



The Gut-Brain Connection: How Microbiota and Diet Influence Major Depressive Disorder

Shreya Wunnava

Mountain House High School, 1090 S. Central Park, CA, 95391

Email: wunnavashreya@gmail.com

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ABSTRACT

The gut-microbiota-brain (GMB) axis is a critical bidirectional communication system linking gastrointestinal function with mental health. This review synthesizes current evidence on how dietary patterns modulate the gut microbiota to influence the risk and severity of Major Depressive Disorder (MDD). Diets rich in fiber and fermented foods, such as the Mediterranean diet, promote eubiosis—a healthy microbial state characterized by a high abundance of beneficial phyla like Firmicutes and Bacteroidetes. These microbes ferment dietary fiber to produce anti-inflammatory short-chain fatty acids (SCFAs), which support gut barrier integrity and reduce systemic inflammation. Conversely, the Western diet, high in processed foods, sugars, and saturated fats, induces dysbiosis. This state is marked by an overgrowth of pro-inflammatory bacteria like Proteobacteria, leading to increased intestinal permeability ("leaky gut"), translocation of lipopolysaccharide (LPS) toxins, and chronic systemic inflammation. Diet-induced dysbiosis is mechanistically linked to MDD through several pathways: (1) the shunting of tryptophan away from serotonin synthesis and towards the neurotoxic kynurenine pathway; and (2) the dysregulation of the Hypothalamic-Pituitary-Adrenal (HPA) axis, resulting in glucocorticoid resistance, hypercortisolemia, and reduced hippocampal volume. These processes contribute to neuroinflammation, disrupted serotonin signaling, and the development of treatment-resistant depression (TRD). The findings underscore that dietary intervention, alongside prebiotic and probiotic supplementation, represents a promising therapeutic strategy for managing MDD by restoring microbial balance and mitigating inflammatory and neuroendocrine pathways.

Keywords: Mental Health, Gut-Brain Axis, Gut Microbiota, Diet, Dysbiosis

INTRODUCTION

The gut-microbiota-brain (GMB) axis is a highly complex physiological system containing the microbiota, their metabolic products; the enteric nervous system; the sympathetic and parasympathetic branches within the autonomic nervous system; and the neuroendocrine system, all of which collectively impact one's overall brain function, neuronal signaling, and mental well-being (Wang & Wang, 2016). The microbiome comprises six bacterial phyla: Firmicutes, Bacteroidetes, Actinobacteria, Proteobacteria, Fusobacteria, and Verrucomicrobia. Most of the identified

species in the gut belong to the two phyla Firmicutes and Bacteroidetes, which constitute about 70% of the total microbiota (Magne et al., 2020). Gut microbes influence physiology through multiple pathways and mechanisms, including signaling along the GMB axis. One major function of the GMB axis involves the synthesis of short-chain fatty acids (SCFAs), which initiate anti-inflammatory pathways. SCFAs are produced when gut microbiota hydrolyze dietary fiber, a process that contributes to neurotransmitter synthesis (Notting et al., 2023). However, this hydrolysis can only occur in the presence of dietary fiber and specific microbiota capable of producing metabolites such as SCFAs. In contrast, other microbiota contribute to pathology by stimulating immune cells to release cytokines and toxins (Misiak et al., 2020). Furthermore, certain strains can produce hormones that influence body and brain functions (Madison & Kiecolt-Glaser, 2019). Together, these microbial processes – both advantageous and harmful – influence serotonin production pathways, and severity of inflammation in the brain, thereby modulating the risk or severity of MDD (Shin et al., 2015, Stokes, 1995). The presence of specific microbiota capable of producing the appropriate molecules to help avert MDD is critical. Proteobacteria and Fusobacteria directly contribute to dysbiosis by altering the diversity and composition of gut microbiota (Iebba et al., 2016). Intestinal permeability, which permits toxins such as lipopolysaccharide (LPS), a molecule found on the outer membrane of Gram-negative bacteria, triggers neuroinflammation and oxidative stress in the central nervous system (Hashimoto, 2023). This interaction is known as dysbiosis, and alters the normal microbial population and changes the production of neurotransmitters and metabolites, disrupting normal brain signaling, emotional regulation, and cognitive functions (Severino et al., 2024). By contrast, eubiosis denotes a healthy microbiome, characterized by increased levels of the specific microbiota phyla such as Firmicutes and Bacteroidetes, which produce neurotransmitters, SCFAs, and metabolites that support gut and brain health. Firmicutes and Bacteroidetes promote anti-inflammatory effects and control immune-regulatory mechanisms (Iebba et al., 2016). Implementing fiber-rich, plant-based diet fosters microbial diversity, modulates the production of cytokines, and ultimately, regulates communication between the gut-brain axis (Mugada et al., 2025).

