

The bioactive compounds of probiotic foods/supplements and their application in managing mental disorders

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ABSTRACT

Background: Probiotics have recently become popular among all generations, ranging from children to the elderly. They are living microorganisms known to improve gut flora by establishing and maintaining gut health via molecular mechanisms that involve various bioactive compounds produced and released throughout the body, which may cause a bacteria-host interaction. These bioactive compounds of probiotics may be bacteria or other compounds that are associated with various neurotransmitters, which produce different actions on the body. Changes in gut microbiota composition have been associated with various diseases, including mental disorders such as Alzheimer's/dementia, Parkinson's, schizophrenia, stress, anxiety, and depression. Clinical reviews and studies on both animals and humans have given mixed results regarding the efficacy of probiotic foods and supplements in managing mental disorders. In our review, we advocate for probiotic foods to be functional foods, but we are unable to accept probiotics as an effective treatment for the management of mental disorders due to indeterminate evidence.

Keywords: Probiotics, bioactive compounds, mental disorders, Alzheimer's disease, dementia, Parkinson's, schizophrenia, stress, anxiety, and depression

HISTORY

The consumption of fermented foods can be traced throughout history back to ancient civilizations, before even the era of Phoenicia. Cheese and fermented milk were favorites among the Greeks and Romans, and food such as bread and drinks like wine can be dated back to what many sacred texts consider the beginning of time [1]. Fermentation is an anaerobic process where bacteria convert sugar into lactic acid, which acts as a preservative [2]. While these ancient peoples were unaware of what was fermenting their food, they learned from observation that they could control the length of time that certain foods would ferment before they could eat and still enjoy them.

Elie Metchnikoff, also known as the father of modern probiotics, demonstrated in the early 20th century that regular consumption of lactic acid bacteria in fermented dairy products was

associated with enhanced health and longevity in Bulgarian peasant populations [3]. This inspired scientists to conduct more research on the microbiology of human processes.

The term “probiotics” was first used in 1953 by Werner Kollath, who derived the word from the Greek words, “pro”, meaning “for”, and “biot”, meaning “life”. In 1965, Lilly and Stillwell defined probiotics as “substances secreted by one organism which stimulate the growth of another” [4]. 9 years later, Parker described probiotics as “organisms and substances which contribute to intestinal microbial balance.” 15 years later, Fuller proposed that probiotics are “live microbial supplements which beneficially affect the host animal by improving its microbial balance.” As research in probiotics became more prevalent, a consensus definition of probiotics was adopted in 2001 by the United Nations Food and Agriculture Organization (FAO) and the World Health Organization (WHO) [5]. With a minor adjustment, the 2001 definition still holds true today. Probiotics are currently defined as “live organisms that, when administered in adequate amounts, confer a health benefit to the host” [6].

Because of the health benefits that probiotics offer, they are considered to be a functional food by many. While there is no official definition for the term “functional foods”, the Functional Food Center (FFC) defines them as “natural or processed foods that contain biologically active compounds; which, in defined, effective non-toxic amounts, provide a clinically proven and documented health benefit utilizing specific biomarkers for the prevention, management, or treatment of chronic disease or its symptoms” [7].

The objective of this review is to examine recent findings on the bioactive compounds in probiotics and how they can be used to manage mental disorders.

BIOMARKERS OF PROBIOTICS

Probiotics contain biologically active organisms in them, such as bacteria or yeasts. Probiotic foods most commonly contain the Gram-positive lactic acid bacteria *Lactobacillus* and *Bifidobacterium* [8]. Other bacteria such as *Lactococcus*, *Bacillus*, *Pediococcus*, and *Streptococcus* are also used in probiotic research today [9, 10]. Main yeasts, such as *Saccharomyces*, have also been studied (table 1), along with other genera such as *Kluyveromyces*, *Pichia*, and *Candida* [11].

Table 1. Commonly used probiotic bacteria and their known functions in the foods these genera are found in.

