REVIEW ARTICLE

Emerging Role and Place of Probiotics in the Management of Pediatric Neurodevelopmental Disorders

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Abstract

The current decade has witnessed significant developments with the latest therapeutic agents for managing various infectious diseases to complex hemato-oncological conditions, leading to a decrease in morbidity and mortality, while improving the quality of life (QoL), and increasing the life span. Non-communicable diseases (NCDs), which are on the rise across all age-groups, are being driven by unhealthy lifestyles and improved mental health issues. The current therapeutic agents were found to offer only symptomatic relief of varying efficacy and significant adverse effects, leading clinicians to evaluate other options for the management of both neurodevelopmental and neurodegenerative disorders. The role of gut microbiota has emerged as a potential target for the treatment of both neurodegenerative diseases and neurodevelopmental disorders like attention-deficit hyperactivity disorder (ADHD)/autism spectrum disorders (ASD) as a result of the decoding of the human genome and advances in our understanding of the human gut microbiome, including its interactions with the human brain. This review has been undertaken to understand on date level of understanding of human microbiota and towards identifying probiotic strains with proven efficacy and safety. According to recent investigations, several *lactobacillus* strains, including *L. Paracasei 37*, *L. Planetarium 128, L. reuteri DSM 17938*, and *Bifidobacterium longum*, have been effective in treating children's neurodevelopmental disorders such as ASD and ADHD. Future clinical studies are nonetheless required to confirm the long-term safety and effectiveness of probiotic strains in managing the primary and comorbid symptoms, hence improving patient and family quality of life.

Keywords: Dysbiosis, Gut-brain axis, Neurodevelopmental disorders, Psychobiotics.

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Introduction

The current century has seen the control of infectious diseases with the addition of the latest therapeutic agents in the armamentarium with the advent of antimicrobials, antivirals for management, and vaccines for prevention with improvement in healthcare access and system across many nations. This has resulted in an increase in life expectancy, improvement in lifestyle, and disposable income. A comprehensive review has indicated that an increase in urbanization and the adoption of a sedentary lifestyle from the conventional traditional lifestyle concerning food, hygiene, and habits has resulted in a significant increase in NCDs like cardiovascular diseases, metabolic diseases, and brain/neurological disorders. With a 37% loss of healthy life years, a decline in QoL, an increase in complications, and comorbid conditions, mental health conditions are now the number one cause of disability-adjusted life years (DALYs) among NCDs, posing a serious threat to overall health and treatment costs. Neurological disorders are those ailments that cause obvious brain damage. Examples include stroke and ischemia. While ADHD and ASD both show aberrant brain development, neurodegenerative disorders include the gradual degeneration of neuronal cells, as is the case with Alzheimer's and Parkinson's disease progression. Psychiatric diseases include mood problems, which frequently influence adults with schizophrenia in terms of behavior and mental functioning.[1] This review attempts to highlight the most recent findings, information, and the advantages of gut microbiota on human health, particularly on neurodevelopmental like ASD and ADHD in children along with the role and place of specific Psychobiotics as an adjunct to the current treatment, offering relief from both core symptoms and associated comorbid conditions.

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Neurodevelopmental Disorders in Children

Complex neurodevelopmental disorders like ASD and ADHD are physiologically based illnesses with a prevalence of one in 44 in the case of ASD and up to 50% in the case of ADHD among children. Further research confirmed that clinicians identify children with ASD as early as the first 1000 days of the window period and diagnosed later which is often associated with comorbid conditions.[2] Further studies have indicated that ASD, ADHD, and mood/anxiety are often related to sleep disorders.[3] Inadequate sleep is commonly seen in 40% of healthy children and children with 80% of them often develop neurodevelopmental disorders. Research further confirmed the co-existence of ASD in 50% of young children diagnosed with ADHD and 80% of ASD children developing ADHD.

