




# Probiotics Effect on Psychiatric Illnesses and Autism

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In 2020, the World Health Organization reported that mental disorders (e.g. schizophrenia, bipolar disorder, depression, dementia and eating disorders) affect 1 in 4 people. Depression is the most common disorder, affecting 4.4% of the global population.<sup>[1,2]</sup>

There is a mutual relationship between gut microbiota and the brain, instantiated in reciprocal connectivity via the autonomic nervous system.<sup>[3]</sup> Moreover, studies have shown that dysbiosis of the intestinal microbiota can trigger neuropsychiatric problems such as schizophrenia, bipolar disorders and depression.<sup>[4]</sup>

The studies reviewed here indicate that diet may be associated with cognitive disorders. A Western-type diet, which is high in fats and sugars, increases the risk of anxiety and depression, while a Mediterranean-type diet is associated with reduced rates of depression.<sup>[5,6]</sup>

It is known that a diet rich in tryptophan reduces stress-related mood disorders by regulating serotonin levels.<sup>[7,8]</sup> In addition, omega-3 polyunsaturated fatty acids and a diet rich in flavonoids has been shown to reduce the risk of depression.<sup>[7,9]</sup>

## ABSTRACT

However, unbeknown probiotic consumption began centuries ago when fermented foods such as bread, wine and beer were introduced to the human diet. Recent technological advances in medicine have made it possible to examine the intestinal microflora and its relationship to mental health and autism.

**Keywords:** Autism, mental health, microbiota, probiotics.

Probiotics are living microorganisms.<sup>[10]</sup> They are found in fermented products, such as kefir and pickles.<sup>[11]</sup> Research has shown that probiotics, as part of a healthy diet, are effective as anxiolytic and anti-depressive agents.<sup>[12]</sup>

Probiotic consumption increases the levels of neurotransmitter gamma-aminobutyric acid (GABA) and the neuromodulator serotonin in the central nervous system, which are critical in depression. Low proinflammatory cytokine levels, previously found to be inversely associated with mood disorders, were observed in rodents treated with probiotics.<sup>[13,14]</sup>

## Major depression

Many studies have found significant improvement in patients with major depression as a result of taking probiotic supplements, whereas some clinical studies in healthy subjects have found no significant effect of probiotic consumption on stress and anxiety.<sup>[15,16]</sup>

## GASTROINTESTINAL MICROFLORA AND AFFECTING FACTORS

While the gastrointestinal tract is sterile at birth, the normal microflora is formed in early infancy and remains. The sources of the newborn's gut flora are the vaginal and fecal flora of the mother during birth.<sup>[17]</sup> 48 hours after birth, there are enterobacteriaceae, staphylococci and streptococci in the column; on the 2<sup>nd</sup> and 5<sup>th</sup> days bifidobacteria

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are found, and after a week, pathogens such as enterococcus and clostridium are reduced.<sup>[18]</sup> The colonization factors are affected by the food eaten by the mother, the mother's gestational age, mode of delivery - normal birth or C-section - baby's diet (breast milk or formula), and probiotic intake.<sup>[17,18]</sup> Pathogens such as enterococcus and clostridium are reduced.<sup>[18]</sup> The colonization factors are affected by the food eaten by the mother, the mother's gestational age, mode of delivery - normal birth or C-section - baby's diet (breast milk or formula), and probiotic intake.<sup>[17,18]</sup>

Between 400 and 1,000 different bacterial species live in the human intestine, and they can weigh up to 1 kg.<sup>[19]</sup> There are  $10^{11}$  cells and 100 trillion bacterial cells per gram of colon content. The number of bacteria in a human body exceeds the number of body cells.<sup>[20]</sup>

Most of the microorganisms are located in the colon. Firmicutes make up 70 percent of the colon microbiota.<sup>[21]</sup> The functions of the bowel microbiota are: stimulation of innate immunity, the synthesis and metabolism of some nutrients, hormones and vitamins as well as ensuring the removal of the toxins.<sup>[22]</sup>

### **The Regulatory Mechanism of the Bowel Microbiota on Brain Development and Function**

Recent animal studies have shown that the physiology and the habitat of the microbiota are altered by the secretion of the hormones and neurotransmitters triggered by stress and emotional changes.

