

ROLE OF PROBIOTIC SUPPLEMENTATION ON CHILDREN WITH AUTISM SPECTRUM DISORDER

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REVIEW

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ABSTRACT

Introduction – Autism spectrum disorder (ASD) is one of the neglected problems which keep increasing worldwide and contributing high burden for the parents and sufferer. Currently, there are still no definitive or effective therapy existed. Probiotics are living beneficial microorganisms which can confer health benefits as management agent in ASD children. This paper will evaluate the role of probiotics as a promising management approach to ASD based on the novel knowledge thus increasing the patient's quality of life.

Methods – A literature review evaluating the role and effectiveness of probiotics in managing children with ASD is constructed with inclusion criteria based on PICOS framework. The article search strategy is using boolean operator with the main keyword “Autism Spectrum Disorder”, “Probiotic”, “Management” to get structured and specific results. Data extracted from *Pubmed*, *ScienceDirect*, and *Cochrane* databases with and only papers published from 2011-2021 that are included.

Results – The author reviewed 8 articles that met inclusion criteria. Studies were conducted globally in children of various ages and the probiotic intervention varies in dose and durations. All studies stating that probiotics are effective to improve the symptoms of children with ASD. The Improvement is related to autism symptoms, gastrointestinal symptoms, microbiome variety, and laboratory findings.

Discuss – The improvements by probiotics are correlated to some mechanisms including control of gut integrity, restore good microbiome variety, maturation of the host immune system, signaling to CNS via ENS, correcting “opioid excess”, and oxytocin maximization.

Conclusion – Probiotic has a role in managing children with ASD by improving the symptoms based on the gut-brain axis approach. In future research, it is suggested to evaluate the long-term safety and efficacy and possible combination therapy of specific bacterial species of probiotic in clinical trial research.

Keywords: autism spectrum disorder, probiotic, management, supplementation.

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INTRODUCTION

Autism spectrum disorder (ASD) is one of the neglected problems which keep increasing worldwide, especially in Indonesia¹. The number of children with ASD in various countries keeps increasing, with the latest data showing a rapid increase to 1 in 59, as the prevalence of children with autism in Indonesia was 1 in 50 in 2013.¹ Current epidemiological studies also reported prevalence rates in general population of 58-67/10.000, suggesting that ASD affects many families thus becoming an important culprit in public health problem.²

ASD is a complex group of neurodevelopmental disorders characterized by impaired social interactions and communication together with repetitive and restrictive behaviours². Autism represent the primary type of ASD. ASD has been challenging the parents and sufferers because it increases the burden to the parents in the matter of financial,

time, and effort aspect and also severely affects daily functions and sufferer's quality of life.^{3,4} Often parents feel embarrassed by having “special child”. These conditions not only trigger a loss to the basic needs of children but also causing the child to suffer more in the future. Thus, effective management supported with a good understanding of the disease is needed. Many factors have been associated with incident of ASD including genetic and environmental factors.⁵ Although remain elusive, many findings take a scope in the role of environmental factors, especially in the gastrointestinal aspect as many children with ASD exhibit gastrointestinal symptoms that accompany their neurological alterations, which may be associated with the gut microbiome.^{6,7} The gastrointestinal symptoms are suspected to correlate with the severity of ASD.⁸ Microbiome which is defined as the combination of bacteria and its genetic material confers multiple physiologic advantages and disadvantages to human in many fundamental

aspects of life. Microbiota's role in health and disease is complex. Dysbiosis, which is alterations in normal flora of gut result in an increase in pathogenic microbes that disrupt homeostasis, has been reported as a trigger to multiple system problems, one of them is gastrointestinal-CNS.^{9,10} This is called by gut-brain axis.¹¹ This unity of communication network consists of central nervous system (CNS) and the enteric nervous system (ENS).¹¹

Currently, there are still no definitive or effective therapy existed. Treatments and managements that are used widely such as educational therapy and pharmacological approach are basically only focusing on the symptoms but not on the fundamental problem.¹¹ Based on these findings, an approach to microbiome modification may provide a better solution in managing children with ASD, one of the most enterprising research is by using probiotic.¹²

Probiotics are living beneficial microorganisms which can confer health benefits if consumed sufficiently in many conditions starting from cardiovascular to neurological disease.¹² Therefore, the author aimed to evaluate role of probiotics as a promising management approach to ASD based on the novel knowledge in order to increase the quality of patients' life.

METHOD

Approach used in this article is literature review. A literature review evaluating the role and effectiveness of probiotics in managing children with ASD is written based on the guideline. Data extracted from *Pubmed*, *ScienceDirect*, and *Cochrane* databases with and only papers published from 2011-2021 that are included.