The entire developmental process of children with ASD is affected, including behavior, problem-solving skills, self-care abilities, socialization abilities with language and communication issues, and executive operational expertise.[4]

Clinical manifestations of ASD rely on the age, cognitive, and language capacities of the specific kid, excluding co-occurring conditions, even though the severity and breadth of symptoms differ widely from child to child. The Diagnostic and Statistical Manual's (DSM-5) recent recommendations categorize ASD into two subcategories, which incorporate:[5]

1. Social connection and communication, including issues with emotional and social reciprocity, displaying in other than verbal communication during interaction in a group of people, and challenges involved in a relationship right from initiating to management.
2. Limited, stereotypical, and repetitive patterns of behavior, including sensory issues, confined interests, insistence on uniformity, rigid adherence to routines, and strange repeated movements or actions.

The guidelines indicated for ADHD diagnosis are based on the clinical symptoms and the child's psychosocial and environmental aspects.[6,7]

An exploratory study demonstrated that the management of ASD is challenging as it is often difficult to identify, in addition to its overlapping nature.[8] According to studies, ASD is characterized by a wide range of behavioral, cognitive, and emotional disturbances as well as a high rate of co-occurring mental health issues like ADHD, anxiety, depression, and phobias. It also includes intellectual disability, speech, and language impairment, a need for restrictive diets, problems with sleep and sensory processing, and genetic conditions.

Current Management of ASD/ADHD

According to current knowledge, ADHD is a neurodevelopmental condition that affects up to 5% of children and 2.5% of adults worldwide, indicating that among children, ADHD is diagnosed with an imbalance in cognition, and behavior leading to inattention, with an increase in motor activity and impulsivity.

Studies have shown that several genetic, biochemical, and environmental variables can affect ADHD.[9] Data indicates the beneficial effects of nutritional supplementation, as an add-on to the existing therapies toward better resolution and core symptom control among children and adolescents.[10] The latest research has demonstrated a strong linkage of ADHD to the neural circuits responsible for attention and confirmed that in ADHD, catecholamine regulation at the prefrontal cortex is the cornerstone of the treatment as attention and cognition are retained. However, behavioral therapies are the mainstay of ASD management to address the condition's primary symptoms.[11]

The pharmacological therapies used today, which include stimulants and antipsychotics, though the preferred treatment option, studies showed varying efficacy with up to 30% of children either not responding or accompanying an increase of adverse events, thereby affecting the overall treatment adherence and compliance.[12] One of these medications' drawbacks is their inability to treat co-occurring disorders like sleep problems and hyperactivity that are linked to ASD and ADHD assisted by aggression and anxiety behavior (whose severity increases with the child's age) but do not address the core symptoms when taken for a short duration and if used for a longer duration of time, they may lead to metabolic complications and death of premature children.[13,14]

With the absence of a standard protocol for the management of ASD/ADHD, studies concluded that the approach has become multi-dimensional. As a result, clinicians are showing their inclination for non-pharmacological agents like dietary and nutritional supplements, which include the micronutrient supplementation of minerals, multiple vitamins (Zinc, Vitamin-D), and peptides comprising L-carnosine (2 studies in ASD and 1 study in ADHD among children) followed by phospholipids like phosphatidylserine, ketogenic diet, fatty acids, and gluten-free, thus, in conjunction with psychosocial techniques, they were reported to have specific impacts on distinct ADHD or ASD condition symptoms like rehabilitation, revalidation, and psychological interventions, towards improving the QoL of both child and family members with a decrease in stress, anxiety, and improvement in auditory memory.[15]

The autism research institute has emphasized that early intervention, improves the prognosis, but permanent treatment usually lasts for an infinite time posing a burden on the family and the child concerning social challenges with colleagues, other family members, and society, leading to the emergence of undesirable behaviors, like aggression or self-aggression.

