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The entrancing relation between diet and gut microbiota, a possible key target to exploit treatment options for depression and anxiety: insights from animal models, human studies and *in vitro* research – a review

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The human gut microbiome has received considerable attention since it has been demonstrated that it changes with obesity, diabetes, liver illnesses, cancer and neurological diseases and has been pointed out to be of key importance for the treatment of obesity-related and neurological diseases. Focusing on the neurodegenerative diseases, gut resident microbiota seems to interfere in normal brain functioning. Recent advancements in research shed light on the detailed physiology of the microbiome, its active role in disease and health, its relationship with stress and how modifications in the gut microbiota tend to influence behavioral changes. The dynamic nature of the microbiome stimulates the CNS signaling mechanism, which contributes to its active role in healthy homeostasis. This review aimed to highlight the role of microorganisms in the maintenance of normal homeostasis, their influence on mood disorders such as depression and anxiety, their potential implications in the management and treatment of depressive disorders.

KEY WORDS: anxiety / depression / diet / gut-brain axis / microbiome / mental health

Despite years of research on the topic, the underlying cause of most psychiatric disorders remains unknown [Plana-Ripoll *et al.* 2019]. The pathophysiology of depression and anxiety has emerged as a challenging problem to solve [Gaspersz *et al.* 2018]. Not only are depressive and anxiety syndromes heterogeneous, with a wide range of causes, but symptoms such as suicidality and remorse are often difficult to replicate in animal models [Gould *et al*. 2017]. Among other factors, the hypothalamic-pituitary-adrenal (HPA) axis, monoamine neurotransmitters, the environment and inflammation, as well as early life events have all been implicated [Lawrence *et al.* 2017].

According to the World Health Organization [2017], an overall number of persons suffering from depression worldwide in 2015 exceeded 300 million. Anxiety problems affect about the same number of people. Depression is a prevalent illness that affects about 3.8% of the world's population, with rates of 5.0 and 5.7% among adults and adults over 60 years old, respectively (2021). The World Health Organization (WHO) released a survey in February 2021 on the two most frequent psychiatric illnesses afflicting the global population, i.e. depressive and anxiety disorders, revealing that Brazil leads the world in anxiety disorder prevalence and ranks sixth in depression rates. In turn, over 47 million of ill people are North Americans. A serious mental illness affects 4.6% of the US population.

While the gut communicates with the CNS via the parasympathetic and sympathetic nervous systems (the Gut-Brain Axis), the CNS communicates with the gut's muscle and mucosal layer via both afferent and efferent autonomic pathways (ANS). In this view, the gut microbiota is shaped by preliminary life events and environmental factors, such as nutrition and migration, and influences many of the elements that may be indulged in psychiatric diseases [Li *et al.* 2018]. The gut microbiota have a "symbiotic relationship" with humans supplying them with nutrients and habitat, while also positively affecting the immune, endocrine, gastrointestinal (GI) and neurological systems. They carry out necessary functions such as digestion of complex indigestible polysaccharides, food processing, vitamin synthesis and microbial inhibition [Salvucci 2019]. The Human Microbiome Project (HMP) is investigating the human microbiome using a number of methods, including 16S ribosomal RNA gene sequence analysis, metagenomic profiling of whole group

DNA, taxonomic profiling and integrated sequencing matching to reference microbial genomes [Muthaiyan 2020]. Adopting a balanced diet containing prebiotics and probiotics combined with regular physical activities can significantly reduce the risk of many diseases, including depression and anxiety [Owen and Corfe 2017]. Microbiota-modulating methods provide a feasible therapeutic option for the development of new therapies for CNS disorders, with probiotic supplementation potentially playing a significant role in treatment of depression and anxiety.

Several clinical as well as preclinical studies have shown that the gut microbiota perform an essential role in maintaining healthy homeostasis by providing neuroactive substances including gamma-aminobutyric acid and serotonin to the brain-gut microbiome [Sivamaruthi *et al.* 2019]. Their disruption increases the risk of mood swings and other CNS disorders. This will benefit future probiotic medical potential and scientific understanding of the gut-brain axis. This review significantly contributes to current research on probiotics, prebiotics, diet and their association with mental well-being, filling a significant research void.

The gut microbiome composition, dysbiosis and the influence of diet

The gut microbiota, which are primarily found in the colon, are quite unique to each individual and seem to remain relatively constant throughout the individual's lifetime; nevertheless, daily transient fluctuations (transient dysbiosis) are typical. The gut microbiota composition is also linked to genetic, maternal and environmental bacteria. All mammals were assumed to be sterile before birth, according to Barko *et al.* [2018], with inoculation with microorganisms occurring at the time of birth. In fact, dysbiosis, or changes in the microbiome's composition linked with diseases or conditions that disrupt the microorganism-host equilibrium, has been identified

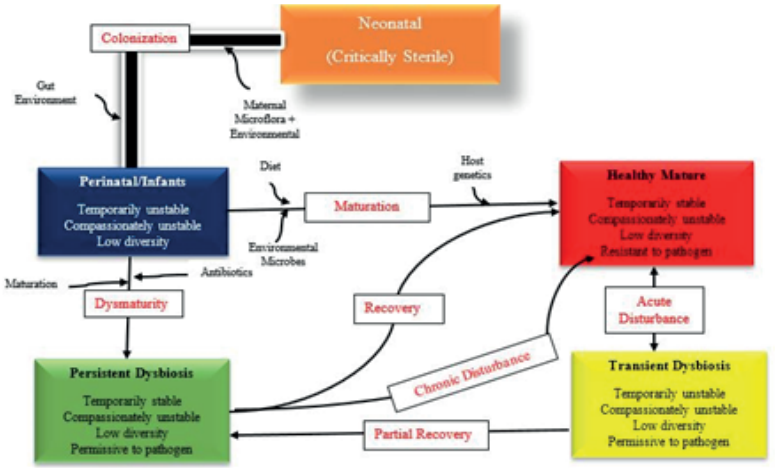

Fig. 1. Gut microbiome composition and the dysbiosis scenarios. Source: Barko *et al*. [2018].

as one of the metabolic pathways mediating this association. Dysbiosis is defined by a decrease in microbial species diversity (unbalanced microbiota), changes in the intestinal and systemic inflammatory milieu as well as altered metabolic interactions between microbes and hosts [Barko *et al.* 2018] – Figure 1. These occurrences, as well as the permanent and transitory dysbiosis scenarios, are clearly seen in Figure 1.

