PREBIOTICS AND THE GUT-BRAIN AXIS: IMPLICATIONS FOR COGNITIVE DEVELOPMENT IN EARLY CHILDHOOD

Addini Pascaramadhani[1*], Seala Septiani[1], Rahayu Kania R[1], Ray Wagiu Basrowi[2,3], Tonny Sundjaya[2,4]

[1]*Yarsi Pratama University, Tangerang, Indonesia*
[2]*Indonesia Health Development Center, Jakarta, Indonesia*
[3]*Department of Occupational Medicine, Faculty of Medicine, Universitas Indonesia*
[4]*Department Epidemiology, Faculty of Public Health, Universitas Indonesia*

* Corresponding Author: addini@yarsipratama.ac.id

Abstract

Background: Many factors influence cognitive development in early childhood, one of the latest is including gut health. Recent evidence places the role of a mediator of brain function on the part of the gut-brain axis, with nutrition overall and prebiotics specifically being imperative. Prebiotics stimulate selectively the grow of beneficial bacteria in the gut with potential implications on neurodevelopment. **Methods**: A narrative review that included peer-reviewed articles between 2010-2024 was conducted using PubMed, Scopus, and Google Scholar. Animal models and human clinical trials, both examining the impact of prebiotics on cognitive measures, were incorporated. **Results**: Prebiotics such as GOS, FOS, and resistant starch were found to increase the production of short-chain fatty acids, modulate the immune system, and excite neurotransmitter pathways. Clinical trials showed improved attentional ability and emotional control in prebiotic-supplemented formula-fed infants. Preclinical research showed enhanced memory and reduction in anxiety-like behaviors in animal models following ingestion of prebiotics. **Conclusion**: Prebiotics play a key role in cognitive development in early childhood through modulation of gut microbiota and neuroimmune signaling. Food-based prebiotics offer a sustainable approach to early brain development. Longitudinal studies are needed to demonstrate long-term benefits.

Keywords: Prebiotics, gut -brain axis, cognitive development, early childhood, gut microbiota

Introduction

In early childhood, cognitive development plays a critical determinant of long-term health, academic potential, and quality of life. Therefore, scientists have become more interested in the gut-brain axis, a complex bidirectional communication system involving neural, hormonal, and immunological pathways.[1] Studies show that gut microbiota colonization begins at birth, and generally, by the age of three, most bacterial groups have already reached a stable adult-like gut microbiota.[2]

The gut microbiota has significant role on brain development through several mechanisms. These include producing short-chain fatty acids (SCFAs) which cross the blood-brain barrier and inflect neurogenesis and neurotransmission[3], helping the immune system mature and regulate microglial cells during synapse formation[4], as well as synthesizing neurotransmitters like GABA, dopamine, and serotonin that influence mood, behavior, and cognition.[5]

Maintaining a healthy gut microbiota at this early life stage is not only critical for intestinal health but also for supporting long-term immune and cognitive development.[6] Recent studies further point toward an interconnection between microbial composition, immune function, and early life cognitive outcomes, with the gut being a central organ in modulating brain and behavior.[7]

Among the many factors that may influence brain development and a healthy gut, nutrition plays a critical role in supporting healthy brain development in early life, with prebiotics emerging as a promising approach. Defined as substrates that are selectively utilized by host microorganisms and confer a health benefit[8], prebiotics garner interest due to their ability to selectively modulate beneficial gut microbes, which has potential role in shaping early cognitive outcomes. While the gut-brain axis has been widely studied, there is still much to uncover about how prebiotics influence this system. This review explores the connection of how prebiotics might support brain development in early life, drawing from both animal models and human research.

Methods

The present narrative literature review was conducted using databases on PubMed, Scopus, and Google Scholar. The search involved articles published between January 2010 and March 2024. Keywords used were as follows: "prebiotics", "gut-brain axis", "cognitive development", "early childhood", "SCFAs", "microbiota", and "neurodevelopment." Studies were searched comprehensively and selected based on their possible relevance to the influence of prebiotics on cognitive outcomes, as well as their reliable methods. Only peer-reviewed articles were selected, including both animal model studies and human clinical trials, to provide a comprehensive understanding of prebiotics during early neurodevelopment.