Emerging Treatment Options

According to data, oxytocin administration is one of the new targeted treatments that may help children with ASD. However, this treatment's role has only been studied in terms of its immediate effects, so it is not the only option that can help these kids with repetitive behaviors, social reciprocity, or emotion recognition. There is conflicting evidence about the effectiveness of lovastatin, bumetanide, and cannabidiol for their psychotropic qualities in treating the basic symptoms of ASD in children.[16]

Current Management and the Place for Probiotics

Currently, the management of neurodevelopmental, neurodegenerative disorders, and neuropsychiatric conditions involves symptomatic management, with the available medications working at the receptor level typically having limited efficacy and/or heavy tolerability loads, they only provide temporary relief. In order to prevent and cure neurological, neurodegenerative, and mental problems, particularly in children, it is necessary to find more efficient, affordable, and accessible therapies. Research has shown that disease modifiers can fulfill the need along with the current management, as an adjunct with synergistic effect as they act at the physiological level for an enduring clinical outcome.

The Role and Place of the Small Brain

The gut microbiome is the most diverse and rich in species of all the microbiomes in the human body, according to studies on the relationship and coexistence of humans and bacteria. Microbiota colonizing the gastrointestinal tract plays a vital role in shaping both the present and future health, either with positive effects or negative effects, within or outside of the gastrointestinal tract (GIT). The research further emphasized the possible beneficial effects of 33 million microbiome genes on the host genome which consists of 27 thousand genes. For the sake of optimum health, illness prevention, and management, it is crucial to comprehend the early

determinants that affect the spatiotemporal acquisition of the microbiota. Although the acquired gut microbiota is dynamic and tries to remain stable during the lifespan, they may be affected by various factors during the first 3 years of life.[17]

This review is an effort to investigate the role of the gut microbiota in developmental disorders and the potential benefits of their manipulation by particular probiotics as an addition to the current therapeutic options for providing relief to kids and teens suffering from either ASD or ADHD with the current evidence that is adding to the understanding of the human gut microbiota as well as the future directions was searched and gathered from various sources.

Evolution of Gut Microbiome

It has been discovered that the gut microbiome of infants develops quickly as a result of the current environmental conditions. This microbiome is frequently characterized by variations at both the species diversity level and at the individual strain level, and by the end of the first three years of life, it resembles an adult microbiota.[18]

From longitudinal studies, it is established that at birth, the infant's gut remains sterile which soon starts colonizing with the microbiota acquired during delivery either through vaginal, fecal, or skin-to-skin contact with the mother.[19,20] Previous research has emphasized that the actual microbial diversity initiation starts with the infant feeding of mothers milk which has large amounts of antibacterial substances, secretary immunoglobulin A (IgA), lactoferrin, and human milk oligosaccharides (HMO) , which provide food for the colonized bacteria to grow in number as well as increase their diversity, particularly the *Bifidobacteria*, which dominate over other bacterial species in the infant's gut favouring lactate digestion and when the child is in transition from mothers feed to solid food introduction, changes tend to occur in gut microbiome composition with a shift of *Bifidobacterium* abundance to Bacteroides and firmicutes abundance, favouring carbohydrate digestion.[21]

The introduction of solid food should not happen before 90 days, according to studies on the timing and effects of complementary feeding on the diversity of the gut microbiota. Doing so may significantly alter the child's gut microbial diversity through increased butyrate production, which increases oxidative stress in the gut and increases the child's risk of obesity and immune disorders. Hence, solid food should be introduced at an appropriate time.[22]

The human gut has the colonization of 10^{13}–10^{14} microorganisms belonging to various species of bacteria, protozoan, fungi, etc., which are interrelated and are derived from around 1000 species, thereby creating a microecology within the gut.[23] Studies showed that the immune system's maturation, the production of short chain fatty acids (SCFA) like acetic acid, propionic acid, and butyric acid, the promotion of the digestion of carbohydrates, fats, and proteins, as well as maintaining the health of the microbiota, are all functions carried out within the gastrointestinal tract (GIT). In addition to these, gut microbiota regulates GI barrier integrity, and vitamin synthesis, and consequently, detoxification within GIT plays a vital role in the treatment of certain disorders. The ingested components derived from them pass through Blood B and reach central nervous system (CNS), for its development, suggesting their role beyond the gut.[24]