Among environmental factors, nutrition is a significant determinant of the the gut microbiota composition, emphasising potential therapeutic dietary interventions to regulate microbial diversity, composition and stability [Leeming *et al*. 2019]. In fact, food is thought to account for more than half of the microbial structural differences in mice. Dietary techniques in disease management through gut microbiota modification have a 20% potential in mice as well as humans, showing that dietary strategies in disease management through gut microbiota modulation have a 20% potential both in mice and humans. The gut microbiome of subjects fed a common Western diet and those fed a fiber-rich diet differ significantly [Bibbò *et al*. 2016]. Diet and the chance of developing mood disorders have been linked in studies. Because of its high fat and refined sugar content, the Western diet among other things contributes significantly to intestinal dysbiosis. While a change in the gut microbiota can be induced by diet, these changes appear to be transient. A certain diet may upgrade the growth of specific bacterial strains, causing hosts to modify their fermentative metabolism, which affects intestinal pH and can lead to the establishment of a pathogenic microbiota. Routine diets are expected to have a greater impact on gut flora than dramatic dietary shifts [Leeming *et al.* 2019].

As displayed by Figure 2, among other things the gut microbiota aid nutrition absorption, metabolism, homeostasis, cell signaling and energy production.

Anxiety and depression can be triggered by stress-related factors. In this respect diet and the microbiome seem to have a direct influence on these states [Madison and Kiecolt-Glaser 2019], as a change from an unhealthy to a balanced diet dramatically reduces the risk of disease. The consumption of complex polysaccharides helps in the recovery of the microbiome; these substances are fermented by bacteria that dissolve lactic acid as the fundamental metabolic product as well as short-chain fatty acids (SCFA) – Frampton *et al.* [2020]. Acidification promotes a suitable environment for the development of bacteria of the *Bifidobacterium* and *Lactobacillus* genera, reducing bacterial populations related to the circulation of lipopolysaccharides, strongly involved in the generation of pro-inflammatory cytokines [Weitkunat *et al.* 2017]. SCFAs, mainly butyrate, propionate and acetate produced as by-products of microbial fermentation, are also involved in reducing inflammatory processes [Ohira *et al*. 2017] and they are the arbitrators for the colonic inflammatory response (CIR) [Maslowski and Mackay 2011, Sommer and Dantas 2011]. Inflammation due to stress contributes to the process of depression and anxiety [Barnes *et al*. 2017, Peirce and Alviña 2019]. The influence of diet on the microbiota population was demonstrated in a study where ten healthy participants received treatment based on the animal and plant diet to monitor variations in the gut microbiota profile. It was observed

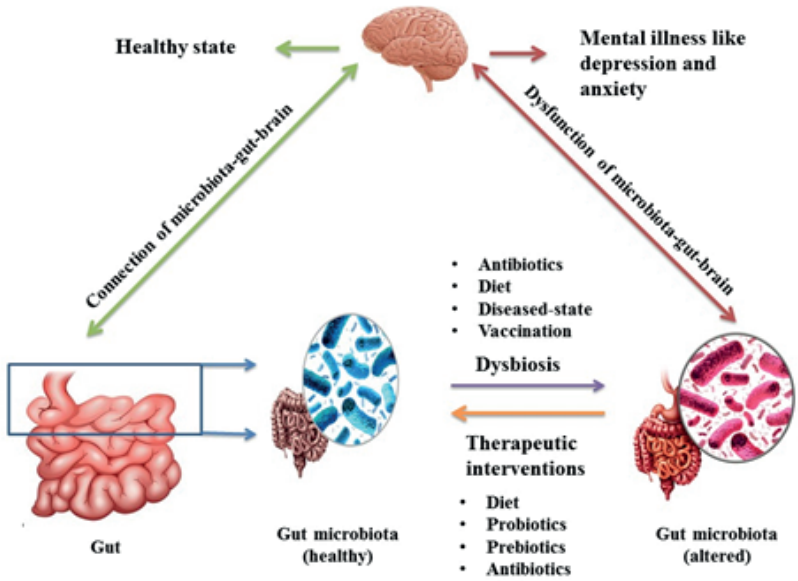

Fig. 2. A complex relationship between the microbiome, diet and mental illness.

that indigestible fiber from the poor diet reduced anti-pathogenic microbe diversity [Maslowski and Mackay 2011]. Similarly, an unhealthy diet (high in oils and fats) causes maladaptation of the microbial population, an increased risk of inflammation, obesity and intestinal disorders [De Filippo *et al.* 2010, Sherwin *et al.* 2016]. In addition, one study indicated that healthy participants consuming foods high in fiber and low in fat content had a greater Proteobacteria and Firmicutes phyla population. In comparison, those who consumed foods high in fat and low in fiber had more abundant Actinobacteria and *Bacteroides* populations [Wu *et al*. 2011].

