Prebiotics, as Promising Functional Food to Patients with Psychological Disorders: A Review on Mood Disorders, Sleep, and Cognition

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ABSTRACT

Objective: Manipulating the intestinal microbiota for the benefit of the mental health is a concept that has become widely acknowledged. Prebiotics, the nondigestible nutrients, can proliferate intrinsic beneficial gut bacteria, and so provide an alternative strategy for effectively altering the enteric ecosystem, and then brain function. This review summarizes findings from studies using prebiotics to improve mental health and psychological disorders.

Methods: Pub Med, Google Scholar, Scopus, and Science Direct databases were searched by using "prebiotics", "psychological disorder", "mood disorder", "depression", "anxiety", "stress", "sleep", and "cognition" for the studies aiming the application of prebiotics and the beneficial effects of them in mental health and psychological disorders' control and/or treatment.

Results: Prebiotic consumption improved psychological and biological measures of mental disorders such as depression, anxiety, and stress in individuals with mood disorder. Overall, the results showed that, through modulating the gut microbiota composition, prebiotics can beneficially affect mental health, modulate psychological disorders, and improve cognitive function and sleep/wake cycle disruptions.

Discussion: Prebiotics can improve mental health, mood, and psychological function. Habitual diets rich in dietary prebiotics would be linked to reduced risk of developing symptoms of psychological disorders; however, additional studies are necessary.

Key Words: prebiotics, psychological disorders, mood, depression, anxiety, stress, sleep, cognition

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Introduction

A psychological disorder, also known as a mental disorder, is a pattern of behavioral or psychological symptoms characterized by a clinically significant disturbance in an individual's cognitive, emotion regulation, or behavior that are usually associated with significant distress in social, occupational, or other important activities (Lai et al., 2018). Psychological disorders affect over one billion people all over the world. Common mental disorders refer to a range of anxiety and depressive disorders. Globally, it is estimated that 4.4% of the global population suffer from depressive disorder, and 3.6% from anxiety disorder (FAO/WHO, 2017). Traditionally...
mental disorders have been treated with a range of therapies, however, research has started to emerge which suggests that dietary factors influencing gut microbes may significantly reduce the symptoms of these disorders. Modification of the gut microbiota could be associated to psychological diseases since the first stages of life. Preclinical and clinical evidence suggest that the gastrointestinal microbiota influence psychological illnesses, including depression, anxiety, and stress (De Palma et al., 2017; Homayouni et al., 2012; Azami et al., 2017). Diet, and eating behaviors can affect the composition and metabolic functions of the human gastrointestinal microbiota. Clinical research has revealed diet quality, as well as specific dietary components and dietary supplements aid in prevention or treatment of symptoms of psychological disorders. Specifically, prebiotic fiber consumption and probiotic supplements reduced anxiety symptoms and had anti-depressant effects in humans (Wallace and Milev, 2017; Ejtahed et al., 2011). Prebiotics refer to nondigestible (by the host) food ingredients that have a beneficial effect through their selective metabolism in the intestinal tract. Previous researches suggest that ingestion of prebiotics may lead to improved psychological performance (Smith et al., 2015; Homayouni et al., 2013).

Delineating the relationship between prebiotics, gastrointestinal microbiota, and mental health is important for future applications of diet therapy for the treatment of psychological disorders. In present paper we have reviewed and discuss the efficacy of prebiotics on the management of psychological disorders including depression, anxiety, and stress, and cognition. Present review could be the basis for more extensive studies on the effect of prebiotics on mental disorders improvement.

Neurological Disorders and Gut-Brain Axis

The gut is closely connected to the brain via 200-600 million neurons. 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. 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 (Fig. 1).

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. Both endocrine and neural pathways are involved in signaling gut immune responses to brain. The neural pathways

![Figure 1. The by-directional communication between gut and nerve system](image-url)
involved in the microbiome-gut-brain axis include the sympathetic and parasympathetic autonomic nervous system and the local enteric nervous system (Forsythe et al., 2010).

Modulation of gut microbiota through consumption of prebiotics or probiotics might improve health by replacing harmful microbes by useful ones. It is believed that the primary mechanisms of action of prebiotics and probiotics are to contribute to, and/or modify, the functions of the gut microbiota (Abdolhosseinzadeh et al., 2018; Pourjafar et al., 2018; Rad et al., 2012).

