Effects of prebiotics, probiotics intervention in children with autism spectrum disorder – A systematic review

Gayathri M. Rao[1], Saritha Kamath U.[2], Rakshith[3]

[1]Department of Biochemistry, Kasturba Medical College, Mangalore, Manipal Academy of Higher Education, Manipal, Karnataka, India

[2]Department of Medical Laboratory Technology, Manipal College of Health Professions, [3]Department of Medicine, Melaka Manipal Medical College, Manipal, Manipal Academy of Higher Education, Manipal, Karnataka, India-576 104

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Corresponding author: **Saritha Kamath U.** Email: saritha.kamath@manipal.edu

ABSTRACT

Gastrointestinal (GI) microbiota is one of the determining factors in handling the neuronal and psychological features in Autism spectrum disorder (ASD) and corrected by restoring the microbiome environment by the supplementation of pre and probiotics. Purpose of this article is to draw evidence by systematic review for the effects of prebiotics, probiotics intervention in children with an autism spectrum disorder. Selected data sources were searched for relevant literature and included as per the set criteria from January 2019 to August 2019 by two authors and the third author resolved discrepancy. Finally, 4 articles were selected for the in-depth review as per the format by considering inclusion and exclusion. Probiotics and prebiotics have shown good effects in improving some of the symptoms of autism spectrum disorder. However, available evidence is limited. More studies are required to obtain a better conclusion in this area by increasing the sample size.

Keywords: Prebiotics; probiotics; autism spectrum disorder.

INTRODUCTION

Autism spectrum disorder (ASD), a behaviorally defined condition with a severe neuro-developmental disorder. Characteristic features include difficulty in social or emotional reciprocity, interactions, communication, restricted range of behavior, and imagination may be due to suffusing impairments in several important areas of the brain. Along with these, a greater frequency of GI complaints in ASD patients (1) the observed variable symptoms include diarrhea, constipation, stomach pain, or bloating. The GI conditions may be refractory to traditional therapy (2). Though these are the characteristic features, detailed etiology behind the manifestations are still not clear.

Disturbance in microbial ecology may be associated with many disorders. One of the recent studies reported a close association between gut environment and anxiety disorders (3) more generally, the function of intestinal flora in the gut-brain axis. The development of gut microbiota happens along with growth, development, and increase of neurons in the young brain (4). Recent studies provided insights into potential pathways and mechanisms linking the microbiota to the brain (5).

Copious evidence support that microbiomes and their metabolites can alter the normal gut-brain axis homeostasis, a bidirectional communication, between the central nervous system (CNS) and gut. A disorder of the microbiota-gut-brain axis is evolving as a projecting issue in autistic behaviors (6). Many studies pinpoint the possibility of environmental risk factors and associated co-morbidities to explain the neurobehavioral symptoms of the disorder. Abdominal discomfort, nausea, and diarrhea or constipation are co-morbid gastrointestinal symptoms of ASD individuals (7, 8). In addition, animal models studies showed that certain microbial variations in the gut result in the altered digestive, immunological, and metabolic processes are consistent with the clinical presentation of autism. Growing evidence shows that a shift in gut microbiota contributes to the pathophysiology of various disease and support its key role in the maintenance of homeostasis including CNS disorders (9).

Several research, both animal and human, strongly support a correlation between intestinal microbiota, and the development and/or manifestation of various neuropsychiatric conditions (10-12). Several study reports reveal the close association between gut microbiota, brain oxytocin level, and social behavior (13, 14). The cause of these GI problems is uncertain, but it appears linked partly to the abnormal intestinal flora, and probably the excessive use of oral antibiotics may modify the gut flora. Several studies by different research groups documented a higher level of use of oral antibiotics in children with autism versus normal children (15-17). Research also indicates an increase in autism-related microbiota diversity in children with an excess of Bacteroidetes found linked to serious autistic cases (18).