BACTERIA	FUNCTIONS	ASSOCIATED FOOD
<i>Lactobacillus</i> <i>Lactococcus</i> <i>Enterococcus</i> <i>Oenococcus</i> <i>Pediococcus</i> <i>Streptococcus</i> <i>Leuconostoc</i> [79]	Convert hexose sugars to lactic acid, inhibiting growth of harmful bacterial species	Yogurt, cheese, sauerkraut, pickles, sourdough, wine
<i>Bifidobacterium</i> strains [79-81]	Resistant to bile salts, important in probiotic bacteria survival Treat constipation, diarrhea, colitis, and gut inflammation	Fermented dairy products such as milk and kefir
<i>Saccharomyces</i> strains [79]	Treat diarrhea, IBS, IBD, and ulcerative and pseudomembranous colitis	Wine, bread, beer, kefir, kombucha

Established Major Mechanisms of Action of Probiotics

The specific mechanisms of various probiotics are still widely unknown. However, they are related antagonistically to the positive affects gut microbiota and other microorganisms, through various mechanisms, as elucidated below by Bermudez-Brito *et al.* [78].

Major mechanisms of the actions of probiotics:

1. Enhancement of the epithelial barrier
2. Increased adhesion to intestinal mucosa
3. Inhibition of pathogen adhesion
4. Competitive exclusion of pathogenic microorganisms
5. Production of antimicrobial substances
6. Modulation of the immune system

These mechanisms, while extensively studied, still require further detail before probiotics can be safely consumed as functional food products. It is understandable to then, examine the effect of gut bacteria on the rest of the body, particularly the brain, which controls many autonomic and non-autonomic functions.

THE GUT-BRAIN AXIS

In the last decade or so, the concept of the “gut-brain axis” has been heavily researched. Surprisingly, this concept has actually been in existence for over 200 years, starting from the 19th century [22]. A connection between intestinal health and mental health, as demonstrated by the gut-brain axis, suggests huge potential implications for the management and regulation of mental disorders via probiotic supplementation.

The gut-brain axis (GBA) refers to a bidirectional communication between the central and enteric nervous system, linking emotional and cognitive centers of the brain with peripheral intestinal functions, which can be seen within table 2 [23]. The idea of a gut-brain axis was first conceived in 1765, when Scottish physician Robert Whytt developed the concept of “nervous sympathy” to describe the holistic mechanisms by which internal organs communicated with each other [24]. Nineteenth century models of the gut-brain axis asserted that digestive dysbiosis caused dysfunction in emotions [22]. Particularly in 19th century England, indigestion was dubbed the national disease of the country, most likely due to poor and/or varying diets resulting from rapid industrialization and urbanization [25]. As the nineteenth century came to a close, scientists leaned more towards a reductionist approach, but realized that it could not explain clinical phenomena such as stomach problems resulting from violent or depressing events [26].

Today, we now know that the gut-brain axis’ role is to monitor and integrate gut function as well as to link emotional and cognitive centers of the brain with peripheral intestinal functions and mechanisms [23]. We know this is due to the many studies that researchers have published with the aim of more fully examining the extent of the gut-brain axis’ impact on mental health.

Mechanisms of the Gut-Brain Axis

The central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), and the limbic system all participate in the communication that occurs on the gut-brain

axis. Pro-inflammatory cytokines activate the limbic system through secretion of the corticotropin-releasing factor (CRF), which leads to the release of cortisol from the adrenal glands [41]. Essentially, this shows that neural and hormonal lines allow the brain to influence the activities of intestinal functional effector cells while these cells are also under the influence of the gut microbiota [42]. Currently, there is no consensus on the mechanisms by which probiotics work specifically on the gut-brain axis. There is some evidence to believe that they may involve modifying gut pH, antagonizing pathogens through production of antimicrobial compounds, stimulating immunomodulatory cells, and competing for pathogen binding sites as well as nutrients and growth factors [47].

Table 2. Bacteria commonly found in the human gut microbiome and the neurotransmitters they communicate with.