Many important molecules that have neuroactive functions are produced by microorganisms.<sup>[23]</sup> Some strains can produce specific neurotransmitters and neuromodulators. Dopamine, noradrenaline, GABA, serotonin, catecholamines and acetylcholine are produced by bacteria. These bacteria can be found in the intestinal microbiota.

*Lactobacillus spp.* and *Bifidobacterium spp.* produce GABA.<sup>[24]</sup> *Escherichia spp.*, *Bacillus spp.* and produces acetylcholine. Neurotransmitters secreted from intestinal bacteria are released by the epithelial cells of the lumen.<sup>[25]</sup>

In contrast, molecules in the enteric nervous system can activate neural signaling in the central nervous system and thus control some of the functions of the brain. Various bacterial strains have been shown to mediate behavioral effects via the vagus nerve.<sup>[26]</sup>

Tryptophan is the amino acid precursor of the neurotransmitter serotonin as well as of the active metabolites in the kynurenine pathway. Only 5% of the systemic tryptophan is metabolized into serotonin. Indoleamine 2,3 dioxygenase - one of the two enzymes that activates this metabolism - is found in all tissues and the other - tryptophan 2.3 dioxygenase - is found in the liver. These two enzymes control cytokines and corticosteroid. Their increased activation can lead to serotonin depletion and thus to a depressive mood.<sup>[27]</sup>

Through microbial fermentation of dietary fibre, short-chain fatty acids (SCFA) are produced in the colon. SCFAs are known to have neuroactive properties. For example, it has been found that feeding rodents with overdosed propionate has triggered neuro-inflammatory responses and behaviour related to neurodevelopment disorders.<sup>[28]</sup>

Propionate is used as a food preservative and it is reported that it is associated with increased incidences of autism. SCFA's also regulate the immune system of the bowel which has effects on the central nervous system.<sup>[29]</sup>

## **PROBIOTICS EFFECTS ON MENTAL HEALTH**

Many studies have shown that probiotics have health benefits. However, other studies on the relationship between probiotics and mental health have shown contrary effects.<sup>[30]</sup>

A double blind, placebo-controlled study, using various probiotic types, (*B. longum* R0175 and *L. helveticus* R0052), found beneficial effects on anger/hostility, depression, and anxiety.<sup>[31]</sup> Consumption of a yogurt that contained *L. casei* improved the mental health of healthy subjects.<sup>[32]</sup> The consumption of probiotic supplements, (*B. bifidum*, *L. casei* and *L. acidophilus*), for 4 weeks in 40 adult individuals who had depression led to significant improvements in their mood.<sup>[33]</sup> *L. acidophilus* Probiotics Effects on Mental Health. The effects of probiotics on mental health.<sup>[34]</sup> *L. acidophilus*, reduced the severity of autism in 33 children.<sup>[35]</sup> A recent study on probiotic consumption, (*B. longum* and *L. helveticus*), has shown significant results in treating mood disorders.<sup>[36]</sup>

## **WHAT IS AUTISM AND HOW IS IT DIAGNOSED?**

The term autism was first coined by American child psychiatrist Leo Kanner in 1943, to describe a

syndrome of 11 symptoms, including repetitive motor behaviors, obsession and echolalia. Such behavioral models are used in the diagnosis of autistic children to this day. Research has uncovered connections between diet and autism, centering on fatty acid metabolic pathways.<sup>[37]</sup>

Short-chain fatty acids (SCFAs), namely, acetic acid (AA), propionic acid (PPA), and butyric acid (BA), provide energy to colon cells after the probiotics breaking down the dietary fibre. SCFAs (especially propionates) have broad effects on the physiology of the nervous system and are associated with the pathogenesis of autism spectrum disorder (ASD). In fact, higher levels of AA and PPA found in food preservatives are known to induce autistic-like behaviors in rodents as well as children with an ASD diagnosis.<sup>[38,39]</sup>

