Probiotics Suppress the Depression: A Look at the Possible Mechanisms of Action

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Abstract

Manipulating the intestinal microbiota for the benefit of the mental health is a concept that has become widely acknowledged. Emerging evidence suggests that modifying the composition of the gut microbiota via probiotic supplementation may be a viable adjuvant treatment option for individuals with depression. The aim of this chapter is to illustrate the possible pathways through which gut microbiota may influence depression. PubMed, Scopus, and Web of Science databases were searched by using "probiotics", "depression", and "mechanism" key words for searching the studies aiming the application of probiotics and the beneficial effects of them in depression control and/or treatment. Findings of relevant studies suggest that probiotics could be considered as a promising adjuvant treatment to improve depression. The results of previous investigations suggest that modulation of inflammation, affecting the hypothalamic-pituitary-adrenal (HPA) axis, and interference with neurotransmitter signaling are the potential pathways through which probiotics may influence depression. Probiotics can alleviate depressive symptoms through several mechanisms; however, additional studies are necessary.

Keywords

Depression · Mechanisms · Probiotics

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15.1 Introduction

Depression is a common mental disorder, which can be long-lasting or recurrent, substantially impairing an individual's ability to function in their daily life (Vilagut et al. 2016). In recent years, there has been major interest in exploring the link between the health of the gut and mental health (Schmidt 2015a, b). Several pathways have been identified that describe how gut microbiota may influence depression (Uher and McGuffin 2010). Altered microbiota has been linked to neuropsychological disorders such as depression. Traditionally, depression has been treated with a range of therapies including antidepressants and talking therapies; however, research has started to emerge which suggests that probiotics, live microorganisms that exert health benefit on the host when ingested in adequate amounts, may significantly reduce the symptoms of depression. Fortunately, studies have indicated that gut microbiota may be modulated with the use of probiotics, antibiotics, and fecal microbiota transplants as a prospect for therapy in microbiota-associated diseases. Probiotics are regulated as dietary supplement foods and now are available in capsules, tablets, packets, or powders and are contained in various fermented foods, most commonly yoghurt or dairy fermented drinks. The primary rationale for using probiotics involves restoring microbial balance. The administration of probiotics which contains beneficial bacteria may restore the microbial balance in the gastrointestinal tract (Li et al. 2020). It has been argued that gut microbiota may play a role in bidirectional communication between the gut and the central nervous system (Arneth 2018). The aim of this chapter is to illustrate the possible pathways through which gut microbiota may influence depression.

15.2 Neurological Disorders and Gut-Brain Axis

The gut is closely connected to the brain via 200–600 million neurons (Furness 2006). Bidirectional communication between the gut and the brain has long been recognized; that is, signals from the brain can influence the motor, sensory, and secretory modalities of the gastrointestinal (GI) tract and, in turn, visceral messages from the gut can influence brain function (Grenham et al. 2011; Tabrizi et al. 2019) (Fig. 15.1). Recently, there is expanding evidence for the view rethinking the gut-brain axis as the concept of a gut microbiota-brain axis due to the crucial role of gut microbiota in the bidirectional gut-brain axis (Cryan and Dinan 2012). It is now well recognized that the organisms of the gastrointestinal tract make important contributions to health and disease, including mood and cognition, and psychopathology. Nevertheless, we are still a long way from understanding the potential mechanisms underlying this connection complexity.

Although it has long been recognized that major disturbances in gut flora can affect central nervous system function, it is only now emerging that "normal" gut microbiota might have a role in mood and psychopathology (Forsythe et al. 2010). Both endocrine and neural pathways are involved in signaling gut immune responses to the brain. The neural pathways involved in the microbiome-gut-brain axis include

