identified as organic acids [64]. Organic acids have a specific antibacterial effect because of the drop in pH and the presence of undissociated acid [65].

Researchers discovered that the mice treated with probiotics had much higher amounts of Short-Chain Fatty Acids (SCFAs) and beneficial bacteria in their gut flora than the control group, including Oscillibacter and Prevotella [66]. SCFAs, the form of small organic

monocarboxylic acids, are the primary byproducts of the anaerobic fermentation of indigestible polysaccharides, like dietary fiber and resistant starch, by the microbiota in the large intestine [67]. SCFAs are organic monocarboxylic acids with a chain length of up to six carbon atoms. Depending on the amount of fiber in the diet, the makeup of the microbiota, and the length of the gut transit, the gut produces 500–600 mmol of SCFAs every day, with the majority of these compounds being acetate (C2), propionate (C3), and butyrate (C4) [68]. Following the synthesis, colonocytes absorb SCFAs primarily through sodium dependent monocarboxylate transporters (SMCTs) or H+-dependent monocarboxylate transporters (MCTs) [69]. Although colon-derived SCFAs only reach a small portion of the systemic circulation and other tissues, their impacts on various organs and systems have lately been extensively documented [70]. By encouraging the secretion of gut hormones like glucagon-like peptide 1 (GLP1) and peptide YY (PYY), as well as ɤ-aminobutyric acid (GABA), and serotonin, SCFA interaction with their receptors on enteroendocrine cells promotes indirect signaling to the brain *via* the systemic circulation or vagal pathways (5-HT) [71]. A crucial part in brain development and the maintenance of CNS homeostasis appears to be played by SCFAs in maintaining BBB integrity, which is closely linked to the controlled transit of chemicals and nutrients from the circulation to the brain. Germ-free (GF) mice have decreased production of tight junction proteins including claudin and occludin, which causes the BBB to be more permeable from intrauterine life to adulthood, providing evidence that SCFAs modulate the BBB function [72]. Additionally, monocolonization with SCFA-producing bacterial strains or recolonization of these adult animals with a complex microbiota restores the BBB's integrity [73].

SCFAs produced by probiotic also known to have an impact on microglia. Although how the SCFAs regulate the development and function of microglia are yet unknown, the activation of FFAR2 is possible because FFAR2-deficient mice showed microglia that were similar to those reported in GF mice [74]. It has been demonstrated that antibiotic-induced changes to the variety of gut bacteria have an impact on neuroinflammation with altered microglial morphology [75]. Moreover, butyrate administration produces morphological and functional alterations in the microglia toward a homeostatic profile and suppresses LPS-induced proinflammatory modifications and depressive-like behaviour in both vitro and *in vivo* [76]. Similar to this, it has been demonstrated that acetate treatment of microglia primary culture reduces inflammatory signaling by IL-1β, IL-6, and TNF-α expression and p38 MAPK, JNK, and NF-κB phosphorylation [77]. It has also been demonstrated that SCFAs can influence neurotrophic factors, including nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and BDNF, which control the growth, survival, and differentiation of neurons and synapses in the CNS and are crucial for learning and memory as well as a variety of brain illnesses [78,79]. BDNF expression, neurogenesis, and neuronal proliferation in mice, as well as facilitation of long-term memory consolidation, were enhanced by sodium butyrate [80]. The mechanism of probiotic effect on CNS summarized in Figure 1.