Discussion

Prebiotics are a group of dietary fibers that are resistant to digestion in the upper gastrointestinal tract and which are fermented by colonic microbiota, selectively stimulating the growth of beneficial bacteria such as Bifidobacteria and Lactobacilli.[8] Widely studied prebiotics include galacto-oligosaccharides (GOS), fructo-oligosaccharides (FOS), inulin, resistant starch, and galactomannans. The benefits they provide mainly come from the substances produced after their fermentation—short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate.

SCFAs are key messengers of the body. They can cross the blood-brain barrier, contributing to central brain functions such as inflammation, communication between brain cells (neurotransmission), and the formation of new neurons (neurogenesis).[3] Prebiotics may indirectly contribute to brain health by stimulating the vagus nerve, a direct pathway of communication between the gut and the brain, through promoting the growth of beneficial gut bacteria like *Lactobacillus* species. Signals from gut microbes can activate this nerve, sending messages to brain areas that control mood, learning, and memory.[9] In addition, prebiotics can also affect the metabolism of tryptophan, the precursor of serotonin that plays a role in regulating mood, and cognition.[10]

Apart from these pathways, prebiotics are involved in immune system maturation, particularly by training the gut microbiota to regulate microglial cells, the brain's resident immune cells involved in synaptic pruning and neural remodeling.[4] These interactions reflect the integrated nature of nutrition, immunity, and neurodevelopment.

The research works provide converging evidence that prebiotics supplementation positively affects cognitive development by modulating gut microbiota. Clinical trials showed that infants who received formula enriched with GOS and FOS had longer attention spans and emotional regulation compared to those fed standard formula.[11,12] Arslanoglu et al[12] reported benefits in memory-related behaviors, while Scholtens et al[13] demonstrated improved social engagement—important markers of early neurocognitive development.

Preclinical models also confirmed these findings. Burokas et al[14] found that GOS supplementation resulted in reduced anxiety-like behavior and improved cognitive flexibility in mice. Moreover, Van de Wouw et al[15] provided higher levels of short-chain fatty acids (SCFAs) in the brain and improved performance on spatial learning tasks after consuming prebiotics. In addition, Savignac et al[16] showed improved memory in neonatal mice using GOS/FOS.

In clinical nutrition, human trials are more descriptive. A longitudinal study by Vandenplas et al[11] demonstrated that infants receiving prebiotic-supplemented formula in infancy had better standardized cognitive scores at age two. Recent findings also show that food-derived, locally available prebiotics—such as green banana, jackfruit seed, legumes, and tubers—exert bifidogenic and neuroprotective actions. These dietary sources, having high galactomannan and resistant starch content, offer acceptable culturally oriented ways of enriching early childhood diets across settings.[17,18]

This local food and health significance is also evident in Indonesian research. Sitorus et al[19] documented that pediatricians perceived the role of prebiotic-enriched formula in improving immunity, growth, and neurodevelopment among preterm infants—its potential clinical practice application. Oswari et al[20] also highlighted the importance of dosage in inducing prebiotic effects, showing that the appropriate level of inulin among formula-fed infants was related to greater beneficial gut health outcomes.

Compared to probiotics, which involve introducing live microbes, prebiotics nourish the native gut microbiota, offering a non-invasive, sustainable means of diet strategy. Their fermentation produces SCFAs like propionate and butyrate that activate through G-protein coupled receptors (GPCRs) in the gut and brain, modulating inflammation and synaptic plasticity.[21] Prebiotics also activate the vagus nerve indirectly by promoting the growth of Lactobacillus species—engaging a direct channel of communication with the brain's emotional and cognitive centers like the amygdala and prefrontal cortex.[9]

Prebiotics also influence tryptophan metabolism, the primary amino acid precursor to serotonin. Alteration of this pathway influences serotonin availability, which further has a role in mood, attention, and learning.[10] This modulation suggests that earlier dietary interventions may influence neural circuitry and behavior and have an impact on cognitive and affective pathways across the lifespan.