Diet and mental health

In recent decades diet and mental health have attracted considerable interest of scientists worldwide. Studies are being conducted to determine the correlation between diet and stress in infants, teenagers and adults [Sherwin *et al*. 2016]. High intake of sugar, fat and unhealthy food in adolescents and children are linked to many psychiatric problems [O'neil *et al.* 2014]. Alterations in gut microbiota concentrations resulting from stress can indicate vulnerability to mental illness in children [Lewis *et al*. 2014]. A stressful life generates potential risks that code for psychopathology, resulting in adverse alterations in the gut microbiota that can be manifested during cognitive development and may continue into adulthood. A nutritious diet has been connected with a lower risk of depression [odds ratio (OR) 0.84; 95% confidence

interval (95 percent CI) 0.76-0.92; p>0.001) according to studies [Lai *et al.* 2014]. Another meta-analysis found that eating a balanced diet lowers the risk of depression (relative risk 0.68, 95% confidence interval 0.54-0.86) – Psaltopoulou *et al*. 2013]. For example, a prominent case in infant monkeys was tracked, whose mother experienced stress throughout her pregnancy cycle and significant changes in the offspring's gut microbiota concentration were investigated. Indeed, observational studies in animals concluded that initial colonization of gut microbiota affects stress response mechanisms in the young. Preclinical studies also indicated that early-life stress is linked to depression, which alters gut microbiota concentrations [Bailey *et al*. 2004]. Unfavorable life events linked to depression are more likely to result in mental illness in offspring.

As an emerging area, treatment studies are being conducted to clarify various biological processes that may aid in the exploration of the hidden potential of gut microbiota [Bested *et al*. 2013]. Several intriguing indications were made in the early 1990s on how certain mental diseases, such as depression and anxiety, are linked to our gut and how toxins from our GIT (gastrointestinal tract) and dietary habits speed up the development of melancholy and anxiety in people (Fig. 2). Because of technological advancement, evidence that behavior and the brain are associated primarily with the gut microbiota has been presented in literature showing that the gut microbiome is linked to sadness and anxiety, according to persuasive data [Mayer 2011, Collins *et al*. 2012].

The gut microbiota affect a variety of neurotransmitters, including serotonin and tryptophan (precursors to serotonin). Scientists have discovered a method to treat mental illness in humans by harnessing the active capacity of gut microbiota in modulating and regulating stress responses, cognition and actions. Irritable bowel syndrome (IBS), a GI condition with psychiatric comorbidity, is caused by altered gut microbiota. In-depth studies are conducted to reveal the fascinating potential of these diverse organisms. Recent research has shown that probiotics are advantageous to our mental health and help to amplify brain functioning [Sherwin *et al*. 2016].

Mental health trends, focus on anxiety and depression

As the prevalence of relatively common mental diseases, such as depression and anxiety, has increased in recent decades, mental health has become a growing concern not only in the United States, but around the world [Friedrich 2017, Jorm *et al*. 2017]. Furthermore, between 2010 and 2020 an increase in depressive symptoms paved the way to an increase in teen suicide deaths [Twenger *et al.* 2019, Ionescu *et al.* 2021]. Adults, especially those residing in rural communities with greater social isolation and insufficient access to adequate mental health services, are experiencing a rise in suicide rates [Curtin *et al*. 2016, Kegler *et al.* 2017, Hedegaard *et al*. 2018]. The World Mental Health Organization (WHO) examined 21 nations and found that approximately 1/10th of respondents had an anxiety disorder, but roughly only 1/4th of those affected received care and that many of the services were deemed inappropriate [Alonso *et al.* 2018].

Gut microbiome's influence on depression and anxiety

Advanced biochemical and metagenomic technologies has revealed a significant association between the composition of the gut microbiome and the onset of mental illnesses such as anxiety and depression [Rogers *et al*. 2016, Tognini 2017, Jiang *et al*. 2018]. Ogunrinola *et al.* [2020] recently revised the gut microbiome and reported that "The human microbiome comprises bacteria, archaea, virus, and eukaryotes which reside within and outside our bodies" [Ogunrinola *et al.* 2020]. Regarding this diversity of microorganisms, the human gut is the home to a diverse range of bacterial phyla, with over 1,000 different bacterial species [Zou *et al.* 2019]. As stated by Neugent *et al*. [2020], the colon has pH, temperature, O_2 and microbial density equal to 6.7, 37°C, 0.5-1.1 mmHg and 10^{11} microorganisms/mL. Qualitatively, the two most common bacterial groups, Firmicutes and *Bacteroides*, account for more than 70% of the microbiota, although Fusobacteria, Actinobacteria, Proteobacteria and Verrucomicrobia are also present, but at low percentages [Ogunrinola *et al.* 2020]. Even so, we are only now beginning to grasp the full scope of this microbial variety's consequences for human health and illness. Several studies started to show fascinating patterns in mental wellbeing. Compared to safety controls, patients with major depressive disorder (MDD) have a distinct fecal microbiome composition: the microbiome of MDD patients contains more Bacteroidetes, Proteobacteria and Actinobacteria, but fewer Firmicutes. These people had higher levels of *Allistipes* and *Enterobacteriaceae*, but lower levels of *Faecalibacterium*, which was inversely linked to depression severity [Jiang *et al*. 2015]. Likewise, patients with a generalized anxiety disorder (GAD) have a relatively reduced incidence of five genera in their feces: *Sutterella*, *Faecalibacterium*, *Eubacterium rectale*, *Lachnospira*, and *Butyricoccus* [Jiang *et al.* 2018]. Due to their known development of SCFA substances, these genera may be necessary to mental wellbeing [Van de Wouw *et al*. 2018, Baxter *et al*. 2019]. Lowered SCFA development in GAD patients may lead to a disruption of the intestinal barrier, compromising proper immune function and eventually contributing to cognitive impairment [Morris *et al*. 2017].