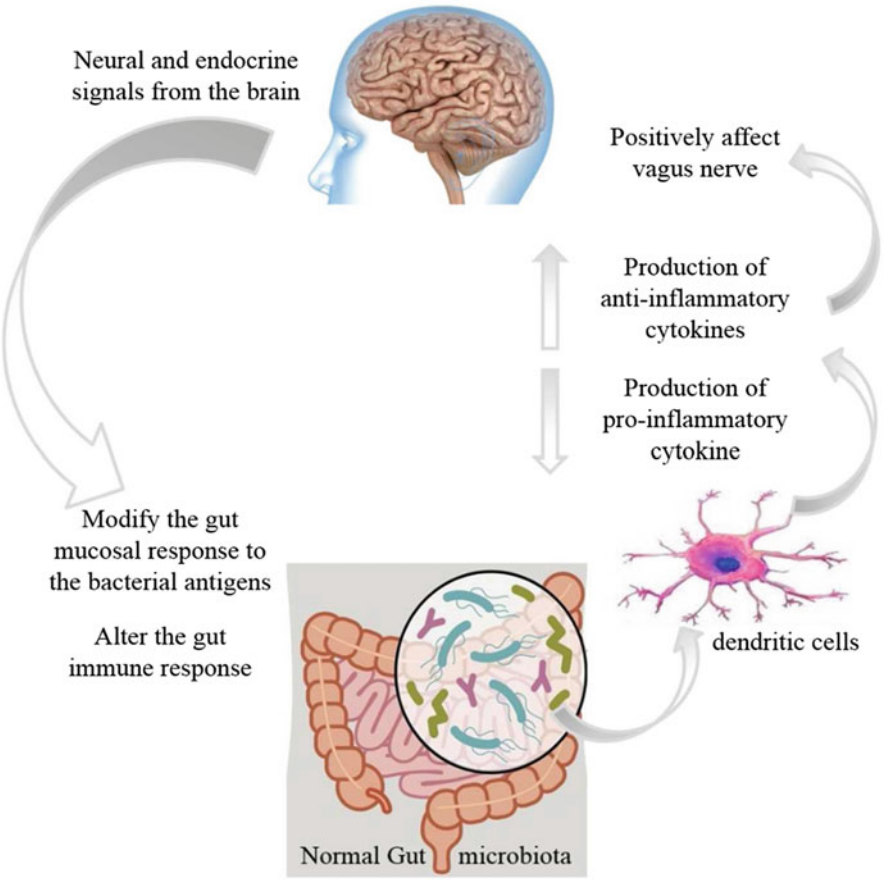

Fig. 15.1 The bidirectional communication between the gut and the nervous system (Grenham et al. 2011)

the sympathetic and parasympathetic autonomic nervous system and the local enteric nervous system.

Modulation of gut microbiota through consumption of probiotics might improve health by replacing harmful microbes with useful ones (Hemarajata and Versalovic 2013). It is believed that the primary mechanisms of action of probiotics are to contribute to modify the composition and function of the gut microbiota. The effect of gut microbiota on the brain can be established through several mechanisms. One of these involves the inhibition of histone deacetylase activity induced by the short-chain fatty acids (SCFAs) which are the end products of prebiotic fermentation by intestinal microorganisms. This may be responsible for the imbalance in histone acetylation levels and transcriptional dysregulations observed in neurodegenerative disorders (Dinan and Cryan 2017). Another proposed mechanism of interconnection of the gut and the brain is related to a direct effect of SCFAs on GI cells. This induces

the production of hormones, such as leptin, which have a beneficial impact on the central nervous system and, consequently, on memory and cognition (Rea et al. 2016). Another mechanism to be considered when linking gut microbiota and brain activity involves the interference of gut microbiota in the levels of different neurotransmitters and neuromodulators, particularly serotonin, γ-aminobutyric acid, and dopamine (Dinan and Cryan 2017). Dysregulation of brain activities promoted by dysbiosis may have a tremendous impact on a number of diseases, notably in mood disorders (Umbrello and Esposito 2016). The hypothalamic-pituitary-adrenal (HPA) axis is another interesting mechanism that makes the bridge between the gut and the brain (Berding and Donovan 2016). The HPA axis regulates the adaptive responses to stressors, such as environmental stress or systemic pro-inflammatory cytokines, in vertebrates. Activation of the HPA axis leads to the secretion and release of the corticotropin-releasing factor (CRF) from the hypothalamus and of the adrenocorticotropic hormone from the pituitary gland, resulting in the production of cortisol from the adrenal glands (Carabotti et al. 2015). It has been reported that gut microbiota may modulate the HPA axis, which, in turn, may regulate gut microbiota (Carabotti et al. 2015). However, the routes of communication between the gut microbiota and the brain are not fully elucidated, possibly through neural, endocrine, and immune pathways, which could be affected by gut microbiota or microbiota-generated metabolites.

