

## Gut microbiota's effect on mental health: The gut-brain axis

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### Abstract

The bidirectional communication between the central nervous system and gut microbiota, referred to as the gut-brain-axis, has been of significant interest in recent years. Increasing evidence has associated gut microbiota to both gastrointestinal and extragastrointestinal diseases. Dysbiosis and inflammation of the gut have been linked to causing several mental illnesses including anxiety and depression, which are prevalent in society today. Probiotics have the ability to restore normal microbial balance, and therefore have a potential role in the treatment and prevention of anxiety and depression. This review aims to discuss the development of the gut microbiota, the linkage of dysbiosis to anxiety and depression, and possible applications of probiotics to reduce symptoms.

### Introduction

Healthy gut function has been linked to normal central nervous system (CNS) function.<sup>1-4</sup> Hormones, neurotransmitters and immunological factors released from the gut are known to send signals to the brain either directly or via autonomic neurons. The existence of the gut-brain axis was proposed in the landmark study by Sudo and colleagues that discovered the impaired stress response in germ-free mice. Other studies using germ-free mice not only supported this existence, but also the idea that the gut-brain-axis (GBA) extends even beyond these two systems into the endocrine, neural, and immune pathways.<sup>2,5</sup>

Recently, studies have emerged focusing on variations in the microbiome and the effect on various CNS disorders, including, but not limited to anxiety, depressive disorders, schizophrenia, and autism.<sup>2,8,9</sup> This review focuses on the GBA in the context of anxiety and depressive disorders. Therapeutic interventions to treat dysbiosis, or disturbance in the gut, and mitigate its

effects on the GBA are only recently coming to the forefront as more is known about this unique relationship. As a result, research has been done on the use of probiotics in treatment of anxiety and depression both as standalone therapy and as adjunct to commonly prescribed medications. These findings as well as their potential impact on treatment are discussed in this paper.<sup>4,9</sup> An overview of the role of the gut microbiome, from its development, to its relationship with the emotional and cognitive centers of the brain, while also providing ideas for future research, are included in this review.

The microbiome is defined as all microorganisms in the human body and their respective genetic material. The microbiota is defined as all microorganisms in a particular location, such as the GI tract or skin.<sup>10,11</sup> This distinction is relevant as this review will focus on the microbiota of the gut in the context of the gut-brain axis, though there will be discussion of the human microbiome where appropriate.

### Materials and Methods

This literature review is based on English-language articles sourced from PubMed. Keywords searched included: microbiome development, neonatal microbiome, negative aspects of probiotic use, anxiety and depressive disorders, gut brain axis, anxiety, depression, hypothalamic-pituitary axis (HPA), stress and the microbiome, microbiome composition, intestinal bowel disease, cytokines, TNF- $\alpha$ , interleukins, leaky gut, anxiety, depression, and prostaglandins. Antibiotics were not included in the search as the authors felt it was beyond the scope of the discussion regarding the existing microbiome, stress responses, and their relationship with depression and anxiety disorders. No geographical limitations were included in the search. Publications were initially excluded if they were published before 2010. However, in order to include an in depth understanding of the research, articles published before 2010 were included if they were cited in research published after 2010. This review contains articles published through July of 2017.

### Results and Discussion

#### Development of the microbiome

The microbiome is initially developed via vertical transmission through the placenta, amniotic fluid, and meconium.<sup>12-14</sup> Two animal study suggested that fetuses

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See online Appendix

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exposed to prenatal stress in the form of maternal stress develop a gut microbiota with decreased *Bifidobacterium*.<sup>14,15</sup> Two separate studies concluded that the mode of delivery affects the initial microbiome and gut microbiota. Infants delivered vaginally had higher amounts of bacteria in their gut compared to infants delivered by Cesarean section.<sup>12,13</sup> Beginning with the first week of life, gastric colonization is highly dynamic. This critical period during birth and GI development is essential for newborn health and immunity.<sup>16</sup> Microbiota underdevelopment during this period has been correlated with numerous stress states including late-onset sepsis,<sup>17</sup> cardiovascular disease, and atopic disease.<sup>18</sup>