Gut microbiome and the brain

The hypothalamic-pituitary-adrenal (HPA) axis plays a significant role in depression and anxiety disorders and it can be altered by changing the gut microbiome makeup [Luo *et al.* 2018]. Mice growing in germ-free (GF) environments showed that a stressful stimulus and high concentrations of corticosterone and the adrenocorticotrophic hormone (ACTH) result from a highly reactive or over-reactive HPA axis [Sudo *et al.* 2004]. Another epigenetic study found that gene expression in the brains of GF male mice differed considerably from that of control mice. The observable difference was noted in the hippocampus, striatum, cerebellum and cortex [Heijtz *et al*. 2011]. These significant changes in the hippocampus and cortex cause

the HPA axis to act differently [Bellavance and Rivest 2014]. The GF male brain included different amounts of neurotransmitters, with an increase in dopamine, norepinephrine and serotonin turnover in the striatum and a decrease in dopaminergic turnover in the frontal cortex, striatum and hippocampus [Crumeyrolle-Arias *et al.* 2014]. The plasticity-related proteins, synaptophysin and PSD-95, were discovered in abundance in the striatum, while nerve growth factor-inducible protein A was found in several locations of the brain. GF mice also showed lesser expression of brain-derived neurotrophic factors [Clarke *et al*. 2013]. A complex and bi-directional communication network between the GIT and CNS is called the 'Gut-Brain Axis' (Fig. 3) – Mayer [2011].

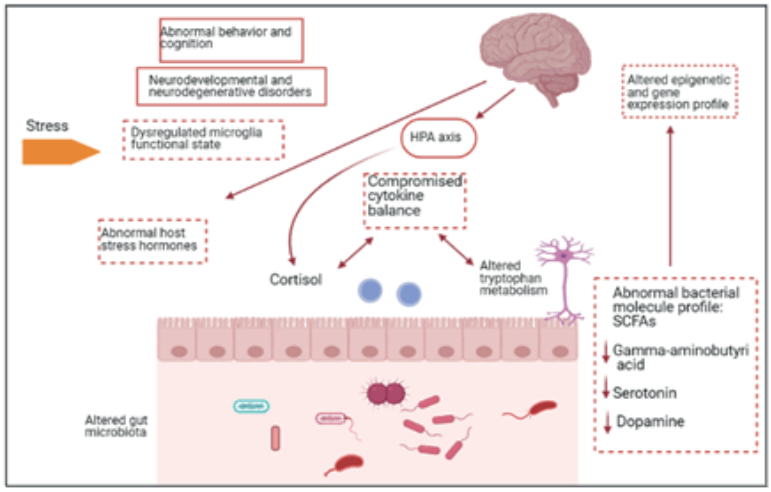

Fig. 3. Mechanisms involved in bidirectional communication of the gut and the brain in response to various stimuli including stress.

Luminal content and other bacterial products affect different sites in the brain by being absorbed in the bloodstream. The bacterial mass interacts with the nerves and endocrine cells residing in the gut to deliver signals to the brain. After careful analysis of experimental data it has been suggested that gut microbiota secrete biologically active products, which can directly or indirectly influence the brain. This involves factors such as LPS (well-known but non-specific), which perform a role in activating Toll-like receptors (TLRs) four on microglial cells, causing the inflammatory cytokines to be released into the CNS, or it may indirectly cause the secretion of inflammatory cytokines from the GI tract [Maes *et al*. 2012]. Stress and depression alter the release of inflammatory mediators, consequently increasing intestinal permeability, thus facilitating the communication of the microbiota with the main cellular signaling pathways, favoring low-grade chronic inflammatory processes evidenced in depression [Kelly *et al*. 2015]. In the intestinal tract, the vagus nerve, spinal nerves and a variety of afferent nerves are hypothesized to send information from the intestinal

lumen to the CNS (Fig. 4). GF mice were fed *Bifidobacterium infantis* orally and as a result c-fos could be applicable as a marker for neuronal activity across the neuraxis after peripheral activation. As reported by [Bullitt 1990], expression was enhanced considerably and immediately in the hypothalamus. However, with the administration of capsaicin in neonatal GF mice this response was partially suppressed [Sudo 2012]. Vagal afferent nerve fibers can die as a result of this event, although pretreatment with granisetron, a serotonin type 3 receptor antagonist, can prevent this effect [Sudo 2016]. The result showed that information formed in the gut is transferred to the brain when serotonin from enterochromaffin cells was exposed to gut bacteria and acted as serotonin type 3 receptors on capsaicin-sensitive afferent nerve terminals.

Some gut bacteria produce SCFAs after metabolizing indigestible dietary fibers or oligosaccharides [Høverstad and Midtvedt 1986]. Most SCFAs are absorbed from the colonic mucosa and can be used as source of energy for epithelial proliferation, hydration, mineral absorption and mucus secretion [Kasubuchi *et al.* 2015]. There is a very profound influence of butyric acid (a type of SCFAs) on the CNS. Animal experiments showed that the antidepressive action of behavioral activation (BA) is produced by *Clostridium* spp. This is conceivable in view of BA's inhibitory effect on histone deacetylase [Tsankova *et al*. 2007]. The concentrations of neurotrophic factors in the frontal lobe and hippocampus increased after BA therapy [Schroeder *et al.* 2007]. Nevertheless, it is not certain whether the physiological concentrations of BA can affect the CNS under normal circumstances. Overall, it is evident that mice who developed without a normal gut microbiome suffered noticeable changes in the brain, which may lead to severe mental issues, e.g. depression and anxiety.