Aside from being facilitated by SCFAs action, probiotics also promoted positive impact on CNS through inducing production of Insulin-Like Growth Factor 1 (IGF-1). Recent study by Schwarzer et al. (2023) found that chronic malnutrition causes a state of GH resistance characterized by low levels of circulating IGF-1, which causes stunting. Upon administration of strain of *Lactiplantibacillus plantarum* (strain Lp^{WJL}) in diet-induced stunting mice model which then recognized by NOD2 pattern recognition receptor induces the proliferation of intestinal crypt cells, induction of type I interferon-regulated genes, synthesis of IGF-1, and enhancement of postnatal growth in conventional mice with malnutrition [16]. The other species of probiotics which has been known to have similar promoting IGF-1 production is *Lactobacillus rhamnosus*. The administration of L. rhamnosus increases the serum IGF-1 3-5 times [81]. IGF-1, one of the Insulin-Like Peptide (ILP) family members, is a powerful growth factor in the central nervous system (CNS) having pleiotrophic effects on all major cell types [17]. IGF-1 is largely produced in the liver, where it is controlled by growth hormone (GH) production from the pituitary. It plays a crucial role in the somatrotropic axis, working after GH to support anabolic processes and tissue growth all through life [82]. Moreover, IGF1 is produced locally in numerous organs, including the brain. It acts in practically every tissue in the body to stimulate tissue development and maturation by activating both the mitogen-activated protein (MAP) kinase and PI3K signaling pathways [83]. IGF-1 administration in cerebellar de-afferentation models causes reinnervation and restoration of olivo-cerebellar pathways in both young and adult rats. Moreover, IGF-1 administration restores the levels of various synaptic proteins that are impacted by de-afferentation, including calbindin, glutamate receptor 1 (GluR1), GABA, and glutamic acid [17]. One study found that acute IGF-1 administration significantly increased excitatory synaptic transmission, with the excitatory post-synaptic

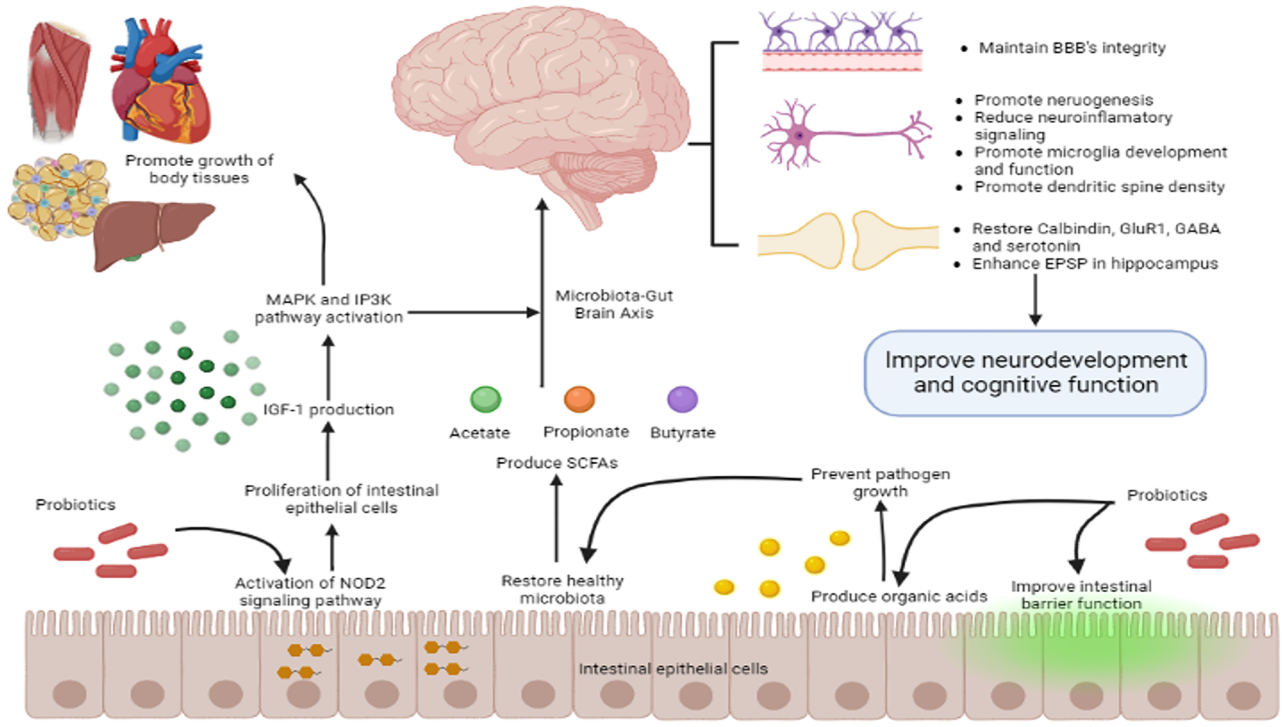

Figure 1. The probiotics effect to the CNS.