15.3 Probiotics and Depression

Several studies have used an overall diet approach to evaluate the association between nutrition and mental health (Akbaraly et al. 2009; Sánchez-Villegas et al. 2009), but there is also considerable research looking at isolated nutrients and their impact on mental health. Central to this research are probiotics (Dinan and Quigley 2011). Probiotics are transient entities that colonize the GI tract and influence various pathways. It has been well established that probiotics have therapeutic effects on many GI disorders (Elangovan et al. 2019); however, with the emergence of the gut-brain axis, it has been discovered that their therapeutic effects extend beyond the gut and into the central nervous system (Mörkl et al. 2020). In recent years, there has been major interest in exploring the link between the health of the gut and mental health (Schmidt 2015a, b). Modulation of inflammation, affecting the hypothalamic-pituitary-adrenal (HPA) axis, and interference with neurotransmitter signaling are the potential pathways through which gut microbiota may influence depression (Uher and McGuffin 2008). It has been found that treatment with probiotics may improve symptoms associated with MDD (major depressive disorder) by increasing neurotransmitters' availability and/or decreasing levels of inflammatory markers. The potential of probiotics to be used as a novel treatment for MDD could have a major impact on those seeking antidepressant treatment by reducing the stigma, latency, and side effects associated with typical antidepressants (Wallace and Milev 2017). Despite extensive preclinical data, the clinical effects of probiotics on

mental health have yet to be studied comprehensively in a sample of depressed patients.

15.4 Mechanisms of Probiotics' Antidepressant Effect

15.4.1 Modulation of Inflammation

During the past decade, there has been renewed interest in the relationship between the brain, gut microbiota, and immune system, as well as in the study of microbiota changes as a possible source of inflammatory activity in mood disorders. In other chronic conditions, such as irritable bowel syndrome (IBS), inflammatory bowel disease (IBD), diabetes, and obesity, the association between gut microbiota composition, inflammation, and depressive symptoms has been attributed to a process known as intestinal dysbiosis (Pflughoeft and Versalovic 2012). Intestinal dysbiosis is conceptualized as a state in which there is an alteration of normal intestinal microbiota and has been highly associated with chronic low-grade inflammation in humans (Cani and Delzenne 2009). Consequently, it has been hypothesized to be involved in the pathophysiology of MDD (Rogers et al. 2016).

The results of animal studies, particularly those involving manipulation of the microbiota, support the association between microbiota abnormalities and depressive-like behaviors. Such studies have opened up new avenues of investigation for the pathophysiology of MDD as well as for the development of novel treatment interventions. The cumulative evidence suggests that modifying the composition of the gut microbiota, for example, using a probiotic, might be a viable treatment option for individuals with MDD (Park et al. 2018).

One possible pathway through which probiotics initiate their psychotropic effects is the link between gut bacteria and immunity. Immunoglobulin A and immunoglobulin M mediate inflammation and responses to lipopolysaccharide which have been shown to be elevated in depressed patients (Maes 2011). Moreover, a link has also been made that implicates higher inflammatory interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in depressed patients (Dowlati et al. 2010). Research within an animal model has shown that gastrointestinal inflammation appears to induce anxious behavior and cause alterations to the central nervous system biochemistry (Bercik et al. 2011).

Previously, the effects of probiotic supplementation on the biomarkers of inflammation have been reported (Badehnoosh et al. 2018). As the circulating levels of inflammatory biomarkers might be reduced by modulating gut bacteria composition, the therapeutic application of probiotics in mood disorders would seem a reasonable proposition. It has been demonstrated that fecal microbiota transplantation (FMT) from depressed humans to germ-free (GF) mice increased depressive-like behavior in recipient mice (Zheng et al. 2016). The findings from this study provided the rationale for an ongoing clinical trial with the primary aim of evaluating the effect of FMT capsules versus placebo on depressive symptoms in patients with MDD. One clinical trial has been conducted that examined the effects of probiotic

supplementation on symptoms of depression in patients with MDD (Akkasheh et al. 2016). The study was an 8-week randomized, double-blind, placebo-controlled trial that included 40 patients with DSM-IV-defined MDD. The probiotic capsule contained three viable, freeze-dried strains of *Lactobacillus casei*, *Lactobacillus acidophilus*, and *Bifidobacterium bifidum*. The results indicated that patients receiving the probiotic intervention had significantly lower Beck Depression Inventory scores compared to placebo. Notably, the researchers also found significant reductions in inflammatory marker, serum hs-CRP, in the probiotic intervention group compared to placebo.