Role of microbiota in host immune system development

The immune system of the host is influenced by the gut microbiome. A study on GF mice found that their mucosal immune system was undeveloped and their immune response to infection was less effective [Strauch *et al.* 2005]. GF mice demonstrated less anti-inflammatory capacities and tiny regulatory T cells [Östman *et al*. 2006]. The compromised gut microbiome composition showed a microglia defect, which leads to an immature phenotype and ultimately decrease innate immune response [Erny *et al*. 2015]. Previous researches reported that the gut microbiome protects the host, balances intestinal homeostasis and can elicit innate and adaptive immunity [Hooper and Macpherson 2010]. Epithelial cells are said to be the main components of the gut immune system. They express microbial-associated molecular pattern receptors, which activate signaling cascades. The microbiota send signals that make epithelial cells produce antimicrobial products and chemokines. Gut epithelial cells form a physio-chemical barrier that prevents access of microorganisms and their growth in the gut surface. To strengthen their barrier function epithelial cells recruit leukocytes, which can also be used to activate gut adaptive immune responses. The genetic program is responsible for developing gut-associated lymphoid tissues (GALTs) before birth in

mammals [Eberl and Lochner 2009]. However, microbiota-derived signals are needed for the GALT maturation, the release of T cells to mucosal sites, the secretion of plasma cells and IgA recruitment. These signals are in charge of controlling the intensity of B and T cell responses in the intestine [Rescigno and Di Sabatino 2009]. The host's immune system and a majority of the microbiota form a network, according to studies. TLRs produced by epithelial cells are activated by microorganism-derived products. As a result, a proliferation-inducing ligand and B-cell activating factor are generated (BAFF). These cytokines mediate both T-cell-dependent and T-cell-independent IgA class switching results in the gut (Fig. 4). Polymeric Ig receptors of epithelial cells transcytose dimeric IgA generated by plasma cells, whose expression is enhanced by the microbiota into the intestinal lumen [Tsuji *et al*. 2009].

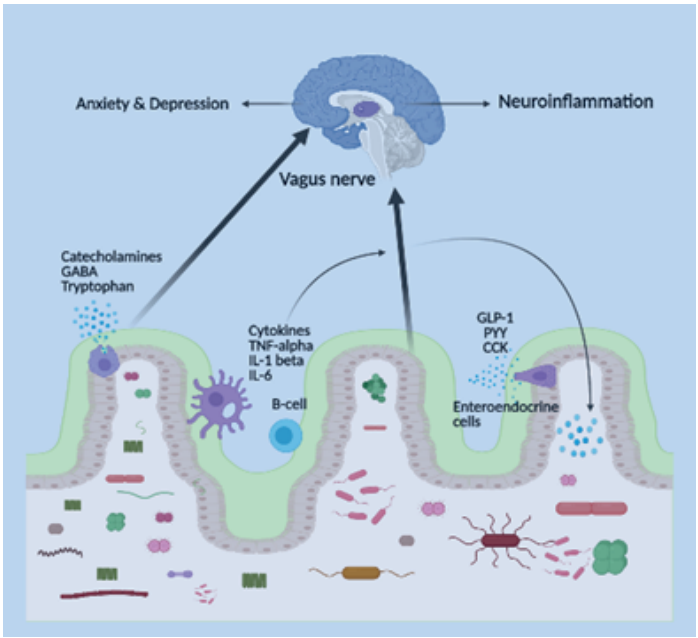

Fig. 4. The effect of microbiota on neuroinflammatory markers and the effect of several inflammatory mediators on anxiety and depression (IL: Interleukin, PYY: Peptide Y, CCK: Cholecystokinin, TNF-α-: Tumor necrosis factor-α).

Stress induced endotoxemia affects brain activity and mental health

Psychological stress possesses an excellent potential to induce pro-inflammatory cytokine production in both mice models and humans [Bailey *et al*. 2011, Baumeister *et al*. 2016]. The stress signals are responsible for these inflammatory changes because they alter the immune system and the intestinal barrier. Immune cells are activated and mobilized throughout the body to fight pathogens and heal lesions induced by stress hormones [Dhabhar *et al*. 2012]. The stress response enhances intestinal epithelial

permeability, which ultimately causes an increase in sodium and water availability. Because of this, endotoxins may enter the bloodstream and trigger 'endotoxemia' [de Punder and Pruimboom 2015]. Stress is linked with intestinal permeability in rats, pigs and humans [Vanuytsel *et al.* 2014]. As strange as it may sound, the brain has an immune system and several recent findings have revealed that it not only actually exists, but is also tightly regulated, thus refuting the assumption that the brain is "immune privileged" [Galea *et al.* 2007]. Peripheral administration of endotoxins causes inflammatory cytokines to be expressed in the brain in many mice models. Neuro-inflammation can be initiated in the brain by the spread of peripheral inflammation via several pathways: (a) afferent neurons convey inflammatory signals to the brain via pathogen-associated molecular patterns and peripheral cytokines, (b) cytokines enter the permeable sections of the blood-brain barrier (BBB), and (c) activated immune cells move to the brain (see Fig. 5).

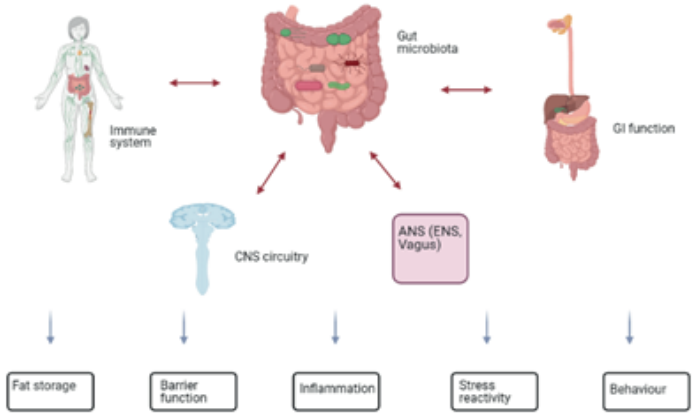

Fig. 5. Bidirectional communication between gut microbiota and components.