The effect of gut microbiota on 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) butyrate, propionate and acetate, which are the end-products of prebiotics fermentation by intestinal microorganisms. This may be responsible for the imbalance in histone acetylation levels and transcriptional dysregulations observed in neurodegenerative disorders. Another proposed mechanism interconnecting gut and 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 central nervous system and, consequently, on memory and cognition. 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. The hypothalamic-pituitary-adrenal (HPA) axis is another interesting mechanism that makes the bridge between gut and brain. 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 pituitary gland, resulting in the production of cortisol from adrenal glands. 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 the communication between gut microbiota and brain are not fully elucidated, possibly through neural, endocrine, and immune pathways, which could be affected by gut microbiota or microbiota-generated metabolites.

**Description of The Effect of Diet on Neurological Disorders**

Observational studies provide evidence linking poor diet quality to neurological disorders, while good diet quality has been connected to a reduced risk of neurological disorders. The habitual intake of specific food groups has been associated with neurological disorders. Specifically, sweets and fast-food are consumed more frequently in stressed and depressed individuals (Mikolajczyk et al., 2009). Contrarily, fruits and vegetables are consumed less frequently by depressed individuals. Interestingly, the intake of dietary fiber derived from fruits and vegetables has been reported to be inversely related to depression symptoms. Dietary fibers -as a dietary compound- are resistant to digestion by human enzymes, e.g. pectins, gums, and fructans, but may be metabolized by microbial enzymes in the gastrointestinal tract. Thus, these dietary fibers can be fermented by resident microbes, resulting in the production of short-chain fatty acids (SCFA). SCFAs may indirectly influence neurological activity by modulating intestinal permeability and systemic lipopolysaccharide circulation (Koh et al., 2016) (Fig. 2).

Inadequate dietary fiber intake deprives microbes of a nutrient source and decreases butyrate producing bacteria. To compensate, secreted mucus glycoproteins may be used by microbes as an alternative energy source, eroding the colonic mucus barrier, and compromising intestinal barrier protection. A reduction in butyrate-producing bacteria may also compromise intestinal barrier protection. Accordingly, an increase in permeability allows the translocation of lipopolysaccharides,
a component of the outer membrane of gram-negative bacteria and pro-inflammatory stimulus, into systemic circulation. Lipopolysaccharides play a significant role in chronic low-grade inflammation, a phenomenon known as endotoxemia. Inflammation is characteristic of neurological disorders (Wang et al., 2012).

A prebiotic is a substrate that is selectively utilized by host microorganisms conferring a health benefit to the host. Most prebiotics are fibers; however, it is not a prerequisite for being considered a prebiotic. As research continues, it is likely that additional dietary components, such as polyphenols, may be recognized as prebiotics. Prebiotics are present within foods, e.g. onions, chicory root, and wheat, or taken in a purified form as a dietary supplement. Prebiotics may attenuate disease by promoting the growth of beneficial microbes and/or reducing pathogenic microbes. Prebiotics have demonstrated psychobiotic effects in human clinical trials. Psychobiotic describes a bacteria or source of support for bacteria that beneficially affects the relationship between the microbiota and brain (Canfora et al., 2017).

Commonly studied prebiotics for mood and behavior improvement include fructooligosaccharides and galactooligosaccharides. Both prebiotics have demonstrated the ability to enhance Bifidobacterium in humans. Although, the bifidogenic effect may be dose-dependent, requiring ≥5.0 g/day to enhance bifidobacteria. Bifidobacteria may promote health benefits by producing B vitamins, antioxidants, and polyphenols; and aiding immune system function by inducing the production of immunoglobulins. Additionally, bifidobacteria contribute to the production of lactate and acetate, which can be utilized by other bacteria in the gastrointestinal microbial community to produce butyrate, a phenomenon known as cross-feeding. High-quality diets, prebiotics, and probiotics may beneficially affect neurological disorders. Habitual diets rich in dietary fiber may be linked to reduced risk of developing symptoms of depression, anxiety, and stress; however, additional studies are necessary (Gagnon et al., 2015).

**Prebiotics and cognitive activity**

Recent research has focused on the effects of various dietary compounds on the performance of cognitive tasks and has found evidence to suggest that nutrition can assist in achieving and maintaining cognitive function. Emerging evidence suggests a beneficial role for prebiotics for cognition (Best et al., 2009) (Fig. 3).