Early nutrition also appears to play a role in shaping the developing gut microbiota. Studies found that breastfeeding was directly correlated with both IgA levels and the number of organisms in the *Bifidobacterium* genus present in the gut and indirectly correlated with IL-6 levels.<sup>13,15</sup> IgA is predominantly a secretory immunoglobulin that provides immunity within the intestines and other mucosal membranes. In contrast, IL-6 is a proin-

inflammatory cytokine that normally presents in acute and chronic inflammation. *Bifidobacterium* is an important part of the infant microbiome,<sup>19</sup> and together with species in the *Lactobacillus* genus, is key in producing gamma-Aminobutyric acid (GABA), an inhibitory regulator of various neural pathways.<sup>20</sup> Breastmilk's ability to increase IgA and *Bifidobacterium* species and to decrease IL-6 levels, and subsequently inflammation, reduces the risk of age-related gastroenteritis.<sup>13</sup>

In comparison, infants fed formula during their first four weeks of life demonstrated a decrease in total number of bacterial species.<sup>15</sup> Breast milk oligosaccharides includes lactose as well as over 1000 distinct non-digestible molecules.<sup>21</sup> Researchers suggest the non-digestible sugars of breast milk provide a prime nutritional source for bacterial fermentation.<sup>12</sup> Breast milk had similar effects in preterm infants who were shown to have a different bacterial makeup, with a predominance of proteobacteria rather than *Bifidobacterium* and *Lactobacillus*. Preterm infants fed breast milk showed an increase only in the number of *Bifidobacterium*, supporting the concept that breast milk's non-digestible sugars create an environment better suited for of specific species.<sup>20</sup>

Cessation of breastfeeding is the primary diet change that leads to an adult-like microbiome.<sup>22</sup> Children who were weaned from breast milk up to age four showed similar patterns of microbiota development as children weaned at an earlier age, indicating that the length of time to transition from breast milk to solid foods was not as important as the transition itself.<sup>22</sup>

The key relationship between the gut microbiota and diet continues throughout life. Diet alterations can have significant impact on the gut bacterial composition in as little as 24 hours.<sup>20</sup> However, the bacterial composition is restored if the change in diet is only temporary. Regardless of the species inhabiting the gut, as long as their symbiotic role is the same, the human host will be able to function as normal.<sup>20</sup> Symbiotic bacteria assist with immune tolerance, intestinal homeostasis, amino acid and vitamin synthesis of the host, leading to a healthy metabolism.<sup>13</sup>

### The adult microbiome

As infants consume increasing amounts of solid food, the microbiome is exposed to diverse energy substrates, developing its carbon metabolism.<sup>22,23</sup> The adult microbiome becomes dominated by the *Bacteroidetes* and *Firmicutes* phyla, rather than the *Lactobacillus* and *Bifidobacterium* genera.<sup>24</sup> Relatively smaller quantities of

the *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, and *Cyanobacteria* phyla, and *Fusobacteria* genus can also be found.<sup>13</sup> However, due to many factors including diet, environment, season, health status, it is almost impossible to define a "normal" microbiome for the average human population. It is important to note that although microbiomes differ between every individual due to genetic diversity, researchers have found that every microbiome falls into one of three enterotypes. These enterotypes differ by which species dominates one's bacterial composition, and include *Bacteroides*, *Prevotella*, or *Ruminococcus* species. The dominant species and therefore enterotype results from the composition of a person's diet. *Prevotella* species enterotype is associated with diets high in carbohydrates versus people eating high amounts of protein are more likely to possess a *Bacteriodes* species enterotype.<sup>25</sup> Interestingly, these enterotypes are independent of environmental components such as age, body-mass index, gender and geographic location and seem to only be dependent on diet and genetics.<sup>26</sup>

A Danish study of the gut microbiome created the concept of high gene count (HGC) and low gene count (LGC), both of which are implicated in digestive health.<sup>27</sup> Due to a functionally more prosperous microbiome, the HGC group had a decreased risk of both metabolic disease and obesity. Important microbiome functions of the HGC group included an increased proportion of butyrate producing organisms, increased propensity for hydrogen production, and reduced production of hydrogen sulfide. It has also been shown that short chain fatty acids offer relevant benefits in terms of regulatory T cell induction as well as blood-brain barrier integrity.<sup>28,29</sup> In contrast, the LGC group had a larger proportion of pro-inflammatory bacteria which predisposed them to IBD and related disorders.<sup>30,31</sup> The Human Microbiome Project confirms this notion with studies of stool specimens demonstrating that humans with a less diverse microbiome were more likely to be diagnosed with IBD.<sup>25</sup>