The article search strategy is using *boolean operator* with the main keyword "*Autism Spectrum Disorder*", "*Probiotic*", "*Management*" in order to get structured and specific results. Inclusion criteria in this review are using PICOS framework consist of: 1). Population, which is children with diagnose of ASD based on Diagnostic and Statistical Manual of Mental Disorders fifth edition (DSM-V), 2) Intervention, which is probiotic and/or related therapy, 3) Comparison, which is placebo, 4) Outcome, which is improvement in any aspect of patients, 5) Study Design, which is clinical trial.

Based on the article searching, the author obtained 455 articles on identification process and then only 11 articles that met because the other articles do not fulfill inclusion criteria (n=436) and cannot be accessed (n=8). In the end, full text analysis showed only 8 articles due to duplication (n=3).

RESULT

Study Characteristics

The author initial search yielded 455 articles, 11 of which were eligible for this literature review. Studies were conducted globally in Italy (n=1), United Kingdom (n=1), Taiwan (n=1), Egypt (n=1), USA (n=2), China (n=1), and Slovakia (n=1). The dosage (1-3 times/day) and interventions durations (1-12 months) were variable. The subject's age was variable (18 months – 12 years).

Effectivity of Probiotic Related to ASD Symptoms

All studies stating that probiotics can be effectively used to improve the symptoms of children with ASD.¹³⁻²⁰ Probiotic supplementation could reduce the total score of ADOS-CSS in

45,2% of children (P<0,05) and also ATEC score (P<0,0001) proven by a notable reduction in the severity of symptoms.^{13,16,19} Evaluated reduced symptoms include speech/communication/language, sociability, cognitive awareness, and behavior of the children compared to the control group. Qualitative analysis also shows that children treated with probiotics had better sleep habits and significant improvement in social intervention.¹⁴ Although some studies stating that there was only minimal improvement in several elements related to ASD symptoms, it was known that the minimal outcome is significant in younger subjects thus underlining that probiotic may ameliorate behavioral or social-communicative traits with younger subjects experienced greater benefits than the older children.^{17,18} In addition, ASD children with GI symptoms treated with probiotics showed normalization of sensory profile score in the multisensory processing subscale (P=0,013) 87% better compared to the control group.¹³ Some studies also evaluating the correlation between known biomarker (i.e TNF- α) and hormone (i.e oxytocin) which were known to be correlated with the severity of autism symptoms.²⁰

Effectivity of Probiotic Related to Gastrointestinal Symptoms

As stated, before that many ASD children exhibit gastrointestinal symptoms, the exploration needs to be done. Most studies stating that probiotics management can be effectively used to reduce abdominal symptoms in children with ASD (P<0,05).^{13,14,16-20} Total gastrointestinal symptoms represented with Total GSI and Total6-GSI improved (P<0,0001) with a significant reduction in constipation, stool consistency, flatulence, bowel movement, and abdominal pain were reported in children treated with probiotic.^{13,14,16} The number of gastrointestinal problems and their severity were found higher in control group with significance shown by a strong positive correlation between the intensity of GI symptoms and the severity of autism, scored on ADI scale (R=0.70, P = 0,01).²⁰ It is also subjectively reported based on general results from both QPGS-RII and GIH questionnaire data and testimony of parents that most of the treated children exhibited global improvement in gastrointestinal symptoms, which is followed by repairment in behaviour.¹⁸ No serious adverse effect was found on these studies.¹⁷

Effectivity of Probiotic Related to Microbiota Analysis

As a "non-genetic contributor", the gut microbiota is suspected to affect the development of ASD because it was found that the composition is different between normal children and children with ASD.¹⁵ Several studies stated that compared to healthy children, ASD patients having a lower variety of beneficial bacteria such as bifidobacteriales and lactobacillus and increased potentially harmful bacteria such as Clostridium and ruminococcus, which may increase the risk of triggering ASD (P<0,05).^{14,16,17,19,20} This dysbacteriosis condition was represented by a different bacterial abundance and there is a correlation between the severity of dysbacteriosis and autism manifestation.²⁰ Probiotic treatment could correct the shifting in the gut microbiome thus correcting the symptoms of children.^{14,16,17}

Effectivity of Probiotic Related to Laboratory Findings

Some studies evaluated the effect of probiotic treatment in children with ASD on biomarkers such as certain cytokines, hormone, and other marker.¹⁸⁻²⁰ Probiotic supplementation

could reduce the intracellular expression of some cytokines by mean of both CD4+ and CD8+ T cell and also TNF- α expression ($P < 0.05$).^{18,20} They are known of having a strong correlation with gastrointestinal symptoms ($R = 0.78$) which upright the general knowledge of involvement of gastrointestinal inflammation and disruption of gut permeability in the severity of autism. This is further supported by a finding that the plasma zonulin level was higher in the untreated group and after probiotic intervention, plasma zonulin levels decreased causing improvement in gut permeability.¹⁹ Also, the level of oxytocin was found to be notably lower in plasma of ASD children and supplementation of probiotic correct the level and autism severity, suggesting significant positive correlation.²⁰