potential (EPSP) in the CA1 area of the hippocampus increasing by 40%. Such electrophysiological techniques provide additional proof of the crucial functions IGF-1 plays in regulating synaptic effectiveness and neuroplasticity in the central nervous system [84]. IGF-1 is necessary for dendritic growth, as shown by the shorter dendrites, decreased dendritic spine density, and aberrant synaptotagmin and synaptophysin levels and distribution seen in IGF-1-/- knockout mice. These investigations suggest that an aberrant synaptic pattern in the developing brain is caused by a lack of physiological IGF-1 signaling in the CNS [17]. While animal studies have shown the positive effect of IGF-1 on CNS, human studies are still lacking. A large-scale cohort from UK, with more than 300.000 participants showed that both low and high concentrations of IGF-1 are correlated with elevated risks of dementia and stroke, while heightened IGF-1 levels are linked to an increased risk of PD, with the lowest risks observed at 18 nmol/L and 26 nmol/L, respectively. This underscores the potential of IGF-1 as a biomarker for categorizing the risk of brain health. Additionally, neuroimaging analyses revealed that increased IGF-1 concentrations are associated with larger volumes of white matter ($\beta = 2.98 \times 10–4$, $p < 0.001$) and the hippocampus ($\beta = 3.37 \times 10–4$, $p = 0.002$) [85]. A study in China showed that the patients with pituitary adenomas that secrete growth hormone (GH) exhibit a noteworthy rise in both gray matter volume (GMV) and white matter volume (WMV), accompanied by a decrease in cerebrospinal fluid volume (CSFV). This suggests a connection between serum GH/IGF-1 and increased brain growth, offering a potential avenue for treating neurodegenerative disorders and brain injuries in humans [86].

Conclusion

This review indicated that there are promising effects linked between the neurodevelopment, cognitive function improvement in stunting and the administration of probiotic regarding MGB axis and neuroplasticity property of the brain through various mechanisms as explained above. Hence, altering the MBG axis as a therapeutic target for disorders marked by cognitive impairment coupled with stunting is an alluring potential, especially in the setting of a neurodevelopmental disease. Until this becomes a feasible treatment strategy, however, there is still much to be done. Most of the studies in this field are conducted in animal models. It is necessary to translate animal data into human models and do additional study to identify the numerous components in the MGB axis. It should also be noted that due to difference in brain structure, the human MGB axis differs greatly from the rodent axis. The long-term effects studies of many of these

probiotic agents in human populations are currently very limited. The fact that probiotics are such a diverse family of substances with different quality control and efficacy makes research into them even more difficult. The time and dosage of probiotic and additional dietary interventions are another thing to consider. Despite this, the discipline has advanced significantly over the past ten years, and significant advances in science and technology should eventually bring us closer to a treatment pathway. It will be very helpful to increase our understanding of a potential area of research if longitudinal clinical studies are carefully planned to examine the microbiological profiles of phenotyped patients over the course of their lives and the long-term consequences of factors affecting its composition.