Leo Kanner mentions that children with ASD are persistent in maintaining sameness/routine and have trouble forming grammatically correct sentences,<sup>(45)</sup>. Physicians play an important role in early diagnosis by testing various symptoms.<sup>[40]</sup> The severity of these symptoms varies significantly among children with ASD. The typical age of onset is >3 years. As these disorders may be mild diagnosis may be difficult children start school. Physicians and teachers could identify a child with ASD easily by comparing their behaviour with other children. Diagnosing children at both ends of the spectrum can be difficult. It would be difficult to distinguish severely afflicted children with isolated autistic symptoms from the ones with serious mental disorders as well as distinguishing children with mild ASD from those who have language disorders or social anxiety.<sup>[41]</sup> Physicians play an important role in early diagnosis by testing various symptoms.<sup>[40]</sup> The severity of these symptoms varies significantly among children with ASD. The typical onset of age is seen after 3 years, and these disorders may be mild and therefore would be difficult to identify before the school age. Medical doctors and teachers could identify a child with ASD easily by comparing their behaviours with other children. Diagnosing children at both ends of the spectrum can be difficult. It would be difficult to distinguish severely afflicted children with isolated autistic symptoms from the ones with serious mental disorders as well as distinguishing a mild ASD from those who have language disorder or social anxiety.<sup>[41]</sup>

In the majority of tests on children with ASD, an ordinary physical examination is applied. The physical examination should include tests for fragile X syndrome or tuberous sclerosis with secondary

causes and dysmorphic features. Currently there is no blood tests or radiological tests to diagnose ASD. Diagnostic yield obtained from biomedical research is low.<sup>[42]</sup> Currently there is no laboratory or radiological tests to diagnose ASD. Diagnostic yield obtained from biomedical research is low.<sup>[42]</sup>

Many parameters on ASD recommend investigation of Fragile X syndrome, regular karyotyping, audiology testing and clinically related DNA analysis for other research.<sup>[43]</sup>

### **A general diagnostic test is summarised below.**

The presence of at least two from the category (1), and one from (2) and (3) and the total number of (1), (2) and (3) should sum up to six (or more) for a diagnosis. (1), (2) and (3) should sum up to six (or more) for a diagnosis.

1. At least two of the following as manifested by an impairment in social interaction
  - (a) A marked deterioration in hand/arm movements, the stance of the body, facial expression, lessened or no eye contact and many other nonverbal behaviours during communication
  - (b) Inability to develop friendships appropriate to developmental level,
  - (c) A lack of interest in seeking to share their achievements or interests with other people (e.g. not showing or sharing objects of interest), objects of interest),
  - (d) Lack of social or emotional reciprocity
2. At least one of the following in communication as manifested by a qualitative impairment:
  - (a) A delay in the development of spoken language,
  - (b) Inability or a marked impairment in initiating a conversation with others for the ones that can conduct adequate speech,
  - (c) Stereotyped or repetitive motor movements, use of object or speech,
  - (d) Uninterested in imaginative or social imitation-based games appropriate to his/her developmental level, uninterested in imaginative or social imitation based games appropriate to his/her developmental level,
3. At least one of the following as manifested by one's restricted, repetitive and stereotyped patterns in behavioural interests and activities.

- (a) Focus on the unusual stereotyped or restrictive interest patterns,
- (b) Inflexible adherence to routines and insistence on sameness
- (c) Persistent preoccupation with objects and tinkering.
- (d) Delays and abnormal functioning in at least one of the following areas before the age of 3
  1. Social interaction,
  2. Language used in social communication,
  3. Symbolic or imaginative play.
- (e) This disorder cannot be explained better with Rett's disorder or childhood disintegrative disorder.<sup>[44]</sup>

## THE INTESTINAL MICROBIOTA AND AUTISM

In recent years, the possible role of the intestinal microbiota in the pathogenesis of autism has been investigated using animal models. Dysbiosis is a symptom of ASD, with possible *Bacteroidetes* and *Firmicutes* phyla imbalance accompanied by increased amounts of *Lactobacillus*, *Sutterella*, *Prevotella*, *Ruminococcus* and *Alcaligenaceae* families in the gut flora.<sup>[45,46]</sup> These findings show that more than half of the patients with ASD and gastrointestinal (GI) symptoms have increased *Sutterella* population. This may play an important role in the pathogenesis of ASD, since *Sutterella* is absent in people with GI symptoms without ASD.<sup>[47]</sup> Studies show that there is an increased population of *Sutterella* and a decreased population of *Prevotella* in people with ASD.<sup>[47]</sup> *Prevotella* is believed to be of high importance to the bowel microbiota and is involved in maintaining the well-being of the colon. Increased *Prevotella* population can have beneficial effects in many areas, eg. improved glucose metabolism. *Prevotella*,<sup>[47]</sup> *Prevotella* is believed to be of high importance to the bowel microbiota and is responsible of the maintenance of the well-being the colon. Increased *prevotella* population can have beneficial effects in many areas, eg. improved glucose metabolism.