This pervasive neuroinflammation can last for up to 40 minutes, as long as the original immune activity [Qin *et al.* 2007]. The timing of the stress is also important; the stress pathway is engaged to counteract an immune response by commencing an anti-inflammatory impact. On the other hand, it generates a pro-inflammatory neuroimmune environment prior to an immune response and stress increases microglia reactivity [Bellavance and Rivest 2014]. Inflammation in the brain can have major mental health repercussions. Microglia that are activated produce reactive nitrogen species (RNS) and reactive oxygen species (ROS), which disrupts the BBB and destroys epithelial cells, contributing to brain toxicity [Kacimi *et al*. 2011]. Modification in gut microbiome composition promotes the development and activity of microglia, which are the immune cells of CNS and participate in neuroinflammation [Erny *et al*. 2015]. Pro-inflammatory cytokines activate the enzyme indoleamine 2,3-dioxygenase (IDO), which boosts tryptophan (Trp) metabolism through the kynurenine (Kyn) pathway [Schwarcz *et al*. 2012].

IDO activation is linked with neuro-inflammatory mood disorders by increasing the secretion of neurotoxins, as indicated by animal research [Parrott *et al*. 2016]. The pro-inflammatory cytokines are involved in the damaging and diversion of tetrahydrobiopterin, which is a necessary enzyme co-factor of monoamine synthesis. Because of this damage, there is a hindrance during neuroinflammation in synthesizing monoamine neurotransmitters, including dopamine, norepinephrine, and serotonin. Altogether, neuroinflammation creates a highly toxic environment for brain functioning and mental health [Miller and Raison 2016].

The gut microbiota-brain axis

Microbial ecosystems, which comprise bacteria, archaea, fungi and viruses, have evolved in close contact with the animal kingdom, including humans [Manrique *et al.* 2017]. These microorganisms, known as the microbiota, may be found on practically every environmentally exposed body surface, including the GI tract, displaying a highest density and number of microorganisms in the human body [Bernstein 2014]. Instead of only existing as passive beings in our bodies, important scientific revelations have highlighted the critical significance of the gut microbiota promoting the proper function of our immune systems, metabolism and development of several organs (Fig. 4). The bacterial communities that dwell in our guts are dynamic organisms that can change their conformation and activity over time because of host effects. Host contributors to change include age and genetics, as well as environmental factors, the most important of which are nutrition and medications [Ghaisas *et al*. 2016].

Although gut microbiota investigations have covered fungi, archaea and viruses a considerable body of information is gathered from the research conducted on bacteria. The population of bacteria contained in the gut microbiota is comparable to the human body's total number of cells [Zhu *et al*. 2010]. The genetic collection found in the entire gut microbiome is considered to be around 232 million genes, significantly boosting human metabolic activity, which is why the gut microbiota is regarded as having the capacity of a human liver [Morais *et al*. 2020].

The gut microbiota serves as a biological regulator and filter, detecting and altering a large number of chemical signals from the environment before they move throughout the body. Gut bacterial communities, by themselves, persist at the host-environment interface and can have a considerable impact on human health [Defois *et al.* 2018]. The complex network containing various biological mechanisms promoting bidirectional communication of the brain and the bacteria residing in the gut is termed 'gut-microbiota-brain.' It is essential in sustaining the GI, CNS and microbial homeostasis systems of animals [Fung 2020]. Communication channels, including both indirect and direct signaling via chemical transmitters, neural pathways and the immune system are all part of these biological networks (Fig. 5). Since numerous biological systems are entangled, several mechanisms and pathways likely function together to facilitate different features of disease pathogenesis. The critical pathways that connect

the autonomic nervous system (ANS) and the enteric nervous system (ENS) are the neuroendocrine, sympathetic, neuroimmune and parasympathetic arms of the ANS and the ENS, while the gastrointestinal system (GI) provides the framework for these pathways. These modules constitute an intricate network of reflexes, with afferents projecting integrative cortical CNS structures and efferents mobilizing smooth muscle in the gut wall. Remarkably, it is increasingly acknowledged that this communication is bidirectional: CNS functioning is affected by microbiota and the CNS also has some impacts on the microbiota conformation with its influences on the GI region [O'Mahony *et al.* 2015].

The gut microbiota aid in regulating homeostasis along with behavior in its host through communication with the nervous system by chemicals involved both in 'direct' and 'indirect' signaling. Behavioral studies in diseases of psychopathological etiology revealed that the resident microbiota and the use of probiotics interfere in a systemic way and can even alter the host's cognitive aspects [Dinan *et al.* 2013]. For example, in preliminary study models SCFAs are lipids generated by gut microorganisms through the fermentation of dietary fiber that can influence the CNS by altering neuroplasticity, epigenetics and gene expressions in the immune system. SCFAs have the potential to affect the host's illness and behavior [Dalile *et al.* 2019].

Physically, neuronal connections connect the gut and the brain. The vagus nerve is the best known of these neurological pathways, extending from the brainstem to innervate the ENS and the gut. The ENS's growth and functions are aided in part by the gut bacteria. The colonic epithelial neuronal innervation is shown to be reduced in GF mice and can be regained with the help of microbial colonization. In mice the gut microbiota also regulate the formation of enteric glial cells, which are essential for gut homeostasis and maintenance of neural networks. As indicated by a recent study which found that stimulation of aryl hydrocarbon receptors in mature mice can maintain gut motility through impacts on the ENS, chemical signaling from the gut microbiota can alter the role of enteric neurons [Obata and Pachnis 2016].

Probiotics, prebiotics and mental health

Living microbial food constituents, "probiotics", have a valuable effect on human health [Markowiak and Śliżewska 2017]. The term has originated from the initial investigations on the impact of particular yogurt bacteria on the complete conformation of the human gut microbiota. Initially, probiotics were considered to have an impact on both animal and human gut microbiota. The particular live microbial food constituents and their influences on human health are investigated both within food media and as single or mixed culture preparations. Several indigestible, but fermentable dietary carbohydrates can stimulate particular bacterial collections colonizing the colon, e.g. bifidobacteria, lactobacilli and eubacteria, which are advantageous for the human host group prebiotics. These sorts of challenging short-chain carbohydrates (SCC) are also known as indigestible oligosaccharides or low-digestible carbohydrates [Yang 2019].