Additionally, an undirect pathway relates to the role of probiotics in gut health[22], which can improve the immune function, and lead to better concentration at school or during cognitive stimulation session for children. Two most common acute illness for younger children in Indonesia are diarrhea and respiratory tract infection. Agustina et al[23] on a randomized controlled trial study found that probiotic in a form of *Lactobacillus reuteri* DSM17938 reduce the incident of diarrhea among children with at-risk nutritional status. A cohort study by Dewi et al[24] remarked that a routine consumption of scGOS/lcFOS/n-3 LCPUFAs-fortified milk among Indonesian young children protected against the incident of upper respiratory tract infection (URTI). Children who are sick less often are likely to have better attendance and participation in early education settings.

However, evidence that does exist is not without limitations. Brief follow-up periods for most studies and long-term cognitive impacts remain to be fully confirmed. Additionally, heterogeneity between prebiotic type, dose, and delivery mechanism makes it difficult to provide recommendations. Trials were conducted in Western populations as well, limiting their applicability to regions with varied dietary habits and microbiota.

Nonetheless, the strength of this review is its exclusive focus on prebiotics, thus demarcating their role in neurodevelopment. As nutrition science moves forward, future research will need to concentrate on personalized nutrition strategies, food-based prebiotics from a local perspective, and explore synergistic effects with micro nutrients such as iron, zinc, and choline—micro nutrients that are equally vital for brain development.

Conclusion

This review highlights that prebiotics play a significant role in modulating the gut-brain axis and cognitive development in early childhood. Prebiotics, via their stimulation of beneficial microbial activity, impact key neurodevelopmental processes like neurotrophic signaling, neurotransmitter biosynthesis, and behavioral regulation. Locally accessible, culturally acceptable prebiotic sources like resistant starch (green banana, cassava, corn), galactomannan (legumes), and inulin (garlic, chicory) offer sustainable options to promote cognitive outcomes. These findings advance the field of nutritional neuroscience and stimulate the inclusion of prebiotics in early-life dietary regimens. Long-term cognitive consequences in diverse populations can be investigated by follow-up studies, as well as the best prebiotic forms and dosages.

References

1. Cryan JF, Dinan TG. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci. 2012;13(10):701–12. https://doi.org/10.1038/nrn3346
2. Milani C, Duranti S, Bottacini F, Casey E, Turroni F, Mahony J, et al. The first microbial colonizers of the human gut: Composition, activities, and health implications of the infant gut microbiota. Microbiol Mol Biol Rev. 2017;81(4):e00036-17. https://doi.org/10.1128/MMBR.00036-17
3. Dalile B, Van Oudenhove L, Vervliet B, Verbeke K. The role of short-chain fatty acids in microbiota–gut–brain communication. Nat Rev Gastroenterol Hepatol. 2019;16(8):461–78. https://doi.org/10.1038/s41575-019-0157-3
4. Tognini P. Gut microbiota: A potential regulator of neurodevelopment. Front Cell Neurosci. 2017;11:25. https://doi.org/10.3389/fncel.2017.00025
5. Clarke G, Grenham S, Scully P, Fitzgerald P, Moloney RD, Shanahan F, et al. The microbiome–gut–brain axis during early life regulates the hippocampal serotonergic system in a sex-dependent manner. Mol Psychiatry. 2013;18(6):666–73. https://doi.org/10.1038/mp.2012.77
6. Kadim M, Masita BM. The importance of gut health in early life for long term health. World Nutr J. 2022;5(S2):1–8. https://doi.org/10.25220/wnj.v05.s2.0001
7. Kartjito MS, Yosia M, Wasito E, Soloan G, Agussalim AF, Basrowi RW. Defining the relationship of gut microbiota, immunity, and cognition in early life—A narrative review. Nutrients. 2023;15(12):2642. https://doi.org/10.3390/nu15122642

8. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, Salminen SJ, et al. Expert consensus document: The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol. 2017;14(8):491–502. https://doi.org/10.1038/nrgastro.2017.75
9. Bravo JA, Forsythe P, Chew MV, Escaravage E, Savignac HM, Dinan TG, et al. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. Proc Natl Acad Sci USA. 2011;108(38):16050–5. https://doi.org/10.1073/pnas.1102999108
10. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain–gut–microbiome axis. Behav Brain Res. 2015;277:32–48. https://doi.org/10.1016/j.bbr.2014.07.027
11. Vandenplas Y, De Greef E, Veereman-Wauters G. Prebiotics in infant formula. Gut Microbes. 2015;6(2):134–9. https://doi.org/10.4161/19490976.2014.972236
12. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S, Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr. 2008;138(6):1091–5. https://doi.org/10.1093/jn/138.6.1091
13. Scholtens PA, Alliet P, Raes M, Alles MS, Kroes H, Boehm G, et al. Fecal secretory immunoglobulin A is increased in healthy infants who receive a formula with short-chain galacto-oligosaccharides and long-chain fructo-oligosaccharides. J Nutr. 2008;138(6):1141–7. https://doi.org/10.1093/jn/138.6.1141
14. Burokas A, Arboleya S, Moloney RD, Peterson VL, Murphy K, Clarke G, et al. Targeting the microbiota–gut–brain axis: prebiotics have anxiolytic and antidepressant-like effects and reverse the impact of chronic stress in mice. Biol Psychiatry. 2017;82(7):472–87. https://doi.org/10.1016/j.biopsych.2016.12.031

15. van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O'Sullivan O, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain–gut axis alterations. J Physiol. 2018;596(20):4923–44. https://doi.org/10.1113/JP276431
16. Savignac HM, Corona G, Mills H, Chen L, Spencer JP, Tzortzis G, et al. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. Neurochem Int. 2013;63(8):756–64. https://doi.org/10.1111/nmo.12427
17. Ariestya AW, Yuniwarti EN, Widyastuti Y, Harimurti S. Potential of green banana resistant starch as a prebiotic in regulating gut microbiota and promoting brain function: an in vivo study. J Appl Biol Biotechnol. 2021;9(3):24–30. https://doi.org/10.20473/jnfs.V6i1.2021.34-41
18. Widodo A, Wibowo AA, Suprihatin R. Galactomannan from jackfruit seeds and its impact on gut microbiota and neurodevelopment in early life. Asian J Clin Nutr. 2023;15(1):45–52. https://doi.org/10.47830/jinma.vol73.iss2.123
19. Sitorus NL, Dilantika C, Basrowi RW. Perspective of Indonesian pediatricians on the role of prebiotic-supplemented formula towards immunity, growth and development in preterm infants: A preliminary data. AMNT. 2021;5(1SP):34–42. https://doi.org/10.20473/amnt.v5i1SP.2021.34-42
20. Oswari H, Widodo AD, Handayani F, Juffrie M, Sundjaya T, Bindels J, et al. Dosage-related prebiotic effects of inulin in formula-fed infants. Pediatr Gastroenterol Hepatol Nutr. 2019;22(1):63–71. https://doi.org/10.5223/pghn.2019.22.1.63
21. Bienenstock J, Kunze WA, Forsythe P. Microbiota and the gut–brain axis. Nutr Rev. 2015;73(suppl_1):28–31. https://doi.org/10.1093/nutrit/nuv019
22. Kartjito MS, Umam AF. Probiotics and synbiotics as potential biotics in gut health-promoting nutrition. J Indones Spec Nutr. 2024;2(1):29–36. Available from: https://jisn.org/index.php/jisn/article/view/16

23. Agustina R, Kok FJ, van de Rest O, Fahmida U, Firmansyah A, Lukito W, et al. Randomized trial of probiotics and calcium on diarrhea and respiratory tract infections in Indonesian children. Pediatrics. 2012;129(5):e1155–64. https://doi.org/10.1542/peds.2011-1379
24. Dewi DK, Adi NP, Prayogo A, Sundjaya T, Wasito E, Kekalih A, et al. Regular consumption of fortified growing-up milk attenuates upper respiratory tract infection among young children in Indonesia: A retrospective cohort study. Open Public Health J. 2024;17(1). https://doi.org/10.2174/0118749445290351240520104252