An anti-inflammatory mechanism is underlying the antidepressant effects of probiotics (Park et al. 2018). There is adequate evidence supporting that (1) inflammation is implicated in the pathophysiology of depression and (2) probiotic consumption reduces inflammation. Considering the potential link between peripheral and brain inflammatory activation, a corollary of the finding that probiotics reduce peripheral inflammation is that probiotics also reduce brain inflammation. As such, it could be conjectured that probiotics have therapeutic efficacy in other disorders characterized by brain inflammatory activation. However, brain inflammation is a complicated notion with disparate etiological roots and therefore overlapping etiology may be a prerequisite in this regard. The anti-inflammatory mechanism was evaluated in a recent study conducted by Abildgaard et al. (2017). In the study, rats treated with a probiotic mixture containing eight different *Bifidobacterium* and *Lactobacillus* species displayed significantly reduced depressive-like behaviors compared to rats treated with a vehicle control. Importantly, this reduction in depressive-like behavior was correlated with a reduction in the level of circulating pro-inflammatory cytokines (i.e., TNF-α, IL-6) (Abildgaard et al. 2017). Considering the anti-inflammatory properties of probiotics, it is possible that probiotic treatment may be effective in a subgroup of depressed individuals with elevated inflammation. However, continued research in this domain is warranted.

15.4.2 Hypothalamic-Pituitary-Adrenal (HPA) Axis and Neurotransmitter Signaling

The hypothalamic-pituitary-adrenal (HPA) axis principal purpose is to maintain homoeostasis to physical and psychological stress. Disruption of the HPA axis has been implicated in the pathogenesis of mood disorders (Cleare 2004). Research using rats has found that probiotics are able to interfere with the HPA response to acute physiological stress, and according to Naseribafrouei et al. (2014), this would indicate a mechanistic connection linking the gut microbiota, HPA, and mood disorders.

Increased expression of pro-inflammatory cytokines (IL-1β, IL-6, TNF-α, interferon gamma (IFN-γ), and C-reactive protein (CRP)) is repeatedly observed in patients suffering from depression and has been associated with specific symptoms of depression (Wallace and Milev 2017). This overall increase in inflammation contributes to depressive symptoms by activating the HPA axis, as well as reducing

the availability of neurotransmitter precursors and altering neurotransmitter metabolism. This inflammation can be caused by increased intestinal permeability. When the tight junctions of the gastrointestinal lining become compromised and permeability increases, it allows toxins and other forms of waste to leak into the bloodstream. Namely, gut-derived endotoxins called lipopolysaccharide (LPS) molecules are found in the outer membrane of gram-negative bacteria. These endotoxins trigger immune activation through Toll-like receptor 4 (TLR4) (Kawai et al. 2001), causing the body to mount a global immune response. It is hypothesized that probiotics may exert their therapeutic effects on the central nervous system by improving the integrity of the gastrointestinal lining, reducing the ability of endotoxins to leak into the bloodstream, and, in turn, decreasing global inflammation. The reduction of this inflammation may result in improved regulation of the HPA axis and neurotransmitter activity.

Direct interference with transmitter signaling may also be linked to depressive states. Gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, can be produced by intestinal bacteria, and probiotics can modify depressive behavior from GABA signaling, at least in the rat model (Bendtsen et al. 2012). These findings appear to indicate the potential benefits of the normalization of intestinal microbiota in the regulation of mood and suggest that probiotic bacteria may serve as a therapeutic treatment for depression. Moreover, there is robust evidence that demonstrates probiotics' ability to change behavior and improve the mood, anxiety, and cognition of rodents by altering neurotransmitter activity. Findings suggest that probiotics have a positive impact on the central nervous system by regulating critical neurotransmitters implicated in depression.

Serotonin, a monoamine neurotransmitter, is biosynthesized from the essential amino acid tryptophan, both in the central nervous system and the gastrointestinal tract. In the central nervous system, it is involved primarily in regulating stress and emotions, appetite, and sleep. In the gastrointestinal tract, it is responsible for key functions such as gastrointestinal motility and intestinal secretions. Alterations in the microbiome have been shown to profoundly influence neurotransmission of serotonin in both the peripheral and central nervous systems. It is hypothesized that probiotics in the GI tract improve central nervous system symptoms associated with MDD by increasing production of free tryptophan and, in turn, increasing serotonin availability (Wallace and Milev 2017). This increase in serotonin may facilitate regulation of the HPA axis and reduce depressive symptoms caused by a depletion of the neurotransmitter.