Prebiotics includes non-digestible dietary components such as non-digestible carbohydrates, enters the GIT. These are the source of food for probiotics in gut/large bowel, helping them grow. The growth of good bacteria provides healthy digestive and immune systems in humans. Prebiotics are crucial to maintain the performance of probiotics

(good bacteria). Probiotics are of beneficial live microorganisms, which enhance gut health and immunity. It has been reported that the probiotics have a modulatory effect on GI microbiota, which in turn may help in the betterment of several pathological conditions the same would be effective even in reverting some of the co-morbidities of ASD.

METHODS

Data sources

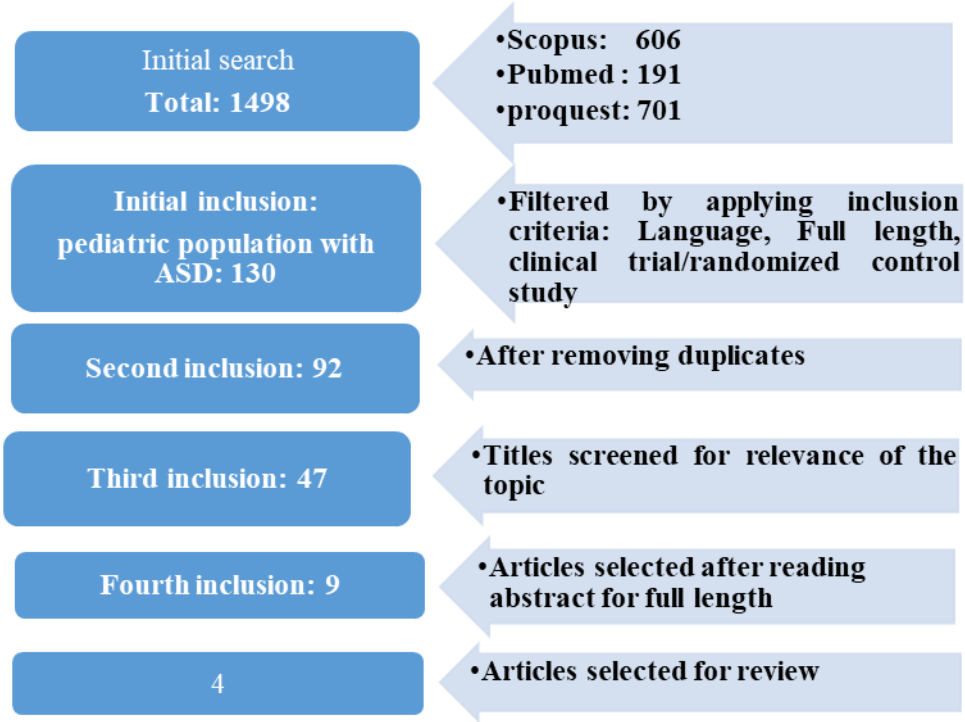
Scopus, Web of Science, Cochrane CENTRAL, EBSCO (CINAHL Plus with Full Text) PubMed / MEDLINE. The relevant literature search did from January 2019 to August 2019.

Study selection

Two review authors independently selected the title of articles through all the mentioned databases. Duplicates were excluded, and the third author assessed the eligibility of all sources by reviewing the titles, and abstracts. Discrepancy identified and resolved through discussion with the help of a third author. All potentially eligible studies read in full-text and assessed for inclusion, independently by two authors. Included articles reviewed and descriptive narrative review was prepared.

Data synthesis

For the final review, we have selected seven full-length articles and checked for inclusion criteria using the format. Among these, three studies considered biochemical parameters after the intervention but no cognitive or neurological symptoms to know the effect. One study utilized both prebiotic and probiotic intervention and microbiological analysis. A study conducted in ASD using double blind, placebo-controlled, crossover-design where they used probiotic as an intervention.



DISCUSSION

Quite a few animal and preclinical studies have suggested that the intestinal flora is one of the pathophysiological elements in neurodevelopmental and neurodegenerative disorders. Moreover, altered gut microbiota composition is concomitant with a variety of neuropsychiatric conditions including autism. However, the mechanism behind their association is still unclear.