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References

[1] UNICEF WHO World Bank Group Joint Child Malnutrition Estimates. 'Levels and trends in child malnutrition', 2021.
[2] WHO and UNICEF. 'The extension of the 2025 Maternal, Infant and Young Child nutrition targets to 2030', 2017. Online]. Available: http://www.who.int/nutrition/healthygrowthproj/en/index1.html.
[3] 'Global Nutrition Report Action on equity to end malnutrition', UK, 2020.
[4] Kementerian Kesehatan RI, 'Riset Kesehatan Dasar 2018', Jakarta, 2018.
[5] Kementerian Kesehatan RI, 'Riset Kesehatan Dasar 2013', Jakarta, 2013.
[6] Lindayani L, Supriatin E, Sudrajat DA, et al. The effect of stunting on cognitive and motor development in toddler children: literature review. Jurnal Ilmu Keperawata Anak. 2020;3(2):31–41. doi: 10.26594/jika.1.2.2020.
[7] Probosiwi H, Huriyati E, Ismail D. Stunting dan perkembangan pada anak usia 12-60 bulan di kalasan S tunting and development among 12-60 month aged children in Kalasan. BKM Int J Community Med Public Health. 2017;33(11):559–564. doi: 10.22146/bkm.26550.
[8] Handryastuti S, Pusponegoro HD, Nurdadi S, et al. Comparison of cognitive function in children with stunting and children with undernutrition with normal stature. J Nutr Metab. 2022;2022:9775727–9775725. doi: 10.1155/2022/9775727.
[9] Kustanto A. The prevalence of stunting, poverty, and economic growth in Indonesia: a panel data dynamic causality analysis. JDE. 2021;6(2):150. doi: 10.20473/jde.v6i2.22358.
[10] Murciano- brea J, Garcia- montes M, Geuna S, et al. Gut microbiota and neuroplasticity. Cells. 2021;10(8):2084. doi: 10.3390/cells10082084.
[11] Simanjuntak BY, Annisa R, Saputra AI. Kajian literatur: berhubungankah mikrobiota saluran cerna dengan stunting pada anak balita? AMNT. 2022;6(1SP):343–351. doi: 10.20473/amnt.v6i1SP.2022.343-351.
[12] Owino V, Ahmed T, Freemark M, et al. Environmental enteric dysfunction and growth failure/stunting in global child health. Pediatrics. 2016;138(6):2–10. doi: 10.1542/peds.2016-0641.
[13] Prado EL, Sebayang SK, Apriatni M, et al. Maternal multiple micronutrient supplementation and other biomedical and socioenvironmental influences on children's cognition at age 9–12 years in Indonesia: follow-up of the SUMMIT randomised trial. Lancet Glob Health. 2017;5(2):e217–e228. doi: 10.1016/S2214-109X(16)30354-0.
[14] Dalile B, Van Oudenhove L, Vervliet B, et al. The role of short-chain fatty acids in microbiota–gut–brain communication. Nat Rev Gastroenterol Hepatol. 2019;16(8):461–478. doi: 10.1038/s41575-019-0157-3.
[15] Rianda D, Agustina R, Setiawan EA, et al. Effect of probiotic supplementation on cognitive function in children and adolescents: a systematic review of randomised trials. Benef Microbes. 2019;10(8):873–882. doi: 10.3920/BM2019.0068.
[16] Schwarzer M, Gautam UK, Makki K, et al. Microbe-mediated intestinal NOD2 stimulation improves linear growth of undernourished infant mice. Science. 2023;379(6634):826–833. doi: 10.1126/science.ade9767.
[17] Dyer AH, Vahdatpour C, Sanfeliu A, et al. The role of insulin-like growth factor 1 (IGF-1) in brain development, maturation and neuroplasticity. Neuroscience. 2016;325:89–99. doi: 10.1016/j.neuroscience.2016.03.056.
[18] Alam MA, Richard SA, Fahim SM, et al. Impact of early-onset persistent stunting on cognitive development at 5 years of age: results from a multi-country cohort study. PLOS One. 2020;15(1):e0227839. doi: 10.1371/journal.pone.0227839.
[19] McCoy DC, Peet ED, Ezzati M, et al. Early childhood developmental status in low- and middle-income countries: national, regional, and global prevalence estimates using predictive modeling. PLoS Med. 2016;13(6):e1002034. doi: 10.1371/journal.pmed.1002034.
[20] Soliman A, et al. Early and long-term consequences of nutritional stunting: from childhood to adulthood. Acta Biomedica. 2021;92(1):1–11. doi: 10.23750/abm.v92i1.11346.
[21] Arini D, et al. Gangguan Perkembangan Motorik dan Kognitif pada anak Toodler yang Mengalami Stunting