DISCUSS

Autism spectrum disorder (ASD) still become a concern worldwide and a novel management approach based on the current finding of ASD, namely gut-brain axis, has become a need to improve the children's quality of life. Overall, gut microbial-based intervention by using probiotics is effective in managing ASD. In this review, probiotics have been shown to regulate ASD in term of reducing the severity of autism symptoms, treating the gastrointestinal problems, correcting the shifted microbiome inside gut which may also lead in many changes in another laboratory biomarker such as cytokines and hormone.¹³⁻²⁰

Even the precise etiopathogenesis of ASD has not been clearly explained, current enterprising research has focused in the interactions between the gut microbiota and the brain in patients with autism which is postulated to influence and modulate emotions, anxiety, and behavior through some proposed mechanisms. First, gut microbiota is contributing in maintaining the permeability of gut.²¹ Dysbiosis is known to cause disruption of the mucosal barrier, proven by many gastrointestinal problems finding in ASD children, that is going result in an increase of gut permeability thus allowing exogenous peptides of the dietary origin or neurotoxic peptides to go to circulation and trigger inflammatory cytokines.^{13,22} This is further supported by the author's current finding of an increase in the plasma zonulin on untreated children as it is known that zonulin is a building block for tight junction and keeping its integrity.¹⁹ Probiotic supplementation could reduce the plasma titer of zonulin and enhancing its gene expression thus improve gut epithelial integrity.^{19,23}

Shifting of the normal microbiome from bifidobacteriales to potentially pathogenic bacteria, such as clostridium, is a common finding in ASD patients.¹⁹ This dysbacteriosis is intensely correlated with the symptoms of gastrointestinal followed by the severity of ASD. One of suspected mechanisms is that *clostridium* could release a toxin which results in the destruction of gut integrity thus leading to a domino effect in gut-brain axis manner.²⁴ Here the author

describes that probiotic supplementation could restore the good microbiome variety thus reducing the effect of toxin and improving the symptoms of children.¹⁶⁻²⁰

Secondly, bacteria inside gut also take place in the process of host immune system maturation. This is done by modulating adaptive and innate immune system, especially T- cells which prevent inflammation and has been proven in this review.¹⁸ Modulated immune system leads to an increase in inflammatory cytokines release which are known to regulate CNS via vagal system.

Thirdly, the gut microbiota has ability to signal CNS via ENS or afferent fibers pathway of vagus nerve. The approach used could be via the release of certain neurotransmitter into the bloodstream. Probiotic supplementation could reduce distress and enteroception caused by Gastrointestinal symptoms and as a result it could ameliorate the multisensorial integration process. Recently, it is also found that some problems related to multisensory processing have been related to the serotonergic system whose levels are regulated by the gut microbiota. Thus, it is hypothesized that probiotics could repair sensory difficulties in term of restoration of the serotonin system that operates also on the reduction of GI symptoms, which in the end result in an improvement of adaptive functioning.¹³

Another interesting possible mechanism are "opioid excess" and oxytocin theories. Children with ASD seems to lack in digestive enzyme activity and impaired protein digestion especially gluten and casein.¹³ Supported by facts that children with ASD also having problem related to gut permeability, this combined condition could be responsible for the elevated levels of urinary dietary peptides, altered plasma amino acid profiles, and high levels of fecal putrefactive metabolites (i.e., propionic acid) reported in children with ASD in this review.¹⁹ The product breakdown can act as opioid receptors and exerts effects on the CNS and neurobehaviour.²⁵ Probiotic supplementation could increase the catabolism of gluten and casein thus becoming an unharmed metabolite.²⁶ It is recommended to combine probiotic management and certain exclusion of diet in order to improve the outcome better.

Oxytocin is a hypothalamic neuropeptide of multiple functions, including modulation of emotional and social communication, bonding, and reward-related behaviors.²⁷ It was known that the deficiency in oxytocin signaling will result in autistic-like behavior thus dysfunction of oxytocin signaling has been postulated to play an important role in pathogenesis of ASD.²⁷ This theory is supported by the author's findings that the level of oxytocin was significantly lower in plasma of children with autism and probiotic supplementation could correct it.²⁰ Another interesting finding is that the problems are not only related to low levels of oxytocin but also the downregulated expression of its gene (OXTR) due to an increase in toxic opioid analog from gluten-casein metabolism thus probiotic supplementation will provide a holistic solution in managing children with ASD.²⁸

CONCLUSION

Probiotic has a role in managing children with ASD by improving the symptoms based on the gut-brain axis approach. Since these findings indicated that probiotic supplementation has a role and effectiveness in managing children with ASD based on current understanding problems, it is suggested to evaluate the long-term safety and efficacy and possible combination therapy of specific bacterial species of probiotic in clinical trial research.

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