Preclinical studies have shown that a 2-4 week dietary supplementation with a prebiotic has beneficial effects on learning and memory, and prevents pro-inflammatory signals that are

![Figure 3. Direct and indirect effects of short-chain fatty acids (SCFAs) on the brain (Best, Kemps and Bryan, 2009).](image-url)
detrimental to cognitive processes. Cognitive improvements in spatial learning and memory post-prebiotic intervention have been reported in both rats and mice (Vázquez et al., 2015). Most recently, precognitive effects of prebiotic administration was explored in an Alzheimer’s mouse model; significantly restoring the latency time in a water maze test, suggesting improvements in learning and memory (Chen et al., 2017). The cognitive improving effect of prebiotics such as COS (chitosan oligosaccharides) and FOS (fructo-oligosaccharide) has been evaluated in preclinical models. In an AD (Alzheimer’s disease) model, the Morris Water Maze was used to evaluate the effect of 200-800 mg/kg of COS. It was reported that cognitive deficits induced by Aβ1-42 (β-amyloid peptides) administration in SD rats were significantly improved after 2-week oral feeding of COS. Similarly, in a D-galactose rat model of AD, FOS administration improved spatial learning and memory in the Morris Water Maze. In a recent investigation examining an executive function in rats, three weeks of daily prebiotic supplementation increased cortical NMDA (N-methyl D-aspartate) receptor functioning and improved cognitive flexibility (Jia et al., 2016). Using a mouse model of vascular dementia, Han et al. demonstrated that arabinoxylan and arabinose -as prebiotics- improved general cognition, as measured by quicker completion of maze (Han et al., 2010). Chunchai et al. showed that consumption of xylooligosaccharide (XOS) restored cognition in obese-insulin resistant subjects through gut-brain axis, leading to improved hippocampal plasticity, brain mitochondrial function, and decreased microglial activation. The study of the effects of oligofructose-enriched inulin on healthy subjects’ cognitive performance showed that episodic memory tasks, namely free recall and recognition memory, were improved (Chunchai et al., 2018).

According to mentioned results of previous researches it can be conclude that cognitive impairment in neurological disorders may benefit from concurrent prebiotic therapy. Despite compelling evidence for the effects of prebiotics on cognitive deficits in animal models, the ability to alleviate cognitive function or enhance cognition needs to be evaluated in humans.

Prebiotics and Mood Disorders (Anxiety, Depression, Stress)

Increasing evidence suggests that the gut microbiota is altered in patients with mood disorders, highlighting a role for the gut-brain axis in neurological diseases. With respect to treatment with either probiotics or prebiotics to modulate the microbiota, there is still a paucity of information that exists describing their effects on mood disorders.

Prebiotics and anxiety

There is increasing evidence that gut microbes can impact nervous system activity. This was first recognized in germ-free mice that were found to have decreased anxiety-like behavior in comparison to mice that had a conventional microbiome. Colonizing the germfree mice with microbes early in life, however, prevented the anxiety-like behavior, suggesting that gut microbes’ impact on anxiety-like behavior. The manipulation of the enteric microbiota with specific prebiotics and probiotics has been shown to reduce the host’s inflammatory response, alter brain chemistry, and modulate anxiety behavior (Tarr et al., 2015).

Tarr et al. indicated that milk oligosaccharides support normal microbial communities and behavioral responses during stressor exposure, potentially through effects on the gut microbiota-brain axis. It has been reported that prebiotics (3’Sialyllactose and 6’Sialyllactose) were able to alter the microbiota community structure compared to mice fed standard laboratory control diet. In addition to maintaining normal microbial community structure, 3’SL and 6’SL were able to support normal behavior in stressor-exposed mice. Mice fed the control diet during stressor exposure displayed anxiety-like behavior in both the open field task and the light/dark preference task, an effect that was absent in mice fed 3’SL or 6’SL. Although the mechanisms by which 3’SL and 6’SL improve anxiety-like behavior are not yet known, it is possible that effects on the microbiota are involved (Tarr et al., 2015). Savignac et al. showed that the prebiotic BGOS (a specific non-digestible galacto-oligosaccharide formulation) has an anxiolytic effect, which may be related to the modulation of cortical IL-1β and 5-HT2A (5-hydroxytryptamine2A) receptor expression. Their findings suggest a potential role for prebiotics in the treatment of neuropsychiatric disorders where anxiety and neuro-inflammation are prominent clinical features (Savignac et al., 2016).