di Wilayah Pesisir Surabaya. J of Heal Sci & Prevent. 2019;3(2):122–128. doi: 10.29080/jhsp.v3i2.231.
[22] Woldehanna T, Behrman JR, Araya MW. 'The effect of early childhood stunting on children's cognitive achievements: evidence from young lives Ethiopia'. [Online]. Available: www.younglives.org.uk.
[23] Prendergast AJ, Humphrey JH. The stunting syndrome in developing countries. Paediatr Int Child Health. 2014;34(4):250–265. doi: 10.1179/2046905514Y.0000000158.
[24] Stiles J, Jernigan TL. The basics of brain development. Neuropsychol Rev. 2010;20(4):327–348. doi: 10.1007/s11065-010-9148-4.
[25] Poh, Bee Koon, Rojroonwasinkul, Nipa, Le Nyugen, Bao Khanh, et al., 'Relationship between anthropometric indicators and cognitive performance in southeast asian school-aged Children', Br J Nutr. 2013;110(S3):S57–S64, doi: 10.1017/S0007114513002079.
[26] Galler JR, Bringas-Vega ML, Tang Q, et al. Neurodevelopmental effects of childhood malnutrition: a neuroimaging perspective. Neuroimage. 2021;231:117828. doi: 10.1016/j.neuroimage.2021.117828.
[27] Roberts SB, et al. A pilot randomized controlled trial of a new supplementary food designed to enhance cognitive performance during prevention and treatment of malnutrition in childhood. 2017.
[28] Hugon P, Lagier J-C, Colson P, et al. Repertoire of human gut microbes. Microb Pathog.2017;106:103–112. doi: 10.1016/j.micpath.2016.06.020.
[29] Leung K, Thuret S. Gut microbiota: a modulator of brain plasticity and cognitive function in ageing. Healthcare. 2015;3(4):898–916. doi: 10.3390/healthcare3040898.
[30] Hickey L, Jacobs SE, Garland SM, Probiotics in neonatology. J Paediatr Child Health. 2012;48(9):777–783. doi: 10.1111/j.1440-1754.2012.02508.x.
[31] Eckburg PB, Bik EM, Bernstein CN, et al. Diversity of the human intestinal microbial flora. Science. 2005;308(5728):1635–1638. doi: 10.1126/science.1110591.
[32] Stewart CJ, Ajami NJ, O'Brien JL, et al. Temporal development of the gut microbiome in early childhood from the TEDDY study. Nature. 2018;562(7728):583–588. doi: 10.1038/s41586-018-0617-x.
[33] Naveed M, Zhou Q-G, Xu C, et al. Gut-brain axis: a matter of concern in neuropsychiatric disorders…!. Prog Neuropsychopharmacol Biol Psychiatry. 2021;104:110051. doi: 10.1016/j.pnpbp.2020.110051.
[34] Kundu P, Blacher E, Elinav E, et al. Our gut microbiome: the evolving inner self. Cell. 2017;171(7):1481–1493. doi: 10.1016/j.cell.2017.11.024.
[35] Borre YE, Moloney RD, Clarke G, et al. The impact of microbiota on brain and behavior: mechanisms & therapeutic potential. Adv Exp Med Biol. 2014;817:373–403. doi: 10.1007/978-1-4939-0897-4_17.
[36] Cerdó T, Ruíz A, Suárez A, et al. Probiotic, prebiotic, and brain development. Nutrients. 2017;9(11):1247 doi: 10.3390/nu9111247.
[37] Mateos-Aparicio P, Rodríguez-Moreno A. The impact of studying brain plasticity. Front Cell Neurosci. 2019;13:66. doi: 10.3389/fncel.2019.00066.