When the human microbiome is challenged with changes in diet, stress, or antibiotics, the physiology of the normal microbiome undergoes change. A dysbiotic state leads to increased intestinal permeability and allows contents such as bacterial metabolites and molecules as well as bacteria themselves to leak through the submucosa and into the systemic circulation, a phenomenon aptly named *leaky gut syndrome*. A study by Zoppi *et al.* demonstrated that the gut microbiota uses the intestinal

endocannabinoid system to control the degree of intestinal permeability.<sup>32</sup> A separate study was able to reduce translocation of bacterial antigens such as LPS by using antagonists to the intestinal cannabinoid type 1 receptor in mice. Specifically, the CB1R antagonists cannabidiol and tetrahydrocannabinol were protective against intestinal permeability, suggesting that cannabinoids could play an important role in treating inflammatory gastrointestinal diseases such as IBD.<sup>33</sup> Increased intestinal permeability leads to detrimental effects on the host immune system, which have been demonstrated in diseases such as inflammatory bowel disease (IBD), diabetes, asthma, and psychiatric disorders including depression, anxiety, and autism.<sup>2,4,10,34,35</sup>

Although most of these studies have focused on bacterial species in the gut microbiome, other studies have elucidated the importance of other microorganisms, such as yeast. A study done by Burrus and colleagues suggested that colonization with *Candida* species may contribute to Autism spectrum disorders.<sup>36</sup> By preventing absorption of carbohydrates and minerals and allowing excessive build-up of toxins, colonization with *Candida albicans* was shown to increase autistic behaviors in children with autistic spectrum disorder. A similar study suggested that it is the interaction between propionic acid and ammonia released by *Candida albicans* that results in increased autistic behaviors.<sup>37</sup> This interaction produces an excessive amount of beta-alanine, which is similar in structure to GABA and has been proposed to be an important contributor to autism spectrum disorders.

### The inflammatory response

Inflammation of the GI tract places stress on the microbiome through the release of cytokines and neurotransmitters. Coupled with the increase in intestinal permeability, these molecules then travel systemically. Elevated blood levels of cytokines TNF- $\alpha$  and MCP (monocyte chemoattractant protein) increase the permeability of the blood-brain barrier, enhancing the effects of rogue molecules from the permeable gut.<sup>38,39</sup> Their release influences brain function, leading to anxiety, depression, and memory loss.<sup>39,41</sup>

Depressive disorders are characterized by both neuroplastic, organizational changes, and neurochemical dysfunction.<sup>42</sup> Illness is thought to begin when there is deregulation of these systems and can largely be attributed to cytokine release secondary to an exaggerated systemic response to stressors.<sup>39,41</sup> Endotoxin infusions to healthy subjects with no history of depressive disorder

ders triggered cytokine release and subsequent emergence of classical depressive symptoms. The study established a direct correlation between increased levels of IL-6 and TNF- $\alpha$  with symptoms of depression and anxiety,<sup>43</sup> indicating that pro-inflammatory cytokines play a role in the development of anxiety and depression. These effects correlated with a state of chronic inflammation and altered immune cells in the peripheral blood. However, TNF- $\alpha$  administered to healthy subjects resulted in no depressive symptoms,<sup>38</sup> suggesting that toxin induced inflammation caused the mood disturbance.

Pro-inflammatory cytokines are also important stimulators of the hypothalamic-pituitary-adrenal (HPA) axis (Figure 1). The hypothalamus releases corticotropin releasing factor from the hypothalamus, stimulating the adenohypophysis to release adrenocorticotropic hormone (ACTH). In turn, ACTH stimulates the adrenal release of cortisol, a known stress hormone that acts as a negative feedback signal in the pro-inflammatory signal transduction machinery.<sup>3,41</sup>

Hyperactivity or dysregulation of the HPA axis is one of the most reliable biological readouts in major depression and anxiety.<sup>39</sup> Rats with activated stress circuits demonstrated anxiety and depressive-like behaviors. Removal of the stimulus normalized HPA hyper-reactivity, as measured by their endogenous corticosterone levels, and in turn reversed or mitigated their abnormal behaviors.<sup>10</sup>

The interconnection of the endocrine, neural, and immune pathways is demonstrated in the relationship between brain derived neurotrophic factor (BDNF) mRNA in the dentate gyrus of the hippocampus and the stress response in germ free mice. BDNF supports the development of neurons and synapses involved in regulation of emotions and cognition; male germ free mice have an increased stress response associated with decreased hippocampus BDNF, which could be reversed by recolonization with *Bifidobacteria* species. Furthermore, the *Bifidobacteria* was shown to alter mRNA expression of GABA receptors and decrease serum cortisol. This change was not seen after the mice underwent vagatomies, suggesting that the parasympathetic nervous system was imperative for the bacteria's effects on their stress response.<sup>24</sup>