Gut microbiota constituting several microbes representing bacteria, yeast, and virus form the gut microbiota. Among these microbes, *firmicutes* and bacteroidetes make up 90% of these germs in the gut microbiota with the remaining 10% constituted of *Actinobacteria*, *Proteobacteria*, *Fusobacteria*, and *Verrucomicrobia*. *Lactobacillus*, *Bacillus*, *Clostridium*, *Enterococcus*, and *Ruminicoccus* belong to *firmicutes* whereas prevotella represents a major genus from bacteroidetes.[25]

Butyric acid is primarily produced in the presence of *firmicutes*, which are crucial for human health, particularly in cognition, SCFA like acetic acid and propionic acid are formed either by fermentation mediated or by bacteroides like *lactobacillus* and *bifidobacterium*, which is important in cognitive neuroeducation (CNE) and autism behaviour.[26]

The ratio of firmicutes to bacteroides, which is crucial for regulating the gut-brain axis (GBA), was found to be lower in children with ADHD, according to several studies.[26] These studies also found that these children had higher levels of SCFA, such as propionic acid and acetic acid, than butyric acid.[27] According to the research, there is a communication pathway between the gut microbes and the 1–5 billion neurons that make up the neuronal systems. This pathway is primarily mediated by the vagus nerve and responds to the microbiota metabolites gut associated lymphoid tissue (GALT), hypothalamic-pituitary-adrenal axis (HPA), neurotransmitters, and neuromodulators like gama amino butyric acid (GABA), dopamine, noradrenaline, acetylcholine, and SCFAs. The vagus nerve modulates up to 90% of impulses going from the gut to the brain and just 10% going the other way.[28]

When evaluating the early life risk factors for gut dysbiosis, the phenomenon of the diversity of the gut microbiome was highlighted, which continues with minor alternation unless otherwise significant changes occur either in diet or administration of oral antibiotics in response to a pathological condition, can greatly alter the gut microbiome homeostasis leading to dysbiosis. In children, dysbiosis is commonly manifested as diarrheal episodes, which, if not addressed can affect the nutritional status, growth, and development of the child. As the child completes three years of age, the gut microbiome becomes relatively stable and starts resembling an adult-like gut microbiome in terms of colonization, species diversity, and composition.[29]

The impacts of the gut microbiota go beyond the GIT because research has shown that any changes to the gut-brain axis can affect how well the human brain functions, either by impairing impulse transmission and causing low-grade inflammation or by increasing oxidative stress, cellular degeneration with an imbalance in energy equilibrium, affecting the cognition, and emotional behavior of an individual leading to the development of neurological disorders. Children with neurodevelopmental disorders like ASD are shown to have a higher incidence of gastrointestinal challenges with increased intestinal permeability followed by a change in gut microbiota diversity, thereby affecting gut homeostasis with a leaky gut and dysregulation of SCFA levels leading to the decrease in acetate acid and butyrate while an increase of valerate.[30,31] Due to its multifaceted contributions to a child's good health, the gut microbiota has consequently become recognised as an organ. This is because more research has been done to determine the causes of its imbalance and to develop prevention strategies that involve manipulating the microbiota with external supplementation. This addresses the causes of the dysbiosis state that leads to eubiosis.

Recent lifestyle changes, better sanitary practises, fewer families, a poor diet, the use of antibiotics, and the birth of infants have all been demonstrated to have a significant impact on the gut microbiome and contribute to dysbiosis. While dysbiosis can happen at any moment in life, research has shown that it frequently

paves the way for the formation of pathological disorders later in life. This suggests the necessity for research aimed at root cause identification and management for eubiosis.

According to epidemiological research, fluctuations in the diversity of the gut microbiota as a whole are mostly caused by changes in the environment, socioeconomic conditions, and lifestyle modifications including diet have resulted in an increased prevalence of non-communicable diseases, which compromises the QoL of an individual and contribute indirectly to increasing the morbidity and mortality at an early age. Therefore, with the introduction of gut microbiota with precision-based interventions, understanding the factors affecting gut dysbiosis, the interaction between the gut microbiome and the host microbiome, as well as the impact of digestion and detoxification, has become a research area towards developing strategies for both prevention and treatment.