[38] Fauth M, Tetzlaff C. Opposing effects of neuronal activity on structural plasticity. Front Neuroanat. 2016;10:75. doi: 10.3389/fnana.2016.00075.
[39] Von Bernhardi R, Eugenín-Von Bernhardi L, Eugenín J. What is neural plasticity?. in Advances in experimental medicine and biology, vol. 1015, Springer New York LLC, 2017, pp. 1–15. doi: 10.1007/978-3-319-62817-2_1.
[40] Budge S, Parker AH, Hutchings PT, et al. Environmental enteric dysfunction and child stunting. Nutr Rev. 2019;77(4):240–253. doi: 10.1093/nutrit/nuy068.
[41] Ahmed T, Auble D, Berkley JA, et al. An evolving perspective about the origins of childhood undernutrition and nutritional interventions that includes the gut microbiome. Ann N Y Acad Sci. 2014;1332(1):22–38. doi: 10.1111/nyas.12487.
[42] Tickell KD, Atlas HE, Walson JL. Environmental enteric dysfunction: a review of potential mechanisms, consequences and management strategies. BMC Med. 2019;17(1):181. doi: 10.1186/s12916-019-1417-3.
[43] Kosek MN, Causal pathways from enteropathogens to environmental enteropathy: findings from the MAL-ED birth cohort study. EBioMedicine. 2017;18:109–117. Apr doi: 10.1016/j.ebiom.2017.02.024.
[44] McGrath CJ, Arndt MB, Walson JL. Biomarkers to stratify risk groups among children with malnutrition in resource-limited settings and to monitor response to intervention. Horm Res Paediatr. 2017;88(1):111–117. doi: 10.1159/000471875.
[45] Syed S, Ali A, Duggan C. Environmental enteric dysfunction in children. J Pediatr Gastroenterol Nutr. 2016;63(1):6–14. doi: 10.1097/MPG.0000000000001147.
[46] Braun TP, Marks DL. Pathophysiology and treatment of inflammatory anorexia in chronic disease. J Cachexia Sarcopenia Muscle. 2010;1(2):135–145. doi: 10.1007/s13539-010-0015-1.
[47] Nataro JP, Guerrant RL. Chronic consequences on human health induced by microbial pathogens: growth faltering among children in developing countries. Vaccine. 2017;35(49 Pt A):6807–6812. doi: 10.1016/j.vaccine.2017.05.035.
[48] Action Against Hunger and United Nations' Childrens' Funds. 'WASH' Nutrition A Practical Guidebook on Increasing Nutritional Impact Through Integration of WASH and Nutrition Programmes', Paris, 2017.
[49] Humphrey JH, Mbuya MNN, Ntozini R, et al. Independent and combined effects of improved water, sanitation, and hygiene, and improved complementary feeding, on child stunting and anaemia in rural Zimbabwe: a cluster-randomised trial. Lancet Glob Health. 2019;7(1):e132–e147. doi: 10.1016/S2214-109X(18)30374-7.
[50] Bhutta ZA, Das JK, Rizvi A, et al. Evidence-based interventions for improvement of maternal and child nutrition: what can be done and at what cost? Lancet. 2013;382(9890):452–477. doi: 10.1016/S0140-6736(13)60996-4.
[51] Dangour AD, Watson L, Cumming O, et al. Interventions to improve water quality and supply, sanitation and hygiene practices, and their effects on the nutritional status of children. Cochrane Database Syst Rev. 2013;8:CD009382. doi: 10.1002/14651858.CD009382.pub2.