Evidences confirm the potential role for prebiotics in the treatment of neuropsychiatric disorders where anxiety and neuro-inflammation are prominent clinical features. It has been proposed that the anxiolytic action of prebiotics may be because of the prebiotics’ anti-inflammatory properties.
**Prebiotics and depression**

Perturbation of gut-brain axis has been shown to exacerbate vulnerability to a range of diseases ranging from visceral pain to mood disorders. Of importance, alterations in the richness and diversity of the microbiota have been observed in depressed subjects. Moreover, fecal microbiota transplantation from depressed patients into rodents can induce certain features characteristic of depression in the recipient animals, such as anhedonia and anxiety-like behaviors. Given this evidence, scientists have begun to believe that targeting the microbiota may open up novel strategies of prevention and intervention for a large spectrum of mood disorders such as depression (Burokas et al., 2017).

Burokas et al. showed that FOS+GOS consumption could improve the heightened anxiety-like behavior and depression-like behavior by increasing hippocampal mRNA levels for a subunit of the GABAB receptor and elevating serotonin level in the prefrontal cortex in Mice model. Moreover animals administered prebiotics showed increased Actinobacteria:Proteobacteria ratio. The decreased Actinobacteria:Proteobacteria ratio was also observed in subjects with major depressive disorder. Evidences revealed that modulation of gut microbiota by prebiotics leads to improvement of mood disorders and depression by elevating SCFAs level in the cecum, reducing plasma corticosterone levels, and manipulating HPA axis (Burokas et al., 2017).

**Prebiotics and stress**

It has shown that exposure to different types of stressors, ranging from social stressors to physical and physiological stressors, can impact the composition of the microbiota with reductions in potentially beneficial microbes often being found. Diet can also impact the microbiota, and different diets, such as those containing high fat contents, are associated with different microbial communities within the gut. Changing the composition of the gut microbiota in turn changes microbial community functions, which has renewed interest in the use of diet to enhance beneficial microbial populations. The modulation of the intestinal microbiota composition by prebiotic administration may be an additional way to reduce the effects of stress given that the microbiota and its specific profiles of biodiversity in the gut significantly influence behavioral, neurochemical, and immunological measures that are relevant to stress-related psychiatric disorders. Interestingly, the observed behavioral, neurochemical, genetic, and neuroendocrine changes after prebiotic administration could be mediated partially by SCFAs. The correlation data strongly support this idea. Indeed, recently it has been demonstrated that SCFAs are key molecules that modulate microgli maturation, morphology, and function. In fact, stress has been linked to the development of both depression and anxiety, with a key contribution of microgli activation as well as of recruitment of peripheral macrophages into the brain to such events (Réus et al., 2015).

Mika et al. tested whether early life supplementation of a blend of two prebiotics, galactooligosaccharide (GOS) and polydextrose (PDX) would attenuate behavioral and biological responses to stress later in life. Their results demonstrate that consumption of prebiotics distinctly attenuate the expression of stress-induced learned helplessness behaviors and furthermore, uniquely modulate gene expression within circuits important for stress resistance in juvenile, male rats (Mika et al., 2017).

Forsatkar et al. (60) evaluated the potential role of the prebiotic MOS (mannan-oligosaccharide) to reduce feed deprivation-induced stress responses in zebrafish. The results showed that feed deprivation significantly influenced cortisol levels and expression of CRH (corticotropin-releasing hormone) gene at the end of the feeding trials, and also after the administration of two routine “aquaculture” stressors. These changes were in some cases; most notably the baseline and most of the times at which cortisol concentrations were sampled, prevented in fish fed the prebiotic supplemented diet which may, in part, be the results of alteration in intestinal microbiota. It has been evaluated the effects of galactooligosaccharide (GOS), on the growth performance, stress resistance and intestinal microbiota of Caspian roach (Rutilus rutilus) fry. They found that GOS improves growth performance, stress resistance and modulates intestinal microbiota by increasing lactic acid bacteria of Caspian roach (Rutilus rutilus) fry. They found that GOS improves growth performance, stress resistance and modulates intestinal microbiota by increasing lactic acid bacteria of Caspian roach fry, a very important fish species in the Caspian Sea (Forsatkar et al., 2017).