To know the critical efficacy of probiotics, in a study conducted by Sanaa *et al.*, 30 autism children of age group 5 to 9 years, evaluated the efficacy of probiotics with *L. acidophilus, L. rhamnosus*, and *Bifidobacteria longum* (19). The study includes the evaluation intestinal microbiota by real-time PCR, gastrointestinal symptoms with severity index. Probiotic supplementation showed an ameliorating effect in autism symptoms compared to baseline level evaluated before the initiation of therapy. The outcome of the study supports the view of probiotic therapy and can be counted in as adjunct therapy. However, further study is needed to substantiate the outcome with an increased sample size and randomized control trial. Megan R. *et al.*, (20) carried out a randomized double-blind controlled trial study of bovine colostrum product a source of prebiotic oligosaccharides in combination with probiotics Bifidobacterium to assess tolerability of the probiotic for 12 weeks. A comparison of GI micro biome and immune factors in children with ASD and GI co-morbidities. Overall a study, with supplementation of

pre & probiotic for the first 5 weeks and only prebiotic in the last 5 weeks with the middle two weeks as washout period without therapy. IL-13 and TNF-α was the other parameter included studying the extent of improvement. A validated questionnaire used to assess the GI function and atypical behaviors, along with side effects. The study, in conclusion, supported an improvement in GI condition after the supplementation of probiotics and prebiotics.

In another randomized, double-blind, placebo-controlled study with 30 autistic children of age group, 4 to 11 years with prebiotic supplementation of Beta-galacto-oligosaccharide (B-GOS) with probiotic bovine colostrum product showed potential benefits. There was no significant effect on GI when treated only with B-GOS, however, a significant reduction in anti-sociability scores (21) has been observed when B-GOS was combined with - gluten and casein-free- exclusion diet suggestive of such approaches might be more appropriate for the improvement of neurological/ psychological features.

The available study report survey provides some evidence of improvement from prebiotic and probiotic supplementation in the behavior of children with ASD (22, 23). The action of probiotics on the brain studied to some extent, and quite a few studies showing its therapeutic benefit during several psychological conditions such as depression and anxiety (24).

Probiotics are able to influence various neuroactive elements, such as gamma-aminobutyric acid (GABA) and serotonin (25, 26). A link between neuropeptide oxytocin, social behavior, and the pathogenesis of ASD also observed (27).

Emerging evidence supports the key role of Gut microbes are one of the key regulators of physiology, immunomodulation, and host behavior. A greater frequency of gastrointestinal symptoms and immune dysregulation is also associated with ASD. It has reported that probiotics are greatly associated with gut physiology because of their role in gut barrier permeability, modulation of inflammatory cytokine action, and other immune mechanisms. The key assumption behind this is that probiotics work across the gut-brain axis to influence neurotransmission and mood states. (28, 29). Probiotics may therefore, play a role in restoring gut microbiota as well as lowering levels of gut inflammation.

Whilst prebiotics and probiotics have shown promising results in preclinical/animal studies (18, 30), the same cannot be considered fully, since a limited number of studies available. The available studies conducted with a small number of subjects and are of area-restricted trials. Since most of the studies are involved in the questionnaire-based evaluation to measure treatment response. Here the point to consider is the status of the patient to communicate/give the feedback and the answer may be the parent's experience. More randomized, meticulous studies involving larger research population and the use of clinician scoring may lead to more robust studies and outcomes.

Limitations

A limited number of studies available and are with a small number of subjects, questionnaire-based studies may lead to bias since the study group having difficulty in communication and the answers could be the experience of the parents solely.

CONCLUSION

More randomized, detailed, mechanism-based, meticulous studies involving larger research population and the use of clinician scoring may lead to more robust studies and outcomes.

CONFLICT OF INTEREST: None.

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