STUDY	BIOACTIVE COMPOUND	NEUROTRANSMITTER	OUTCOME
Komatsuzaki, <i>et al.</i> [82]	<i>Lactobacillus</i>	GABA	<i>Lactobacillus</i> in fermented fish produced 302 mM of GABA from 500 mM of glutamate in culture
Coda, <i>et al.</i> [83]	<i>Lactococcus</i>	GABA	<i>Lactococcus</i> in sourdough bread produced 504 mg/kg of GABA
Asano, <i>et al.</i> [84]	<i>Escherichia coli</i>	Norepinephrine	Substantial levels of norepinephrine were identified in the gut and associated with <i>E. coli</i>
Barneound, <i>et al.</i> [85]	<i>Mycobacterium</i> (Bacillus Calmette-Guerin)	Norepinephrine	Brain norepinephrine levels increased after bacillus Calmette-Guerin was injected
Yano, <i>et al.</i> [35]	<i>Streptococcus</i> , <i>Enterococcus</i>	Serotonin	These gut bacteria regulate 64% of colonic and 49% of serum serotonin concentrations
Hu, <i>et al.</i> [86]	<i>Bacillus</i>	Serotonin	Plasma serotonin levels decreased significantly from 17 to 12 ng/mL in dominant hens after being fed <i>Bacillus subtilis</i> for 14 days
Das, <i>et al.</i> [87]	<i>Escherichia coli</i>	Dopamine	<i>E. coli</i> DH5 α produced 27 mg/L of dopamine in growth media. Synthesis was remarkably enhanced in vivo.
Stephenson, <i>et al.</i> [88]	<i>Lactobacillus</i>	Acetylcholine	A strain of <i>Lactobacillus</i> found in sauerkraut produced ~5 μ g/mg dry weight of cells/hr

As the table (2) above shows, neurotransmitters are important chemicals by means of which communication via the gut-brain axis is possible.

Several studies describe other bioactive molecules that mediate communication between the brain and the gut, including short-chain fatty acids [34, 45], bile acids [45, 46], serotonin [35], and tryptophan metabolites [36]. Short-chain fatty acids represent the major flow of carbon from the microbiome to the host [37]. The essential amino acid tryptophan is known as the precursor of the neurotransmitter serotonin [38]. Numerous studies have shown that tryptophan and/or serotonin have an inhibitive effect on aggressive behavior and post-stress cortisol concentrations [39, 40].

In germ-free (GF) mice, risk-taking behaviors and hyperactivity increased while learning and memory skills decreased compared to standard pathogen-free (SPF) mice [27]. This may be due to the observation that germ-free mice exhibited an increased volume of the amygdala and hippocampus [28]. Germ-free mice also showed changes in expression of the 5-HT1A receptor, neurotrophic factors, and NMDA receptor subunits in the hippocampus [29-31], while also displaying impaired blood-brain barrier function [32] and increased myelination in the prefrontal cortex [33]. In these specific studies, neurophysiological changes can be seen.

It is clear to see that communication between the gut and brain is a concept that still requires much further study; however, current research seems promising. As earlier discussed, mental disorders/illnesses are burdening more and more people worldwide, up to 350 million people [48]. Probiotic supplementation can help with maintaining a properly functioning gut microbiota, which, in turn, can help with managing mental disorders.

PROBIOTIC BACTERIA IN FOOD

Dairy Products

For many, the first probiotics that come to mind are dairy products, such as yogurt and milk. These are the probiotics that have been mainly studied, and a meta-analysis done by Zhang *et al.* [13] indicated an association between fermented dairy foods intake and decreased cardiovascular disease, confirming that dairy products positively influence human health.

Dairy products typically contain *Lactobacillus* and *Bifidobacterium*, and more studies are being conducted to see the effects of these microorganisms in various settings. For example, Li *et al.* experimented with the bacteria *Bifidobacterium breve* in yogurt and found that it showed good stability *in vitro* and an increased survival rate, even when encapsulated with low methoxyl pectin [12]. Davras *et al.* found that the high probiotic content of kefir enabled modulation of many immunological mechanisms such as regulating IgA, IgG, IL-4, IL-10, and IL-12 levels [20]. On the other end of the spectrum, others have also observed that many probiotic foods failed to survive in high quantity, limiting their effectiveness as functional foods. Thus, Fazilah *et al.* [10] set out to increase survival rate by encapsulating *Lactococcus lactis* cells with gum arabic and *Synsepalum dulcificum*, which led to a higher viability than non-encapsulated cells. Much research has been conducted on how dairy products affect the human microbiome, and more is required to establish a consensus.