### Probiotics, inflammation, and the HPA axis

Probiotics are living microorganisms, typically yeasts and bacteria, that have been utilized as supplements to other medications or as alternative treatments for anxiety and depression.<sup>44</sup> Probiotics have also been

studied in the context of suppression of inflammatory cytokines. Some studies have found that human patients suffering from chronic inflammation responded positively to the ingestion of probiotics, as they decreased production of TNF- $\alpha$ .<sup>45,46</sup> In patients with inflammatory bowel disease, probiotics correlated with suppressed levels of pro-inflammatory cytokines, and improved intestinal barrier integrity. This led to a decrease in differentiation of CD4+ T cells into Th2 cells, and inhibition of nuclear factor kappa B, both of which are highly involved in inflammation<sup>47</sup> (Figure 2).

Mothers who consumed probiotics compared to controls were found to have an altered gene expression associated with improved inflammatory responsiveness in the placenta and neonatal gut.<sup>20</sup> Probiotic usage in late pregnancy led to a decrease in

IL-4, IL-10, and *Atopbium*, a species of the *Actinobacteria* phylum, with a concurrent increase in *Bifidobacterium* species.<sup>48</sup> Mothers who consumed probiotics two weeks prior to delivery had babies with altered expression of TLR-related genes in the placenta and neonatal gut; the TLR gene expression varied based on the type of probiotics the mother consumed.<sup>49</sup> These infants were found to directly respond and modify their inflammatory responses to pathogenic bacteria compared to controls.<sup>49</sup> Thus, providing mothers with specific probiotic formulas may protect the infant from persistent metabolic and immunologic disease processes.

Though human symptomatology is the primary interest, animal studies have elucidated the mechanisms underlying the relationship between probiotics and the immune response. Mice with B and T lym-

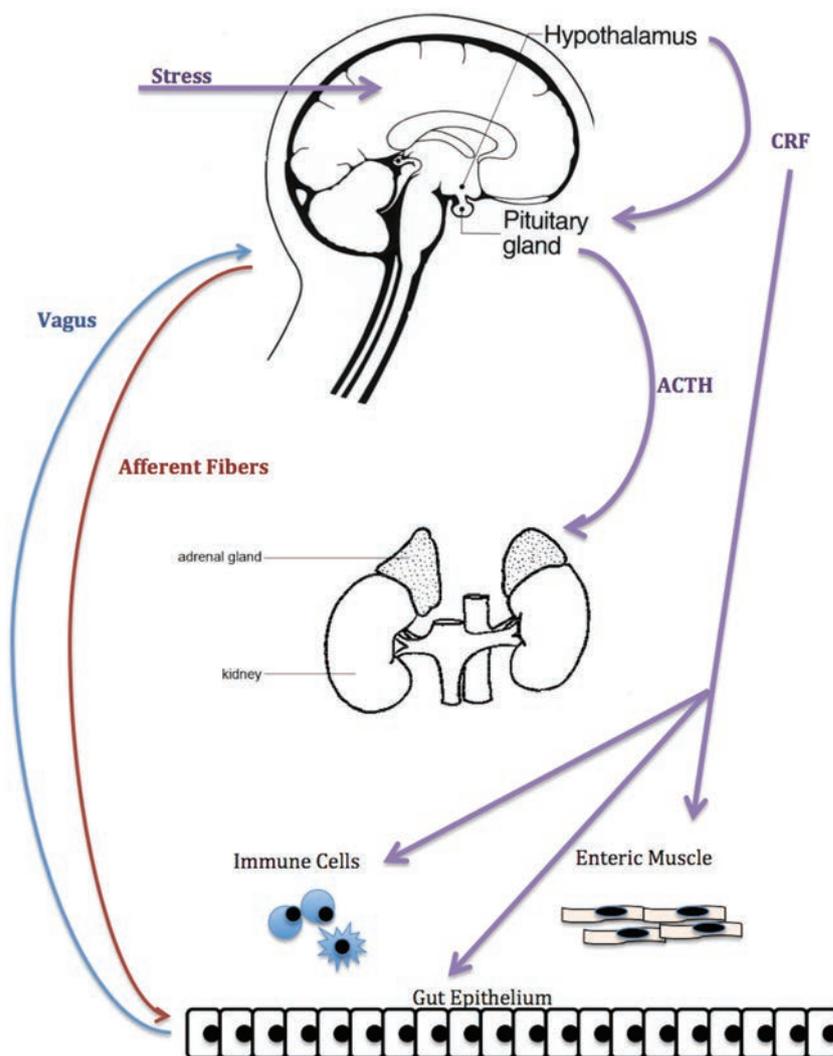


Figure 1. The gut-brain axis pathway. Image created by Megan Clapp and Emily Wilen.