Probiotics are living microorganisms that, when given to a host in sufficient quantities, improve their health. Probiotics have been shown in studies to have strain-specific effects and to have the demonstrated ability to restore gut homeostasis.

The Connection between Central Nervous System and Gut Dysbiosis-associated Disorders

The immune system is found to encourage microbiota colonization by regulating CNS functions and microglial homeostasis. This is in line with the idea of the microbiota-gut-brain axis, in which the gut and microbiota maintain mutual communication and tend to release metabolites and hormones that tend to cross the blood brain barrier (BBB) to reach the brain after passing through the enteral nervous system (ENS). This confirms that gut dysbiosis affects the central nervous system, and probiotic treatment over an extended period has been demonstrated to promote eubiosis with the regulation of the level of corticosteroids responsible for stress, leading to an improvement in the symptoms of depression and anxiety.[32]

Probiotics, Autistic Spectrum Disorder, Attention-deficit Hyperactivity Disorder, and Gut Dysbiosis

According to research based on experimental model findings, neurodevelopmental disorders are a class of pathological illnesses that are frequently characterised by communication and social interaction deficits as well as repetitive behavior in children when interacting with other kids. Additionally, there is a high link between and intensity of GI symptoms and ASD.[33,34] One in two children with ASD were reported to experience GI symptoms such as constipation, vomiting, and flatulence, according to a recent consensus study on the evaluation, diagnosis, and management of GI issues in children with ASD.

Numerous studies revealed that autistic children had greater numbers of harmful bacteria in their guts, which affects the levels of fecal short-chain fatty acids. Acetic acid and butyric acid levels primarily decrease while valeric acid levels rise. Even in animal models, these results demonstrated a correlation between increased constipation and the neurotoxic generation that compromised the function of the epithelial barrier due to alterations in the microbiota and resulted in the emergence of neurodevelopmental disorders (NDD). Among children, Bacteroides fragilis supplementation demonstrated a strengthening of gut-epithelial integrity, improving gut microbiota diversity, and behavioral improvement.[35,36] Gut microbiota manipulation may be an ideal, safe, and advantageous approach to providing relief from some symptoms in children with ASD as an adjunct to the current therapies because probiotics may influence gut microbiota communities to vary the levels of harmful metabolites in ASD children while also reducing GI inflammation and increasing intestinal permeability.[18] Earlier studies using the pyrosequencing method examined the variety of the fecal microbiota in 33 children with ASD and discovered that in comparison to control, ASD children displayed higher amounts of bacteroidetes—which are important microbes in the pathophysiology of ASD along with a lower abundance in firmicutes (mainly *Bifidobacterium*), which are in-line with other studies.[37]

The causes of ADHD are multifactorial ranging from genetic factors and environmental factors. Research has indicated the imbalance between the HPA axis and to neurotransmitter system, has been discovered to have a significant impact on the gut microbiota as any HPA-neurotransmitter system imbalance, will after the neuronal transmission to the brain but also lead to dysbiosis with alternation in microbial diversity.[37]

Researchers found that supplementing with a probiotic formulation containing *Lactobacillus helveticus R0052* and *Bifidobacterium longum R0175* for a month had positive effects in a population that was otherwise generally healthy. These effects included a decrease in anxiety and depressive-related behaviours as measured by both global scores of the hospital anxiety and depression scale (GHADS) and global severity index of the Hopkins symptoms checklist (HSCL90), with a higher reduction in anxiety-related behaviours. The study has highlighted the oral intake of this probiotic formulation among subjects resulted in lower urinary-free cortisol levels as compared to the baseline.[38]