Infants fed the prebiotic, galactooligosaccharides (GOS), for example, had increased fecal Bifidobacteria, and adults fed GOS had attenuated stress-induced neuroendocrine responses and gastrointestinal distress. In addition, mice fed the prebiotics 3’-Sialyllactose and 6’-Sialyllactose had reduced anxiety-like behavior. 

tested in the open-field and GOS reduced anxiety-like behavior produced after an immune challenge stressor (Canfora et al., 2017). It has been explored the effects of two prebiotics (fructooligosaccharides, FOS, or Bimuno®-galactooligosaccharides, B-GOS) on the secretion of the stress hormone, cortisol and emotional processing in healthy volunteers. A decrease in the neuroendocrine stress response in healthy subjects was observed after 3 weeks of Bimuno (B)-GOS treatment compared to placebo. The findings of lowered cortisol awakening reactivity in the group receiving B-GOS prebiotics compared to the placebo group indicate that prebiotic administration may modulate HPA activity in a similar fashion as the administration of probiotic strains directly seen in rodents and humans. The cortisol awakening response is a reliable marker of HPA axis activity which has been found to be increased by work stressors and in individuals at high risk of depression. Insufficient or excessive cortisol reactivity may indicate dysfunctional HPA axis feedback mechanisms, which may provide useful targets for modulation by treatments in certain vulnerability or disease states (Canfora et al., 2017; Forstatkar et al., 2017).

Results revealed that prebiotic intake is associated with decreased stress and altered attention bias. Despite these promising findings to date, there is still limited evidence for the efficacy of probiotic and prebiotic intervention in patients with mood disorders. Additional clinical trials are critical prior to making any conclusions on the efficacy of probiotics and prebiotics in mental health.

Prebiotics and sleep

Exposure to stress negatively affects sleep and the sleep/wake cycle. For example, experiencing work-related stressors, having low social support, or exposure to trauma/combat can all disrupt sleep and the sleep/wake cycle. Preclinical studies testing a variety of animal models of stress in early life or adulthood also report similar outcomes on sleep and the sleep/wake cycle. Stressor exposure, including diurnal rhythm disruption, can produce gut microbial imbalance or dysbiosis. Maternal separation of infant monkeys, for example, produces a selective reduction in gut Lactobacilli; and rats exposed to tail shock stress have rapid reductions of Provetella measured in both fecal and cecum samples. Whereas, mice exposed to chronic social disruption, circadian disruption plus alcohol consumption or 8 weeks of circadian disorganization plus a high fat diet have clear reductions in alpha diversity (Burokas et al., 2017; Thompson et al., 2017). Thus, stressor exposure induces dysbiosis by impacting specific bacteria and by reducing measures of alpha diversity. Taken together, stressor exposure can negatively affect sleep, the sleep/wake cycle and the gut microbiota community structure.

Pre-clinical studies suggest that diets enriched with prebiotic nutrients prevent acute stress-evoked gut microbial alpha diversity reductions and sleep and behavioral disturbances. Prebiotic nutrient administration can influence the gut microbiota and some features of the systemic stress response. Thompson et al. evaluated the effect of consumption of dietary prebiotics, on negative physiological impacts of stress in male rats. The results demonstrated that a diet rich in prebiotics (GOS, PDX, Lf and MFGM) started in early life increases the growth of Lactobacillus rhamnosus and alleviates the stress-induced disruption of REM sleep, diurnal physiology and gut microbial alpha diversity. Rats on the test diet exhibited decreased impact of the stressor, including increased REM sleep rebound following stress, attenuated disruption of the diurnal rhythm of CBT, and prevention of dysbiosis in measures of alpha diversity. They also discovered that the test diet enhanced NREM sleep and this was related to changes in a specific phylum of bacteria (Deferrribacteres) in early-life. Given that sufficient NREM sleep and proper nutrition can impact brain development and function and that sleep problems are common in early-life, it is possible that a diet rich in prebiotics started in early-life could help improve sleep, support the gut microbiota and promote optimal brain/psychological health (Thompson et al., 2017).

Conclusion and Future Perspectives

Reports from previous investigations provide evidence that there is a link between gut bacteria and mental health. The efficacy of prebiotics to treat psychological disorders is less known due to a paucity of studies investigating prebiotics effect on mental disorders. Altered GI microbiota composition has been reported in individuals with psychological disorders. It has been revealed that prebiotic consumption can modulate gut microbiota composition in a way that can positively affect mental disorders. Additional well-designed dietary intervention trials targeting the interconnection of
dietary prebiotics, gastrointestinal microbiota, and psychological disorders are required.

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