Non-Dairy Products

There are also other non-dairy foods that contain probiotic microorganisms. To name a few, there are dark chocolate, green peas, sauerkraut, kombucha, kimchi, beer/wine, green olives, natto, pickles, miso, sourdough bread, and tempeh [14]. In kimchi, *Lactobacillus plantarum* is an isolate

that is the main focus of many researchers. Some of the benefits from consuming *L. plantarum* in kimchi are that they have antioxidant and immune-enhancing properties [16], help manage hypercholesterolemia [15], and have remedial potential against influenza viruses [18]. In sauerkraut, 114 isolates of bacteria were discovered, and 85% of those isolates belonged to the *Lactobacillus* and *Leuconostoc* genera [15]. Other studies found that despite low initial relative abundance, sauerkraut fermentation resulted in a stable and rapidly established community of lactic acid bacteria that certainly met the recommended CFU range for probiotics [19, 20]. In fermented tuna viscera, *H. elongata*, a bacterium able to remove heavy metals in hypersaline environments and *T. halophilus*, a lactic acid bacterium, together were capable of the removal of heavy metals, such as Cd, Pb, and Hg, in SNB and MRS broth [21]. These studies show the diverse health benefits that non-dairy probiotic foods have to offer, illuminating probiotics as a potential functional food.

The FFC's Standards for Identifying Functional Foods

The FFC goes through a systematic evaluation when identifying functional foods. The steps are as follows [7]:

1. Examine the link between a particular food and its health benefits.
2. Determine the bioactive compound(s) responsible for observed health benefits by running in vitro and in vivo studies on both non-living and living specimens.
3. Use in vitro and in vivo studies to determine the mechanism of action by which bioactive compound(s) impart health benefits.
4. Establish daily value that will deliver effective health benefits to consumer while avoiding toxicity.
5. Conduct human studies to determine proper dosage of bioactive compound(s).
6. Develop appropriate food vehicle to combine with bioactive compound(s), resulting in the creation of a functional food product.
7. Ensure proper regulations are met and administer final product to the public.

Once these standards have been met, probiotic foods would be considered functional foods. It is important to notice that one of the most important parts of these steps is the emphasis on bioactive compounds as they appear within four different steps. Bioactive compounds within probiotics can be found within table 2, which shows what bioactive compounds produce or are associated with various neurotransmitters. Without identifying the bioactive compound, there would be minimal evidence of the properties of the food and would make it difficult to define it as functional. With the certain bioactive compounds discovered within probiotics, there are now many exciting applications for probiotics which have yet to be fully and extensively studied, including the potential mental health benefits probiotics confer.

THE IMPACT OF PROBIOTICS ON MENTAL DISORDERS

As early as 2001, the World Health Organization (WHO) determined that 1 in 4 people across the globe would be affected by mental or neurological disorders at some point in their lives [43]. As of 2017, the American National Institute of Mental Health (NIMH) reported that nearly 1 in 5 U.S. adults lived with a mental illness. According to the NIMH, a mental illness is defined as a mental, behavioral, or emotional disorder [44]. Various studies have studied various bioactive compounds

within probiotics and observed communications with different neurotransmitters (table 2). These neurotransmitters, including glutamate, GABA, serotonin, dopamine, and norepinephrine, have been associated with mental illnesses. For example, people who suffer from depression have been observed to release lower amounts of serotonin than those who do not [89]. Studies by Yano *et al.* and Hu *et al.* observed bioactive compounds within probiotics communicate with the serotonin neurotransmitter and affected the levels of serotonin concentration (table 2). In future studies, this could be utilized to increase serotonin levels and thus decrease depressive symptoms. With probiotics having an effect on neurotransmitters within the gut-brain axis and due to the recent abundance of published studies, it is feasible to analyze the effects of probiotic intake on a variety of mental illnesses.