An RCT examining the favourable therapeutic impact of *Lactobacillus reuteri DSM 17938* given to children between the ages of 4 and 18 at a dose of 1×10^8 colony-forming units (CFU) per day for 8 weeks suffering from recurrent abdominal pain due to IBS has been shown to improve the mood as strain modulates the pain within the gut.[39]

The *Psychobiotics* refers to a class of probiotics that have been shown to control the activation of the vagus nerve through neurotransmitters like GABA, serotonin, glutamate, and proteins like BDNF. These neurotransmitters and proteins play a crucial role in regulating the neural excitatory-inhibitory balance towards mood, anxiety, cognitive functions, learning, and memory processes, as well as an increase in appetite.[40] In addition, the balance of the hypothalamic-pituitary-adrenal axis (HPA) and gut microbiome, as any change results in the excessive release of corticosterone and adrenocorticotropic hormone (ACTH) in comparison to stress protective factor (SPF) with an increase of stress and proinflammatory cytokines, activates the HPA with an increase in the permeability of BBB, leading to the precipitation of psychiatric condition called depression.[41]

Current research has concluded that with the available evidence that certain selected *Psychobiotics* strains belonging to *Lactobacillus* and *Bifidobacterium* species like *Lactobacillus Brevis*, *Bifidobacterium dentium*, *Lactobacillus Plantarum*, *Lactobacillus paracasei* (LP-37) and *Lactobacillus Odontolyticus*, modulate the discharge of GABA, serotonin, and acetylcholine, from the enterochromaffin cells of the gut, which otherwise may result in psychiatric disorders.[42]

Psychobiotic's Impact on ASD and ADHD-afflicted Children

The study established the significance of serotonin, which is produced by enterochromaffin cells in the gut and has an impact on the balance of the gut microbiota, particularly with spore-forming bacteria. This paves the way to test and identify an ideal spore-forming probiotic for its beneficial effects beyond the gut to the brain, thereby emerging as one of the ideal probiotic candidates for managing psychiatric diseases.[42]

In an RCT with 17 ASD children aged 4–16 years, *L. Plantarum WEFS1* was administered daily at a dose of 4.5×10^{10} CFU for 7 weeks. The children were divided into 2 groups: Group I received a probiotic during the 2nd feeding period (3 weeks), while group II received a placebo during the 1st feeding period (3 weeks). About 17 kids who finished the trial had their behavioural impacts evaluated using a validated development behavior checklist, and they exhibited improvement in disruptive antisocial behaviours, anxiety, and communication issues.[43]

In another RCT, the impact of a probiotic mixture was evaluated on 85 preschoolers with ASD with a mean age of 4.3 years. *Streptococcus thermophilus*, *Bifidobacterium breve*, *Bifidobacterium longum*, *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Lactobacillus Plantarum*, *Lactobacillus paracasei*, and *Lactobacillus delbrueckii* received a daily dosage for the group II. The probiotic supplement was a combination of 8 probiotic strains, each containing 450 billion CFU (Received Placebo). The results showed that 63 children (74%) completed the study. Children who successfully completed the experiment were given 2 sachets per day for the 1st month and 1 sachet for the next 5. The NGI group treated with probiotics demonstrated a significant decline in ADOS scores as compared to that in the placebo group, with a mean reduction of 0.81 in Total autism diagnostic observation schedule, calibrated severity score (ADOS CSS) and of 1.14 in social-affect ADOS CSS, according to an exploratory secondary analysis on subdivisions of children with or without gastrointestinal symptoms (GI group, $n = 30$; NGI group, $n = 55$). In comparison to the GI group treated with a placebo, the GI group treated with probiotics demonstrated a reduction in GI symptoms along with improvements in adaptive functioning and sensitivity biographies. These results clearly showed the beneficial effects of probiotics with improvements in core symptoms among ASD children irrespective of the child with or without GI symptoms.[44]