MATERIALS AND METHODS

A thorough search of peer-reviewed, current research and the academic literature was conducted using PubMed and Google Scholar from 1995 through September 2025. This time range was used to show both seminal and recent studies on the gut-brain-microbiota axis using keywords “gut microbiota,” “Mediterranean diet,” “Western diet,” “major depressive disorder”, and “dysbiosis”. Articles containing any information connecting the gastrointestinal system to other chronic mental health disorders. Human and animal studies were both considered, as they both directly address the gut-microbiota-brain axis and the impact to dietary patterns and Major Depressive Disorder.

RESULTS

Diet and The Gut Microbiota

Plant-based diets such as the Mediterranean diet are characterized by whole foods (fruits, vegetables, nuts, seeds, and whole grains), healthy fats (olive oil and omega-3 fatty acids), and probiotic-rich foods such as yogurt, kefir, and other fermented dairy products. Notably, foods from the Mediterranean diet are fiber-rich. Soluble fiber is indigestible by humans and can only be digested by specific microbiota. In the anaerobic gut environment, microbiota ferment dietary fiber instead of using aerobic respiration (Raymond, 2022) These fibers are then fermented into short-chain fatty acids (SCFAs) such as acetate and butyrate, helping maintain gut stability. SCFAs promote gut homeostasis and stability and lower the colon's pH, protecting against harmful toxins and bacteria such as Enterobacteriaceae (Narvión et al., 2023). While all dietary fiber is beneficial, specific types of fiber can change levels of fiber-fermenting microbiota and produce different types of SCFAs (Wang & Wang, 2016). For example, more butyrate (a type of SCFA) causes an increase in phyla Firmicutes, and more acetate (another type of SCFA) modulates the environment and levels of phylum Bacteroidetes (Iebba et al., 2016). SCFAs have been known to help control hunger, reduce inflammation, and improve overall brain health. An increase in fiber increases the amount of fiber-fermenting microbiota, creating a cycle of healthy bacteria when eating a high-fiber diet. The diet includes probiotics (live microorganisms) and prebiotics (substrates supporting microbial growth),

contained in fruits, vegetables, and whole grains are commonly seen in the Mediterranean diet. Individuals with deficient gut health may take fiber supplements, such as Benefiber, to support a stronger gastrointestinal system and promote the growth of beneficial probiotic species (Foster et al., 2021; Van et al., 2006). Benefiber contains wheat dextrin, a type of prebiotic supporting the growth of many microbiota, including phyla Actinobacteria, Verrucomicrobia, and Firmicutes. This supplement mimics the impact of plant-based foods on gut microbiota composition.

The Western diet is known to be high in sugar, saturated fats, omega 6 fatty acids, red meat, salt and processed foods overall (Mohammed et al., 2025). This dietary pattern promotes pro-inflammatory pathways, and exacerbates chronic disorders, such as type 2 diabetes, cardiovascular disease, and irritable bowel syndrome. Most western foods exacerbate inflammatory pathways and responses, but a diet high in sugar/ fructose is one of the main factors to gut dysbiosis. Fructose causes high levels of the Proteobacteria, a gram-negative phylum that has LPS as the major component of its outer membrane. Through growth of the Proteobacteria culture in the gut, LPS get released through cell death, overgrowth of cells, and from inflammation in the gut. This ultimately causes the “leaky gut”, where other toxins such as LPS can easily enter the bloodstream. The release of LPS impairs anti-inflammatory pathways, activating the immune system through TLR4, a pro-inflammatory sensory receptor which sends “alerts” to trigger the NF- κ B pathway, a protein complex in cells used to turn on inflammatory genes (Vasques-Monteiro et al., 2021). This process continues to attract immune cells and cause worsening of the inflammation, and further “shedding” of LPS from the Proteobacteria into the gut. This establishes a vicious cycle: LPS toxin release worsens inflammatory signaling, causing pro-inflammatory genes to become functional, perpetuating intestinal damage and further inflammation (Severino et al., 2024).

Although the Western diet has health-supportive components (e.g., higher protein intake, vitamin rich foods, and artificially added fiber and probiotics), daily consumption disrupts gastrointestinal health (Barber et al., 2023). Foods of the Western diet are prepared differently- with much more oil (includes fats, omega-6), and commonly fried. Despite having some nutritional value, the foods are unhealthy due to

preparation. Although the Mediterranean diet is widely recognized for its benefits, certain limitations have been found. Foods from the Mediterranean diet are low in protein and iron – two nutrients necessary for energy and muscle growth. The emphasis on plant-based foods makes it healthy and safe for the gut. The Mediterranean diet may not be ideal for those working to build muscle, but when it comes to gut health, the high-fiber, plant-based approach is one of the most beneficial diets.