Stress, Anxiety, and Depression

Stress is an emotional or mental strain that results from adverse circumstances. In order to study the effects of probiotics on stress, researchers induced early life stress on infant rats and caused early expressions of adult-like fear memory retention. Administration of a probiotic supplement, Lacidofil, not only prevented the transition to adult-like fear memory retention, but also decreased anxiety-like behavior and increased neurotrophic factor protein levels in the basolateral nucleus of the amygdala [53]. This suggests a potential therapeutic effect that may occur for children who experience similar early life stress. In rugby athletes, probiotic supplementation over 27 weeks also resulted in a significantly higher salivary cortisol and salivary alpha-amylase in the probiotic group versus the placebo group [54].

Anxiety is clinically defined as a state of excessive uneasiness and apprehension, typically with compulsive behavior or panic attacks. In one study, 86 college students consumed probiotics every day for 28 days, and there were improvements in panic anxiety, neurophysiological anxiety, worry, and mood regulation [55]. In another study, 111 stressed adults consumed *Lactobacillus plantarum* daily for 12 weeks, which significantly reduced symptoms of stress and anxiety compared to the placebo group as early as 8 weeks [56].

According to the American Psychiatric Association, depression, also known as major depressive disorder, is a disease that causes feelings of sadness and/or a loss of interest in activities once enjoyed [52]. Jang *et al.* [55] found that *Lactobacillus reuteri* and *Bifidobacterium adolescentis* synergistically suppressed occurrence and development of anxiety/depression by a significant amount. Most of the above studies make a case in support of probiotic supplementation as a way to manage stress, anxiety, and/or depression.

Schizophrenia

Mayo Clinic describes schizophrenic patients as those who interpret reality abnormally; they can display symptoms ranging from hallucinations, delusions, and disordered thinking and behavior that impairs daily functioning and can be disabling [49]. People with schizophrenia require lifelong care, but their symptoms can potentially be managed by daily intake of probiotics.

A study conducted in 2017 examined 2 schizophrenic patients' fecal secondary bile acid levels in order to observe the influence of probiotics on these 2 patients [46]. While it seemed that *Lactobacillus rhamnosus* appeared to promote bile acid deconjugation, most of the unconjugated bile acids appeared to be modified into secondary bile acids, and there was no significant change. Another study from 2017 revealed an association between probiotic intake and lower levels of

Candida albicans, but in males only [51]. A review done in early April of this year analyzed 3 studies that compared the use of probiotics to placebo controls. Separate analyses on the effect of probiotic supplementation on positive or negative symptoms of schizophrenia were also run, but there was no significant difference observed throughout the review [50]. The above studies are inconclusive, and more research is necessary in order to come to a unified opinion regarding the effect of probiotics on schizophrenia.

Autism

Autism spectrum disorder (ASD) refers to a range of conditions characterized by challenges with social skills, repetitive, speech and nonverbal communication [58]. Some symptoms are: making little to no eye contact, rarely sharing enjoyment of objects with others, having difficulty maintaining a conversation, having an unusual tone of voice, contradictory expressions to what is being said, having overly focused interests, repeating unusual behaviors, and being sensitive to sensory input [63].

In one study, lower bacterial diversity was observed in toddlers with ASD compared to healthy controls [59]. *Prevotella*, a bacterial genera involved in saccharide metabolism [60] and vitamin biosynthesis [61], was found to be in particularly low concentrations. Seeing that autistic individuals are thought to have impaired carbohydrate digestion [62], consumption of *Prevotella* may be beneficial. In another study, children with autistic symptoms and gastrointestinal distress were given Delpro, a mixture of 5 probiotic strains, for 21 days. 88% of parents whose children participated in the study reported improvements in symptoms [64]. Probiotics may help manage the gastrointestinal symptoms associated with autism, but more research must be conducted in order to achieve full understanding of the underlying mechanism leading to such a result.

Alzheimer's, Parkinson's, and Dementia

Alzheimer's and Parkinson's disease, as well as dementia, are memory loss diseases. The symptoms for all 3 diseases are caused by the destruction of brain cells, which can also lead to behavioral changes [65]. According to the National Institute of Aging (NIA), dementia is a brain disorder that affects communication and daily activity while Alzheimer's is a form of dementia that specifically affects thought and memory [66]. Parkinson's is considered by the NIA to be a brain disorder that leads to shaking, stiffness, and difficulty in walking, balance, and coordination [67].