15.5 Conclusion

Probiotics are proposed to have a range of health benefits. There is an increasing body of research which has reported that the microbiota of the intestines may function beyond the gut. And it is clear from research that probiotics might have favorable effects on mood and psychological problems. Through normalizing basal

intestinal microbiota, applications of particular probiotics appear to improve immune response and reverse the behavioral effects of depression.

Conflict of Interest There is no conflict of interest.

References

Abildgaard A, Elfving B, Hokland M, Wegener G, Lund S (2017) Probiotic treatment reduces depressive-like behaviour in rats independently of diet. Psychoneuroendocrinology 79:40–48

Akbaraly TN, Brunner EJ, Ferrie JE, Marmot MG, Kivimaki M, Singh-Manoux A (2009) Dietary pattern and depressive symptoms in middle age. Br J Psychiatry 195(5):408–413

Akkasheh G, Kashani-Poor Z, Tajabadi-Ebrahimi M, Jafari P, Akbari H, Taghizadeh M, Memarzadeh MR, Asemi Z, Esmaillzadeh A (2016) Clinical and metabolic response to probiotic administration in patients with major depressive disorder: a randomized, double-blind, placebo-controlled trial. Nutrition 32(3):315–320

Arneth BM (2018) Gut–brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: gut dysbiosis and altered brain function. Postgrad Med J 94 (1114):446–452

Badehnoosh B, Karamali M, Zarrati M, Jamilian M, Bahmani F, Tajabadi-Ebrahimi M, Jafari P, Rahmani E, Asemi Z (2018) The effects of probiotic supplementation on biomarkers of inflammation, oxidative stress and pregnancy outcomes in gestational diabetes. J Maternal-Fetal Neonatal Med 31(9):1128–1136

Bendtsen KMB, Krych L, Sørensen DB, Pang W, Nielsen DS, Josefsen K, Hansen LH, Sørensen SJ, Hansen AK (2012) Gut microbiota composition is correlated to grid floor induced stress and behavior in the BALB/c mouse. PLoS One 7(10):e46231

Bercik P, Park A, Sinclair D, Khoshdel A, Lu J, Huang X, Deng Y, Blennerhassett P, Fahnestock M, Moine D (2011) The anxiolytic effect of Bifidobacterium longum NCC3001 involves vagal pathways for gut–brain communication. Neurogastroenterol Motil 23 (12):1132–1139

Berding K, Donovan SM (2016) Microbiome and nutrition in autism spectrum disorder: current knowledge and research needs. Nutr Rev 74(12):723–736

Cani PD, Delzenne NM (2009) The role of the gut microbiota in energy metabolism and metabolic disease. Curr Pharm Des 15(13):1546–1558

Carabotti M, Scirocco A, Maselli MA, Severi C (2015) The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Ann Gastroenterol 28(2):203

Cleare AJ (2004) The HPA axis and the genesis of chronic fatigue syndrome. Trends Endocrinol Metab 15(2):55–59

Cryan JF, Dinan TG (2012) Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. Nat Rev Neurosci 13(10):701

Dinan TG, Cryan JF (2017) The microbiome-gut-brain axis in health and disease. Gastroenterol Clin 46(1):77–89

Dinan TG, Quigley EM (2011) Probiotics in the treatment of depression: science or science fiction? Austr N Z J Psychiatry 45(12):1023–1025

Dowlati Y, Herrmann N, Swardfager W, Liu H, Sham L, Reim EK, Lanctôt KL (2010) A meta-analysis of cytokines in major depression. Biol Psychiatry 67(5):446–457

Elangovan A, Allegretti JR, Fischer M (2019) Microbiota modulation-based therapy for luminal GI disorders: current applications of probiotics and fecal microbiota transplantation. Expert Opin Biol Ther 19(12):1343–1355

Forsythe P, Sudo N, Dinan T, Taylor VH, Bienenstock J (2010) Mood and gut feelings. Brain Behav Immun 24(1):9–16

Furness JB (2006) Novel gut afferents: Intrinsic afferent neurons and intestinofugal neurons. Auton Neurosci 125(1-2):81–85