Vignette

A case study shows how changes in diet can impact gastrointestinal health: A 25-year-old woman was diagnosed with Irritable Bowel Syndrome (IBS) in May 2025 following a dietary switch from a Mediterranean diet to the Southern-style Western diet. She reported symptoms such as: pain in the abdomen, nausea, cramping, and general indigestion/discomfort. These symptoms worsened her IBS, demonstrating that dietary changes can directly impact microbiota composition, gastrointestinal function and overall health. Her personal experience underscores the beneficial effects of the Mediterranean diet, which she followed before her diagnosis of IBS, versus the adverse effect of the Western diet, which contributed to her diagnosis of IBS. Her experience clearly states the association between the Western diet and dysbiosis, when opposed to the positive, eubiotic effects of the Mediterranean dietary patterns.

The Gut Microbiome and Major Depressive Disorder

Altered microbial diversity and heightened intestinal inflammation have been linked to Major Depressive Disorder (MDD) (Hemamalini et al., 2024; Kovtun et al., 2022). Reductions in Bifidobacterium and Lactobacillus, both genera of phyla Actinobacteria and Firmicutes respectively, contribute to increased intestinal permeability (“leaky gut”), allowing toxins such as LPS and cytokines through the gut barrier and initiate cascades of neuroinflammatory pathways (Du et al., 2020). Proinflammatory cytokines, including IL-1 β , IL-6, TNF- α all are elevated during immune responses. Whether cytokines are leaked in the gut or found in the bloodstream through another inflammatory process, they end up reaching the brain through indirect signaling, or crossing the blood-brain barrier (BBB) (Jeon & Kim, 2016). Cytokines signaling activates indoleamine 2,3-dioxygenase (IDO), an enzyme with immunomodulatory effects (Wichers & Maes, 2004). However, in the brain, IDO’s activation by

inflammation has an adverse, double effect. IDO converts tryptophan, an amino acid and precursor for serotonin, into kynurenine. Kynurenic acid is a metabolite derived from the breakdown of tryptophan, causing both neuroprotective molecules and neurotoxic compounds (Moroni et al., 2012). During chronic inflammation, Kynurenine breaks down into Quinolinic acid, and causes excitotoxicity (Jeon & Kim, 2016). Bifidobacterium and Lactobacillus have a direct relationship with the production of tryptophan - supporting serotonin production by diverting tryptophan from the kynurenine pathway. Bifidobacterium has been found to reduce conversion of tryptophan to kynurenine, when similarly, Lactobacillus can metabolize tryptophan themselves, producing metabolites that balance serotonin levels (Du et al., 2020). Reduced serotonin via the Kynurenic pathway is a contributing factor to MDD, exacerbating cognitive impairments and depressive symptoms.

These cytokines can also activate the Hypothalamic-Pituitary-Adrenal (HPA) Axis, the body's primary stress system, causing elevated cortisol and corticotropin-releasing hormone (CRH) levels, both central to stress regulation. IL-1 β , IL-6, and TNF- α are all types of cytokines, which are often known to trigger stress and inflammation responses. CRH signals the anterior pituitary to secrete the adrenocorticotrophic hormone (ACTH), a hormone which stimulates the adrenal glands to release cortisol. This cortisol binds to glucocorticoid receptors (GRs) in the hippocampus, activating the HPA axis without any regulation, resulting in hypercortisolemia due to HPA axis overactivity (Jeon & Kim, 2016). However, persistent chronic inflammatory response and production of cytokines can induce glucocorticoid receptor (GR) resistance, impeding the brain's ability to properly detect cortisol, therefore disrupting the healthy

negative feedback loop (Smoak & Cidlowski, 2004). This causes the HPA axis to be overactive. Hypersecretion of cortisol damages the brain, specifically reducing hippocampal volume, and impairing functions of memory, focus, emotion, and more (Gulyaeva, 2024).

The HPA Axis and Treatment Resistant Depression

Treatment resistant depression (TRD) may arise when HPA axis overactivity and glucocorticoid receptor resistance decrease SSRIs or other antidepressants lose efficacy (Souery et al., 2006). However, a clear consensus of TRD is lacking in the psychiatry community (Jurueña et al., 2009). In normal patients with depression, serotonin levels are low, and signaling is off. However, with treatment that elevates serotonin supply, levels can slowly recover, allowing the system to respond. In TRD, serotonin levels may be adequate or even elevated, but excess cortisol disrupts serotonergic signaling, preventing any normal function. Serotonin receptors (such as 5-HT_{1A}) become less sensitive to serotonin, blocking normal function of serotonin signaling (Khushboo et al., 2022). The prednisolone suppression test (PST) is a commonly used test to measure GR receptor dysfunction. In those without depression, Prednisolone acts as cortisol, binding to the GR receptor to signal the HPA axis to shut down, reducing cortisol production. In patients with severe TRD, prednisolone signaling fails – either from impaired receptor binding, or successful binding, without resulting in gene activation (Ferrara et al., 2019).