[52] Rianda D, Suradijono SHR, Setiawan EA, et al. Long-term benefits of probiotics and calcium supplementation during childhood, and other biomedical and socioenvironmental factors, on adolescent neurodevelopmental outcomes. J Funct Foods. 2022;91:105014. doi: 10.1016/j.jff.2022.105014.
[53] Sheridan PO, Bindels LB, Saulnier DM, et al. Can prebiotics and probiotics improve therapeutic outcomes for undernourished individuals? Gut Microbes. 2014;5(1):74–82. doi: 10.4161/gmic.27252.
[54] Stavrou G, Kotzampassi K. Gut microbiome, surgical complications and probiotics. Ann Gastroenterol. 2017;30(1):45–53. doi: 10.20524/aog.2016.0086.
[55] Wieërs G, Belkhir L, Enaud R, et al. How probiotics affect the microbiota. Front Cell Infect Microbiol. 2019;9:454. doi: 10.3389/fcimb.2019.00454.
[56] Glover LE, Lee JS, Colgan SP. Oxygen metabolism and barrier regulation in the intestinal mucosa. J Clin Invest. 2016;126(10):3680–3688. doi: 10.1172/JCI84429.
[57] Ahluwalia B, Magnusson MK, Öhman L. Mucosal immune system of the gastrointestinal tract: maintaining balance between the good and the bad. Scand J Gastroenterol. 2017;52(11):1185–1193. doi: 10.1080/00365521.2017.1349173.
[58] Plaza-Diaz J, Ruiz-Ojeda FJ, Gil-Campos M, et al. Mechanisms of action of probiotics. Adv Nutr. 2019;10(suppl_1):S49–S66. doi: 10.1093/advances/nmy063.
[59] van Zyl WF, Deane SM, Dicks LMT. Molecular insights into probiotic mechanisms of action employed against intestinal pathogenic bacteria. Gut Microbes. 2020;12(1):1831339. doi: 10.1080/19490976.2020.1831339.
[60] Liu Q, Yu Z, Tian F, et al. Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. Microb Cell Fact. 2020;19(1):23. doi: 10.1186/s12934-020-1289-4.
[61] Monteagudo-Mera A, Rastall RA, Gibson GR, et al. Adhesion mechanisms mediated by probiotics and prebiotics and their potential impact on human health. Appl Microbiol Biotechnol. 2019;103(16):6463–6472. doi: 10.1007/s00253-019-09978-7.
[62] Tuo Y, Song X, Song Y, et al. Screening probiotics from lactobacillus strains according to their abilities to inhibit pathogen adhesion and induction of pro-inflammatory cytokine IL-8. J Dairy Sci. 2018;101(6):4822–4829. Jun doi: 10.3168/JDS.2017-13654.
[63] Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. Nutrients. 2020;12(4):1107. doi: 10.3390/nu12041107.
[64] Kovanda L, Zhang W, Wei X, et al. In vitro antimicrobial activities of organic acids and their derivatives on several species of gram-negative and gram-positive bacteria. Molecules. 2019;24(20):3770. doi: 10.3390/molecules24203770.
[65] Mousavi Khaneghah A, Abhari K, Eş I, et al. Interactions between probiotics and pathogenic microorganisms in hosts and foods: a review. Trends Food Sci Technol. 2020;95:205–218. Jan doi: 10.1016/j.tifs.2019.11.022.
[66] Li J, Sung CYJ, Lee N, et al. Probiotics modulated gut microbiota suppresses hepatocellular carcinoma growth in mice. Proc. Natl. Acad. Sci. U.S.A. 2016;113(9):1306–1315. doi: 10.1073/pnas.1518189113.
[67] den Besten G, van Eunen K, Groen AK, et al. The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. J Lipid Res. 2013;54(9):2325–2340. doi: 10.1194/jlr.R036012.
[68] Fernandes J, Su W, Rahat-Rozenbloom S, et al. Adiposity, gut microbiota and faecal short chain fatty acids are linked in adult humans. Nutr Diabetes. 2014;4(6):e121–e121. doi: 10.1038/NUTD.2014.23.
[69] Silva YP, Bernardi A, Frozza RL. The role of short-chain fatty acids from gut microbiota in gut-brain communication. Front Endocrinol. 2020;11:25. doi: 10.3389/FENDO.2020.00025/BIBTEX.
[70] Fung TC, Olson CA, Hsiao EY. Interactions between the microbiota, immune and nervous systems in health and disease. Nat Neurosci. 2017;20(2):145–155. doi: 10.1038/nn.4476.
[71] Puddu A, Sanguineti R, Montecucco F, et al. Evidence for the gut microbiota short-chain fatty acids as key pathophysiological molecules improving diabetes. Mediators Inflamm. 2014;2014:162021–162029. doi: 10.1155/2014/162021.
[72] Ma Q, Xing C, Long W, et al. Impact of microbiota on Central nervous system and neurological diseases: the gut-brain axis. J Neuroinflammation. 2019;16(1):53. doi: 10.1186/S12974-019-1434-3.
[73] Braniste V, Al-Asmakh M, Kowal C, et al. The gut microbiota influences blood-brain barrier permeability in mice. Sci Transl Med. 2014;6(263):263ra158. doi: 10.1126/scitranslmed.3009759.
[74] Gautier EL, Shay T, Miller J, et al. Gene-expression profiles and transcriptional regulatory pathways that underlie the identity and diversity of mouse tissue macrophages. Nat Immunol. 2012;13(11):1118–1128. doi: 10.1038/ni.2419.
[75] Cerovic M, Forloni G, Balducci C. Neuroinflammation and the gut microbiota: possible alternative therapeutic targets to counteract alzheimer's disease? Front Aging Neurosci. 2019;11:284. doi: 10.3389/fnagi.2019.00284.
[76] Yamawaki Y, Yoshioka N, Nozaki K, et al. Sodium butyrate abolishes lipopolysaccharide-induced depression-like behaviors and hippocampal microglial activation in mice. Brain Res. 2018;1680:13–38. doi: 10.1016/j.brainres.2017.12.004.
[77] Soliman ML, Puig KL, Combs CK, et al. Acetate reduces microglia inflammatory signaling in vitro. J Neurochem. 2012;123(4):555–567. doi: 10.1111/j.1471-4159.2012.07955.x.
[78] Savignac HM, Corona G, Mills H, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem Int. 2013;63(8):756–764. doi: 10.1016/j.neuint.2013.10.006.
[79] Moens F, Van den Abbeele P, Basit AW, et al. A four-strain probiotic exerts positive immunomodulatory effects by enhancing colonic butyrate production in vitro. Int J Pharm. 2019;555:1–10. doi: 10.1016/j.ijpharm.2018.11.020.
[80] Varela RB, Valvassori SS, Lopes-Borges J, et al. Sodium butyrate and mood stabilizers block ouabain-induced hyperlocomotion and increase BDNF, NGF and GDNF