Grenham S, Clarke G, Cryan JF, Dinan TG (2011) Brain–gut–microbe communication in health and disease. Front Physiol 2:94

Hemarajata P, Versalovic J (2013) Effects of probiotics on gut microbiota: mechanisms of intestinal immunomodulation and neuromodulation. Ther Adv Gastroenterol 6(1):39–51

Kawai T, Takeuchi O, Fujita T, Inoue J-I, Mühlradt PF, Sato S, Hoshino K, Akira S (2001) Lipopolysaccharide stimulates the MyD88-independent pathway and results in activation of IFN-regulatory factor 3 and the expression of a subset of lipopolysaccharide-inducible genes. J Immunol 167(10):5887–5894

Li C, Niu Z, Zou M, Liu S, Wang M, Gu X, Lu H, Tian H, Jha R (2020) Probiotics, prebiotics, and synbiotics regulate the intestinal microbiota differentially and restore the relative abundance of specific gut microorganisms. J Dairy Sci 103(7):5816–5829

Maes M (2011) An intriguing and hitherto unexplained co-occurrence: depression and chronic fatigue syndrome are manifestations of shared inflammatory, oxidative and nitrosative (IO&NS) pathways. Prog Neuro-Psychopharmacol Biol Psychiatry 35(3):784–794

Mörkl S, Butler MI, Holl A, Cryan JF, Dinan TG (2020) Probiotics and the microbiota-gut-brain axis: focus on psychiatry. Curr Nutr Rep 9:171–182

Naseribafrouei A, Hestad K, Avershina E, Sekelja M, Linløkken A, Wilson R, Rudi K (2014) Correlation between the human fecal microbiota and depression. Neurogastroenterol Motil 26 (8):1155–1162

Park C, Brietzke E, Rosenblat JD, Musial N, Zuckerman H, Ragguett R-M, Pan Z, Rong C, Fus D, McIntyre RS (2018) Probiotics for the treatment of depressive symptoms: an anti-inflammatory mechanism? Brain Behav Immun 73:115–124

Pflughoeft KJ, Versalovic J (2012) Human microbiome in health and disease. Annu Rev Pathol 7:99–122

Rea K, Dinan TG, Cryan JF (2016) The microbiome: a key regulator of stress and neuroinflammation. Neurobiol Stress 4:23–33

Rogers G, Keating D, Young R, Wong M, Licinio J, Wesselingh S (2016) From gut dysbiosis to altered brain function and mental illness: mechanisms and pathways. Mol Psychiatry 21 (6):738–748

Sánchez-Villegas A, Delgado-Rodríguez M, Alonso A, Schlatter J, Lahortiga F, Majem LS, Martínez-González MA (2009) Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Arch Gen Psychiatry 66(10):1090–1098

Schmidt C (2015a) Mental health: thinking from the gut. Nature 518(7540):S12–S15

Schmidt C (2015b) Thinking from the gut. Nature 518(7540):S12–S14

Tabrizi A, Khalili L, Homayouni-Rad A, Pourjafar H, Dehghan P, Ansari F (2019) Prebiotics, as promising functional food to patients with psychological disorders: a review on mood disorders, sleep, and cognition. NeuroQuantology 17:6

Uher R, McGuffin P (2008) The moderation by the serotonin transporter gene of environmental adversity in the aetiology of mental illness: review and methodological analysis. Mol Psychiatry 13(2):131–146

Uher R, McGuffin P (2010) The moderation by the serotonin transporter gene of environmental adversity in the etiology of depression: 2009 update. Mol Psychiatry 15(1):18

Umbrello G, Esposito S (2016) Microbiota and neurologic diseases: potential effects of probiotics. J Transl Med 14(1):298

Vilagut G, Forero CG, Barbaglia G, Alonso J (2016) Screening for depression in the general population with the center for epidemiologic studies depression (CES-D): a systematic review with meta-analysis. PLoS One 11(5):e0155431

Wallace CJ, Milev R (2017) The effects of probiotics on depressive symptoms in humans: a systematic review. Ann General Psychiatry 16(1):1–10

Zheng P, Zeng B, Zhou C, Liu M, Fang Z, Xu X, Zeng L, Chen J, Fan S, Du X (2016) Gut microbiome remodeling induces depressive-like behaviors through a pathway mediated by the host's metabolism. Mol Psychiatry 21(6):786–796