Jurueña and colleagues (2009) conducted a study on 45 in-patients with major depression (24 responding to treatment, 21 with TRD) and 46 healthy individuals. Participants both received one placebo, and 5 mg of prednisolone on two different nights.

Group	AUC _{Placebo} Mean (s.e.m.)	AUC _{Pred} Mean (s.e.m.)	Suppression,* % Mean (s.e.m.)	Plasma prednisolone levels, ng/ml Mean (s.e.m.)
Controls (n=46)	33.8 (2.5)	16.1 (1.6)	-49.6 (4.0)	66.5 (10.9)
Depression (n=45)	55.1 (5.1)	32.1 (4.4)	-42.2 (4.8)	56.1 (5.1)
P	<0.001	<0.001	0.24	0.40
Patients with depression				
Responding to subsequent treatment (n=24)	53.1 (8.2)	23.5 (4.2)	-52.5 (4.7)	74.9 (17.3)
Not responding to subsequent treatment (n=21)	57.2 (5.7)	41.9 (7.7)	-30.6 (8.2)	54.8 (10.1)
P	0.69	0.046	0.022	0.34

Figure 1. Prednisolone suppression test in depression: Prospective study of the role of HPA axis dysfunction in treatment resistance (Jurueña et al., 2009).

This study demonstrated a pronounced reduction in cortisol suppression from the TRD patients compared to controls. The controls with normal GR function and prednisolone binding had a large drop in cortisol (-49.6% suppression), while those with depression had some GR resistance, and less cortisol suppression (-42.2% suppression). Those without TRD had functional GR receptors and proper suppression – providing proof of the treatment's success. (-52.5% suppression) However, those with TRD had severe GR resistance, and weak suppression (-30.6% suppression). The results (Figure 1) showed a clear decreasing linear relationship between HPA axis dysfunction and cortisol suppression (Jurueña et al., 2009). As depression severity increased across groups, cortisol suppression declined.

This review highlights the complex interactions between gut microbiota and diet, which in turn, connect to brain function. Evidence has consistently shown that the Mediterranean diet, or a diet rich in fiber, fermented foods, and healthy fats, promotes gastrointestinal health and eubiosis. The pattern directly supports anti-inflammatory cascades by increasing the production of short-chain-fatty acids (SCFAs). The Western dietary pattern, however, favors the growth of Proteobacteria and other pro-inflammatory phyla. Western-style diets, high in refined sugars, omega-6 fatty acids, and processed items, release toxic molecules such as lipopolysaccharides (LPS), which, as a result, promotes systemic, chronic inflammation. Microbial changes are associated with disrupted serotonergic pathways, increased activation of the kynurenine pathway, and overall hyperactivity of the Hypothalamic-Pituitary-Adrenal Axis – all of which can intensify or contribute depressive symptoms. These findings suggest that dietary modulation may serve as a promising strategy for managing MDD. Targeted prebiotic or probiotic supplementation could promote microbial diversity, increase the variety of beneficial gut bacteria, and reduce overall systemic inflammatory responses.

CONCLUSION

The gut microbiota exerts a profound impact on mental health by mediating a complex pathway that links the gastrointestinal and nervous systems. Although evidence supporting the impact of the gut-microbiota-brain (GMB) axis continues to grow, current research remains limited in specificity and

scope. The GMB axis represents one of the body's crucial systems, regulating cognition, emotions, and stress responses through the release of neurotransmitters and immune signaling. Chronic inflammation is a central feature of Major Depressive Disorder (MDD), linking dysbiosis to MDD onset and treatment resistance through the Hypothalamic-Pituitary-Adrenal (HPA) axis. Diet-induced alterations can initiate chronic inflammation cascades – releasing cytokines, disrupting serotonin regulation, and ultimately leading to HPA axis dysregulation and further chronic neuroinflammation. This intricate molecular pathway significantly influences not only mental health but broader physiological functions and overall health. Accordingly, dietary strategies that enhance gut health may be a promising approach for the treatment and management of MDD, reinforcing the need for continued investigation into these pathways and mechanisms.

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Correspondence and requests for materials should be addressed to **Shreya Wunnava**

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