phocytes deficient in *Rag1*, a gene responsible for B and T cell maturation, had increased colonic ion transport, resulting in a state of dysbiosis and altered HPA axis status. These mice were treated with probiotics containing *Lactobacillus* species and demonstrated reduced intestinal permeability and restored microbiome and HPA-axis functionality.<sup>50</sup> A separate study used mice with a stress-induced reduction of HPA axis function and neuronal firing. Probiotic therapy maintained neurogenesis and synaptic plasticity in the hippocampus, allowing the survival and differentiation of cells into neurons. These mice also produced lower amounts of stress hormones, and preserved intestinal permeability. The *Lactobacillus* strain in the administered probiotic upregulated BDNF and resulted in increased glucocorticoid regulation of the HPA axis.

Probiotics provide a neuroprotective role by preventing stress-induced synaptic dysfunction between neurons. Treatment for as little as two weeks created an appreciable decrease in ACTH and corticosterone levels in rats, illustrating the suppressive effects of probiotics on HPA axis.<sup>1,4</sup> Probiotics have the potential to diminish the HPA axis response to chronic stressors, and prevent or reverse physiologic damage.<sup>4</sup>

Human and animal studies of probiotics show similar reductions in anxiety and depressive symptoms. Human patients suffering from chronic stress were given a three-week probiotic treatment containing *Bifidobacteria* species. Subjects in the bottom third of the elated/depressed scale demonstrated the most improvement with treatment. These patients rated an overall happier mood on daily analogue scales using six dimensions of mood including energetic/tired, composed/anxious, elated/depressed, clearheaded/muddled, confident/unsure, and agreeable/angry.<sup>51</sup>

In a 30-day study, healthy volunteers

with no previous depressive symptoms were given either probiotics or antidepressants. Those given probiotics showed reduced cortisol levels and improved self-reported psychological effects to a similar degree as participants administered Diazepam, a commonly used anti-anxiety medication.<sup>52</sup> Analogous studies found that probiotic therapy reduced depressive symptoms and improved HPA-axis functionality as well as Citalopram and Diazepam.<sup>53,54</sup>

Comparing probiotics to the antidepressant escitalopram in mice, the probiotics were discovered to have similar effects. They were equally successful in anxiety reduction and were more effective than the escitalopram in maintaining healthy metabolism and body weight.<sup>55</sup> Though researchers have not determined the mechanism of action in humans, those who studied probiotics in rats found that oral ingestion of *Bifidobacterium infantis* resulted in increased tryptophan, a serotonin precursor,<sup>9</sup> and GABA.<sup>56</sup>

Despite treatment with multiple antidepressants, each with different methods of action, roughly 20% of patients do not show improvement in reduction of anxiety or depressive symptoms.<sup>57</sup> The human and mouse studies cited above indicated that probiotics normalize cortisol levels, regulate the HPA axis and reduce circulating pro-inflammatory cytokines. These mechanisms suggest probiotic therapies may confer certain benefits over therapeutic drugs. Advantages include ease of availability, lower cost, less dependence, and fewer side effects compared to pharmaceuticals. Regulation of the microflora composition offers the possibility to improve immune function, homeostasis, and gut inflammation.<sup>58</sup> Despite numerous studies citing the benefits of probiotic treatment, their specific mechanisms of action are often unknown and understudied, unlike prescription

drugs.<sup>59</sup> Thus, dosage becomes an issue, as the mechanisms and long-term effects have yet to be studied in a human population.<sup>60</sup> Probiotics enhance resistance to infectious diseases via excretion of antimicrobial components and increase the concentration of anaerobic gram positive bacteria. However, in some studies, subjects administered probiotics reported fever, headaches, and nausea with increased frequency after a bacterial challenge.<sup>61,62</sup> One study indicated that the probiotics administered in mouse subjects were not sufficient to prevent malefactors from a second immune challenge. This suggests that while probiotics may be helpful in the acute phase, they are not a cure-all in the long term.<sup>50</sup>