In humans cognitive roles are modulated by the CNS, regulated by the brain. If the neuronal system gets damaged, it leads to severe injury to the host because it can cause neurodegenerative diseases such as autism, Parkinson's, Alzheimer's and epilepsy [Ngô *et al.* 2017]. GF mice lacking in microbiota have been found to exhibit poor social behavior as well as anxiety and stress reactivity, according to a number of studies [98]. Furthermore, researchers have shown that some behaviors are triggered by a lack of gut microbiota, which is linked to neurochemical changes in the brain. Many neurotransmitters and their receptors have been found to be altered in various brain areas of GF mice.

Furthermore, the ability of faecal microbiota transplantation to transmit behavioral traits has been confirmed [Hu *et al.* 2018]. It also signified that some microbiota alterations could be a reason rather than an outcome of behavioral changes. Current information attained using GF animals has divulged that neurogenesis, a route that has a vital part in controlling learning and memory, is well-modulated by the microbiome. In addition, the gut microbiota are hypothesized to control functional and structural changes in the amygdala, a critical brain area connected to social and fear-related behaviors in a range of neuropsychiatric illnesses [Tengeler *et al*. 2020]. Furthermore, several studies have revealed that behavior of healthy mice can be changed by administering probiotics, successfully reducing anxiety and depression, thus further stressing the significance of probiotics in reducing stress behaviors [Partrick *et al.* 2021].

Prebiotics are nondigestible dietary components that assist the host via promoting the growth and/or function of one or a limited number of bacteria in the gastrointestinal tract (GIT), therefore improving the host's situation [Gibson and Roberfroid 1995]. Prebiotics are found in several foods such as fruits, legumes and leafy vegetables; these oligosaccharides, present even in human milk (HMO), can promote development of specific bacteria, such as probiotics of the genera *Bifidobacterium* and *Lactobacillus* [Coppa *et al.* 2006, Bindels *et al.* 2015]. Furthermore, *Bifidobacterium* and *Lactobacillus* spp. have a significant impact on the brain-gut axis [Dinan *et al*. 2013].

The impacts of 3'sialyllactose (3'SL) and 6' sialyllactose (6′SL) in the microbiota may also affect the brain. It has been discovered that sialyllactose is a significant source for brain growth and cognitive processes [Wang and Brand-Miller 2003]. Rats fed sialyllactose or galactosylated SA demonstrated increased learning ability in a swimming learning test, which was connected to higher SA and ganglioside content in the brain [Tarr *et al.* 2015].

Some prebiotics may have favorable effects on the CNS through modulating neuroinflammation according to preclinical and clinical research, and hence may be useful in the treatment of anxiety, cognitive impairment and depression [Paiva *et al.* 2020]. All these outcomes predict the broader role of probiotics and prebiotics in health, particularly in the case of depression, anxiety and stress.

Probiotics and prebiotics in stress response

Many organisms support biological machinery when they encounter stress stimuli that show a defensive response. The HPA axis is engaged when stress stimuli are encountered, while corticosterone releasing factor (CRF) is secreted by hypothalamic paraventricular neurons [Nicolaides *et al*. 2015]. CRF supports the production and release of glucocorticoids from the adrenal cortex by stimulating the release of ACTH from the anterior pituitary (cortisol in humans and corticosterone in animals) (Fig. 3). The microbiota promote the growth of the HPA axis and stress response in GF mice, according to research. An inflated HPA axis has been demonstrated in animals that tend to grow in a sterile environment and have increased levels of ACTH and corticosterone when encountering a stress stimulus. Surprisingly, after colonization with commensal bacteria from control mice HPA axis activity is controlled [Vodička *et al.* 2018].

Gut-brain signaling was examined in order to understand the mechanism of *Lactobacillus casei* strain Shirota (LcS)-induced inhibition of HPA activity [Takada *et al.* 2016]. Afferent autonomic nerves have a role in signal transmission from the GI region of the brain, such as the regulation of GI hormones; moreover, particular probiotics can boost GVA function [Pavlović *et al.* 2012]. It is revealed that sympathetic nerve activity is suppressed by signal transfer via abdominal vagal afferent nerves [Torii *et al.* 2013]. The general visceral afferent was activated in a dose-dependent manner within minutes after intragastric administration of LcS, but not by saline, according to this study. Even though the activation mechanism has not been identified, LcS is probably observed instantly in the stomach, as indicated by consequential inactivation of the vagal afferents. Further research revealed increased neuronal excitability in the nucleus tractus solitarii of rats administered LcS. This shows that LcS sends signals to the nucleus of the solitary tract (NTS) in the same way as visceral sensory neurons contacting the gastric vagus do (GVA). Other interpretations revealed that when rats are given LcS orally, it operates on the gut and sends afferent signals to the brain's NTS via the vagus nerve [Choi *et al*. 2020]. The NTS absorbs visceral sensory inputs and delivers inhibitory and excitatory signals to the PVN via ascending pathways, either directly or indirectly. The type of neurons activated by LcS in the NTS is not known yet. However, according to an *in vivo* study it was revealed in the suppression of the HPA axis that LcS probably stimulated the inhibitory circuitry in a way that project to inhibitory gamma-amino butyric acid (GABA) interneurons adjacent to the PVN [Takada *et al*. 2016].