levels in brain of Wistar rats. J Psychiatr Res. 2015; 61:114–121. doi: 10.1016/j.jpsychires.2014.11.003.

[81] Yan J, Charles JF. Gut microbiota and IGF-1. Calcif Tissue Int. 2018;102(4):406–414. doi: 10.1007/s00223-018-0395-3.

[82] Milman S, Huffman DM, Barzilai N. The somatotropic axis in human aging: framework for the current state of knowledge and future research. Cell Metab. 2016; 23(6):980–989. doi: 10.1016/j.cmet.2016.05.014.

[83] Wrigley S, Arafa D, Tropea D. Insulin-like growth factor 1: at the crossroads of brain development and aging. Front Cell Neurosci. 2017;11:14. doi: 10.3389/fncel.2017.00014.

[84] Xing C, Yin Y, Chang R, et al. Effects of insulin-like growth factor 1 on synaptic excitability in cultured rat hippocampal neurons. Exp Neurol.2007;205(1):222–229. doi: 10.1016/j.expneurol.2007.01.029.

[85] Cao Z, Min J, Tan Q, et al. Circulating insulin-like growth factor-1 and brain health: evidence from 369,711 participants in the UK Biobank. Alzheimers Res Ther. 2023; 15(1):140. doi: 10.1186/s13195-023-01288-5.

[86] Yuan T, Ying J, Jin L, et al. The role of serum growth hormone and insulin-like growth factor-1 in adult humans brain morphology. Aging. 2020;12(2):1377–1396. doi: 10.18632/aging.102688.