Prebiotics such as fructo-oligosaccharides and galacto-oligosaccharides are soluble fibers used to stimulate the preexisting gut microbiota. Additional studies in recent years have shown that prebiotics confer similar anxiolytic and antidepressant effects as probiotics as they also diminish stress-induced changes to the colonic microbiota and create stabilized levels of *Bifidobacteria* and *Lactobacilli* populations.<sup>63</sup>

## Conclusions

The bidirectional link between the brain, gut, and microbiome has come to the forefront of the medical research community in the past few years. The growing amount of evidence substantiating this link indicates it will be a valuable area for future medical and nutritional practice, and research. This review demonstrates the importance of a healthy microbiome, particularly the gut microbiota, for patients suffering from anxiety and depression, as dysbiosis and inflammation in the CNS have been linked as potential causes of mental

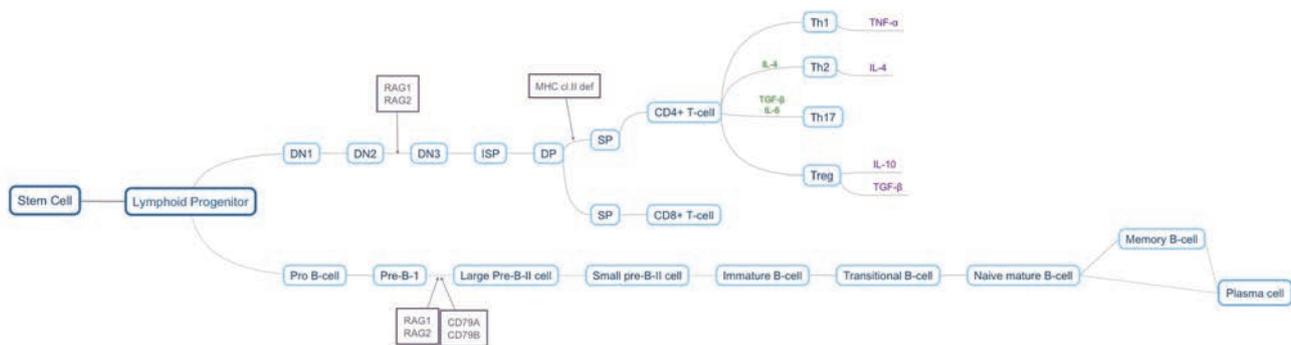


Figure 2. B and T cell development. Image created by Megan Clapp and Emily Wilen.

illness. Of note, studies have shown that probiotics effectively mitigated anxiety and depressive symptoms similar to conventional prescription medications.<sup>7,51,53,54,56</sup>

However, several weaknesses are identified in the course of this selected review. First, research linking TNF, cytokines, and other stressors to the pathogenesis of mental health disorders, particularly anxiety and depression, is lacking, and thus provides an area for future research, particularly regarding levels of intestinal bacteria and their correlation with levels of circulating cytokines.

The utility of probiotics is questionable as no form is currently regulated by the FDA, including natural sources such as yogurt, kefir, or sauerkraut. Patients may be more likely to use these natural sources of probiotics both due to increased accessibility as well as the resurgence in food trends of a return to more ancient food preparation techniques. Recent research has shown that the use of fermented foods in diets did confer gastrointestinal and cognitive benefits.<sup>64,65</sup> However, until more evidence behind the use of probiotics as therapy for anxiety and depressive disorders is available, probiotics in any form cannot be considered a reliable therapy to anxiety and depressive disorders as compared to psychiatric medications. Furthermore, gender differences as well as comorbidities such as obesity, lifestyle, and tobacco and alcohol use may impact the overall benefit of probiotics.

Despite the lack of regulations, patients prescribed mood-altering drugs may benefit from concomitant use of probiotics. The dysbiosis created by the prescribed medications, or resulting from the neurological disturbance itself, may be mitigated by the introduction of beneficial gut flora in a probiotic form. Ultimately, the question that needs to be addressed is can probiotics alone fix the problem, or do they need to be used with mood stabilizers?

The findings above, coupled with the recent surge of interest of gut health in the media, underscore the importance of future research in understanding the gut flora. Anxiety and depression are rising global issues, effective and accessible treatments would benefit millions of people worldwide.

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