Another gram-positive, anaerobic bacterial genus, *clostridium*, has been found to be present at more than 10 times the level found in the feces of control subjects in children with ASD. Moreover, overall

reduced amounts of anaerobic bacteria were found in children with ASD.<sup>[48]</sup> *Clostridium* is one of the largest genera with 180 species.<sup>[49-51]</sup> Although *Clostridium perfringens* has been found in the soil and in the GI tracts of animals and humans, it is known that it can cause various diseases by producing potent toxins.<sup>[51]</sup> *Clostridium histolyticum* is not only higher in patients with ASD, but also in their healthy siblings when compared with controls.<sup>[52]</sup>

Four studies on ASD have recorded lower levels of *Prevotella*. Three of these studies have found a significant effect.<sup>[47]</sup> Liu et al.,<sup>[53]</sup> found higher levels of *Prevotella melaninogenica*. Oral intake of probiotics in patients with ASD have not been found to have positive impact.<sup>[54]</sup>

The rate of *Bacteroidetes/Firmicutes* and the amount of Clostridiales are found to be greater in patients with ASD and GI problems.<sup>[55]</sup>

Emerging evidence suggests that the intestinal microbiota plays an important role in ASD, however the communication between the gut and the brain is limited. It has been suggested that the neuroimmune system contributes to ASD symptomatology through the gut-brain axis.<sup>[56]</sup>

Intestinal microbiota can affect cognitive development and cognitive function directly by modulating the permeability of the blood-brain barrier and changing neurochemical concentrations.<sup>[57]</sup> Neural signals from the gut can reach the brain through the vagus nerve, dorsal root ganglion afferents or via somatosensory afferents.<sup>[58]</sup>

Clinical studies of individuals with ASD have revealed that disorders of the brain are usually accompanied by infections or composition alterations in the gut microbiota, caused by exposure or chronic antibiotic use.<sup>[53,59]</sup>

Some bacterial species, i.e. *Bifidobacterium (bifidum, breve)*, and *Lactobacillus (acidophilus, casei)* are commonly used as probiotics,<sup>[34]</sup> are commonly used as probiotics.<sup>[34]</sup>

Despite the high amounts of *Clostridia*, *Desulfovibrio* and *Sutterella* in the feces of patients with ASD, lower amounts of *Prevotella* and *bifidobacterium* have been found. A limited number of clinical trials were conducted on children with ASD concerning the therapeutic effects of probiotics. Adams et al.,<sup>[59]</sup> found that most probiotics, with the exception of high levels of *lactobacillus*, have no significant beneficial effect,<sup>[59]</sup> revealed that most probiotics, except for high amounts of *lactobacillus*, have no significant beneficial effect.

The number of *Clostridium* species (especially *C. histolyticum* group) found in the stool was greater in children with ASD than in controls. Severely afflicted children with autism had higher levels of *Bacteroidetes* with lower levels of *bifidobacterium*.<sup>[59]</sup>

### Conclusion

Research on the effects of gut microbiota on mental health and autism is in its debut. However, the research that has been done up until now claims that mood disorders that can play a role in the pathogenesis of autism are closely related to the alterations of the gut microbiota. In order to regulate the microbiota, probiotics can be of help. Nevertheless, studies looking at the relationship between autism and microbiota have yet to provide unequivocal support for this thesis. Numerous confounding factors, such as the diversity of the microorganisms consumed and the dosage and duration of application, could play a part in this and these variables should be carefully controlled in the design of future studies. Although therapeutic applications of this research are still unclear, current data suggests that the presence of different types of bacteria in fecal specimens can serve as a diagnostic tool in more than half of ASD cases.

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