After supplementing with *Lactobacillus rhamnoseus* GG for the first 6 months of life in 40 subjects (53.3%) vs 35 children (46.7%) with placebo, it was discovered in an intriguing RCT involving 75 infants at risk of neurodevelopmental disorders in 6 out of 35 (17.1%) children in the placebo group were identified as having ASD or attention-deficit/hyperactivity disorder, but none within the probiotic group (i.e., $p = 0.008$). These findings imply that early administration of *Lactobacillus rhamnoseus* GG, beginning 4 weeks before the anticipated birth, may lessen the likelihood of developing ADHD or ASD.[45]

Another open-label, single-arm trial including 30 kids between the ages 4 and 16 looked at the effects of probiotic supplementation with *Bifidobacterium bifidum* (Bf-688) on the gut microbiomes of people with ADHD. For 8 weeks, each participant took 1 sachet of BF-688, once in the morning and once in the evening. The findings demonstrated that BF-688 considerably decreased *Bacteroidetes* and significantly increased *Shigella*, even after BF-688 was withdrawn for 4 weeks (12 weeks from baseline). Children with ADHD who took the probiotic supplement Bf-688 saw improvements in their hyperactivity/impulsivity, other clinical symptoms, and weight gain. The Bf-688 supplementation also considerably changed the composition of the gut microbiota.[46]

A recent study investigated the beneficial effects of *Lactobacillus plantarum* PS128 (PS128) among autistic boys aged between 7–15 years, meeting the diagnostic statistical manual-V (DSM-V) criteria with 3×10^{10} CFU/capsule/day for 28 days. The results showed that PS128 supplementation has resulted in a significant improvement, with respect to cooperation/respect behavior in addition to the other elements. At the same time, the effect was seen more in younger children, which concludes that the earlier the detection, the better will be the response. More research is required to fully understand how PS128 affects broader symptoms in younger ASD patients.[2]

Using a daily dose of 1.75×10^{10} colony-forming units (CFU) of LPC - 37, once daily for 5 weeks, an Indian study examined the effects of probiotic supplementation on total *lactobacilli*, *Bifidobacteria*, and short-chain fatty acids in children ages 2–5. The findings demonstrated that by lowering the levels of SCFA's, LP-37 is both safe and effective in lowering the risk for diarrhoea and fever during the rainy season.[47]

Researchers hypothesized that habitual stress is a threat factor for the development of mood and stress-related diseases. Clinical substantiation of this indicates that probiotics can impact stress response and mood. An RCT constituting 120 subjects was administered 1.75×10^{10} colony-forming units (CFU) of *Lacticaseibacillus paracasei* Lpc-37®, once daily for 5 weeks. With its regulation of neurotransmitters and BDNF via neurotransmitters like GABA/Dopamine/Serotonin, interaction through the gut-brain axis by vagus nerve stimulation, and activation of the HPA, the LP-37 revealed a reduction in perceived stress while stabilising cortisol levels (Hypothalamic-Pituitary-Adrenal Axis). Pathway leading to patient stress control and improved health and sleep-related recovery. This in turn improves cognition by preventing chronic stress-associated deficits in recognition memory and has proven efficacy in alleviating cognitive dysfunction.

Conclusion and Future Directions

The gap left by the current therapies, which provide long-lasting core symptom relief among ASD/ADHD children, can be filled by *Psychobiotics* with *probiotics* that are properly characterized for their strain specificity, and adequate dosage demonstrating proven efficacy and safety among ASD children. This will enhance their QoL as well as their understanding of the human gut microbiome across age-groups.

In addition to the existing therapies, *Psychobiotics* can be the answer for managing neurodevelopmental disorders, with deeper, independent studies being conducted across the world and in India, to overcome country-specific variations, toward understanding which formulation, strain, dosage, and timing of administration as per the age group can produce desired results of treating the underlying cause with the manipulation of the gut microbiome, thereby offering enduring relief from core symptoms along with QoL of the patient with NDD like ASD/ADHD and others. Studies conducted in other emerging neurodevelopmental conditions like epilepsy, psychiatric disorders, and neurodegenerative disorders are beyond the scope of the view. Long-term clinical studies conducted both in adults and children can show the path for conclusive evidence in the future.

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