In addition, specific nutritional components, including dietary fiber and prebiotics, are a path that helps to control GI bacteria. Several studies have suggested that FOS could be a valuable symbiotic method to boost probiotic bacteria levels and ensure their survival in the GI lumen [Chen *et al.* 2017]. The modulation of probiotic bacteria promoted by prebiotics can significantly reduce stress due to oxidation and neuronal apoptosis in Alzheimer's disease, restore regular energy metabolism and increase cell survival and mitochondrial membrane potential. Importantly, prebiotics are nutrients that promote bacteria with a probiotic potential and are the bacteria that

re-establish homeostasis through their metabolites [Benjamin *et al*. 2011]. Prebiotic substances such as FOS increased fecal Bifidobacteria and Lactobacilli and have been demonstrated to stimulate immunoregulatory dendritic cell (DC) reactivity in several investigations. Bifidobacteria are also significant probiotic species in the GI lumen and they have been shown to improve human health by preserving the balance of resident microbes [Malaguarnera *et al*. 2012].

Role of probiotics and prebiotics in anxiety and depression

Depression is a stress-related mood condition that is connected to a dysfunctional HPA axis. The gut microbiome has been connected to depression regulation in various studies [Juruena *et al*. 2020]. In comparison to a healthy control group, patients suffering from depression have a higher alpha diversity of gut microbiota [Huang *et al.* 2018]. Furthermore, when compared to control groups, people with depression have lower levels of *Bifidobacterium* and *Lactobacillus* [Romijn *et al*. 2017]. According to current research, patients with major depression have different microbiota than healthy people, with a significant rise in the species *Eggerthella*, *Gelria*, *Paraprevotella*, *Turicibacter*, *Holdemania*, and Anaerofilm, as well as a drop in *Prevotella* and *Dialister* levels [Sandhu *et al*. 2017]. A recent investigation reported a negative association between the severity of depression symptoms and *Faecalibacterium* spp. [Jiang *et al.* 2015]. Scientists have demonstrated that when the microbiota of people with severe depression are transferred to animals with no microbiota, the behavioral and physiological aspects associated with depression change as well, indicating a link between dysbiotic microbiota and depression [Valles-Colomer *et al.* 2019]. Different types of diets have been recommended as having either negative or positive effects on depression. A Western diet, for example, appears to be linked to an enhanced risk of depression, whereas a Mediterranean diet appears to downregulate the onset of depression.

Reduced omega-3 polyunsaturated fatty acids have been linked to severe depression in animal models and humans, emphasizing the action of food in the onset of depression. In animal models various probiotic therapies have been shown to be useful in reducing tendency towards depression. In a maternal-separation animal model, for example, administration of a probiotic cocktail containing *Lactobacillus helveticus* and *Lactobacillus rhamnosus* strains was shown to reduce depressed behavior and regulate corticosterone levels [Kavvadia *et al.* 2017]. Furthermore, the administration of *L. rhamnosus* enhances depression and anxiety-associated behavior [Donoso *et al*. 2020]. The link between various *Bifidobacterium* strains and possible antidepressant-like behavior in animals has been confirmed. In maternally separated rats, treatment with a strain of *B. babies* decreased depression and resulted in more mobility episodes during the coercive swim test. Similarly, *Bifidobacterium longum* and *Bifidobacterium breve* strains had an effect on depression and anxiety-related behavior in rats [Evrensel and Tarhan 2020].

The neurotrophin family member brain-derived neurotrophic factor (BDNF) influences various pathways, including the persistence and differentiation of neurons, the creation of neuroplasticity and functional synapses throughout development and adulthood [Hempstead 2015]. The gut-brain axis has been associated with significant alterations in hippocampus BDNF mRNA and protein. Lowered expression of hippocampal BDNF mRNA or protein was linked to upregulated anxiety-like behaviors in infection models leading to modification in the microbiota profile [Sherwin *et al.* 2016]. In these investigations, the reversal of behavioral abnormalities caused by probiotic treatment was linked to a restoration of normal BDNF expression levels [Liu *et al.* 2021].

Prebiotics have been shown in several trials to have potential benefits in the management of mood disorders such as major depressive disorder (MDD) and anxiety [Szklany *et al.* 2020]. Several studies have also found that combining probiotics and prebiotics has favorable neurobehavioral benefits in the treatment of depression disorders [Mika *et al.* 2017]. In turn, Schmidt et al. studied the effects of administering prebiotics (fructooligosaccharides or Bimuno-galactooligosaccharides) in 45 volunteers that were healthy, observing a lower salivary cortisol awakening results as well as a lower attentional vigilance to positive vs. negative information in a dot-probe task in the latter group alone [Schmidt *et al.* 2015].

Clinical trials

In a clinical trial a double blind, placebo-controlled combination of two probiotics was given to healthy individuals in a 30-day trial. Then their results were calculated using several surveys to evaluate psychological stress. The treatment group given probiotics showed relatively less psychological stress than the matched controls [Messaoudi *et al.* 2011].

This gold-standard research enrolled 22 healthy male participants and showed that all those who took 1 billion colony forming unit (CFU) of *B. longum* 1714 had lower levels of perceived daily stress and lower levels of salivary cortisol, the stress hormone, than others taking placebo. Even though it is unclear how the *B. longum* strain affects our health, one possibility advanced by the scientists who participated in this research is that the bacteria release substances that impact vagus nerve signaling, which helps connect the gut to the brain. More information concerning studies involving *B. longum* 1714 can be obtained by health care providers [Wang *et al.* 2019].

A research published in the British Journal of Nutrition in 2011 examined the effect of two probiotics used in combination: *Lactobacillus acidophilus* Rosell-52 and *B. longum* Rosell-175. Fifty-five volunteers were given either of the two probiotic strains or a placebo each day for thirty days, after which their depression and anxiety levels were assessed. According to the findings of that study, this combined probiotic effect promotes psychological health [BAO 2021].

Conclusion

Much of the evidence that came from rodent studies proposed that this bi-directional pathway could increase gut permeability, allowing the gut bacteria and their metabolic products to interact with the immune system, ENS and enter the bloodstream. There is a need to fully understand the different components of the gut-microbiome-brain axis in future studies as this will help in formulating better and more effective prebiotics/probiotics.

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