Mild cognitive impairment, a condition where individuals experience more memory problems than normal, is regarded as a possible precursor to Alzheimer's [68]. Early intervention using *Lactobacillus plantarum*-fermented soybeans was found to improve cognitive functions after consumption of *L. plantarum* ($p=0.02$) [69]. In another study, Alzheimer's patients were divided into a treatment group (3 species of *Lactobacillus* and 3 species of *Bifidobacterium*) and placebo group, and neither ANOVA tests nor t-tests indicated any statistical difference between the two groups [70]. Results of another study showed that kynurenine serum levels significantly increased after probiotic supplementation in Alzheimer's patients, but this did not lead to a significant change in Kyn/Trp concentration [71]. These studies, while inconclusive, pave the way for future clinical studies on the effects of probiotics on neurodegenerative diseases.

Table 3. Efficacy of probiotics on various mental disorders (summary of studies above).

STUDY	MENTAL DISORDER	PROBIOTIC(S)	RESULT	IMPACT
[53]	Stress	Lacidofil (<i>Lactobacillus</i>)	Decreased anxiety-like behavior, seen in amygdala	Decrease in anxiety
[56]	Anxiety	<i>Lactobacillus plantarum</i>	Stressed adults experienced a significant decrease in stress/anxiety symptoms	Decrease in symptoms of stress and anxiety
[57]	Depression	<i>Lactobacillus reuteri</i> , <i>Bifidobacterium adolescentis</i>	Significantly suppressed occurrence and development of anxiety/depression	Decrease in frequency and development of anxiety/depression
[46], [51]	Schizophrenia	[46]: <i>Lactobacillus rhamnosus</i> [51]: <i>Saccharomyces cerevisiae</i>	[46]: Significant increase in secondary bile acid levels in only 1 of 2 patients [51]: Significant decrease in <i>C. albicans</i> in schizophrenic males only	Inconclusive; mixed significant changes in behavioral symptoms
[64]	Autism	Delpro (<i>Lactobacillus rhamnosus</i>)	88% of parents with autistic children in study reported improvement in symptoms	Decrease in autistic symptoms
[69], [70]	Alzheimer's Parkinson's Dementia	[69]: <i>Lactobacillus plantarum</i> [70]: <i>Lactobacillus</i> and <i>Bifidobacterium</i>	[69]: Fermented soybeans significantly improved cognitive function [70]: No statistical difference between placebo and treatment	Inconclusive; mixed significance

ADVERSE SIDE EFFECTS

The National Center for Complementary and Integrative Health (NCCIH) has stated that generally healthy individuals can usually experience mild digestive symptoms such as gas, but nothing worse [3]. However, for individuals with underlying medical problems such as weak immune systems, dangerous infections may arise, and so it is important to exercise caution before accepting foreign microorganisms, such as those in probiotic foods, into the body [3].

Too much consumption of probiotics may lead to bloating, gas, diarrhea, and abdominal pain [72]. Yeast-based probiotics may result in constipation and/or increased thirst [73]. An overabundance of D-lactic acid may also cause temporary confusion, due to its toxicity against human brain cells and potential to cause lactic acidosis [74]. One study even outlines the potential

development of probiotic bacteria into harmful, antibiotic-resistant bacteria [75]. The adverse side effects suggest that healthy individuals should consume probiotic foods/supplements regularly but not too often, and that those with weak immunity should not consume probiotics at all.

CONCLUSION

The question of how effective probiotics are in managing mental disorders remains unresolved. However, since microorganisms that colonize the gut microbiota have been shown to modulate immune response, mood, and behavior by communicating to the brain via the gut-brain axis, they should be continued to be researched. Similarly, when probiotics are consumed, they affect the intestinal microbiome and brain in complex mechanisms that still requires much study. The first step necessary to fuel more research seems to be validating probiotic foods as functional foods, and to raise the awareness of the scientific community regarding the significance of probiotic bacteria in food. Furthermore, probiotics should be put into more foods for future studies. It is essential to examine the effects of different probiotic supplements mixed into food and of foods naturally containing bacteria. Finally, the standardization of experimental design amongst various research labs would have great potential in obtaining replicable and conclusive data.

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