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Journal of Pharmacology & Clinical Toxicology

Review Article

Gut-Microbiota and Mental Health: Current and Future Perspectives

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Submitted: 22 November 2013

Accepted: 02 January 2014

Published: 12 January 2014

Keywords
- Gut-microbiota
- Probiotics
- CNS
- Gut- brain axis

Abstract

Recently, there is a growing interest of research on the relationship of gut-microbiota and neurological disorders. Increasing number of findings suggests the broader role of gut-microbiota in the modulation of various physiological and pathological conditions and it is now well recognized that a bidirectional communication between brain and gut-microbiota is essential to maintain homeostasis. The gut-brain axis includes central nervous system (CNS), the neuroendocrine and neuroimmune systems, autonomic nervous system, enteric nervous system, and intestinal microbiota. Probiotics (i.e., live microorganisms similar to beneficial microorganisms found in the human gut) are reported to modulate a number of disorders including metabolic disorders, behavioral conditions and cognitive functions. This review covers the significance of gut-brain axis in relation to the overall mental well-being. Apart from the recent studies highlighting the importance of gut-brain axis, here we also reviewed the interaction of few herbal medicines with gut-brain axis. Animal studies have indicated that some herbs or their isolated constituents alter the normal gut flora and have prominent effect on behavioral condition such as anxiety depression and cognition. Thus alteration of gut-brain axis by traditional medicines will be a potential strategy for the management of comorbid CNS disorders and gastrointestinal problems.

INTRODUCTION

The concept of the gut-brain axis, a term which describes the complex bidirectional communication system that exists between the central nervous system and the gastrointestinal tract and which is vital for maintaining homeostasis [1,2]. The gut-brain axis is involved in a multitude of physiological processes including satiety, food intake, regulation of glucose and fat metabolism, insulin secretion and sensitivity, bone metabolism [3,4], and lifespan [5].

Emotional or physical stressors may cause disturbances at every levels of the brain-gut axis including the central, autonomic and enteric nervous systems and affect regulation of visceral perception and emotional response to visceral events [6]. Brain communicates with the gut through multiple parallel pathways including autonomic nervous system, the hypothalamic pituitary-adrenal axis, and other connections, which were termed the brain-gut axis [7,8]. Based on previous studies there is strong evidence that exposure to stress, and release of catecholamines and norepinephrine into the GI tract during stress [9], may be responsible for the dysregulation of the gut-brain axis, via changing the GI motility, secretion of mucus and epithelial cells, thus leading to the different diseases of the gut [10]. It is also found that stress doing the early maturity life in animal, produces microbiota changes associated with inflammatory cytokines and increased levels of corticosterone [11]. Epidemiological studies have implicated stress of psychosocial, physical or immune origin as a trigger of first onset or exacerbation of irritable bowel syndrome symptoms [12-14]. In adult irritable bowel syndrome patients, acute stress episodes, chronic social stress, anxiety disorders, and maladaptive coping style determine the illness experience, health care-seeking behavior as well as treatment outcome [15,16]. Stress-related psychosocial factors such as somatization, neuroticism, and hypochondriasis are also important predictors in the development of post-infectious irritable bowel syndrome [17,18]. Microbiota provides the significant protection against incoming bacterial pathogens [19]. It has been shown that microbiota helps and protects the host against the viruses indirectly via activation of the inflammasome which is crucial for defense against influenza

[20,21]. Interestingly, in spite of the fact that microbiota help the host to fight viruses (for example in case of influenza), it may also equally enhance viral infection via influence on virus replication by stimulating the proliferation or activation of target cells [22]. There is a growing appreciation of the critical role played by the commensally microbiota, both in our general wellbeing and in the specific functioning of the brain-gut axis. Interestingly, bacteria may respond directly to stress-related host signals because of interplay between stress and gut microbiota. Thereby, stress may influence the outcome of infections by these bacteria in many hosts [23].

Microbiota and host-metabolism

The human gastrointestinal microbiota represents a complex ecosystem that consists of bacteria, archaea, yeasts, planctomycetes and filamentous fungi and viruses, such as Senegal virus [24-30]. The human gastrointestinal tract typically comprises more than 10 times microbial cells that of the number of human cells in our bodies and containing 150 times as many genes as our genome [31,32]. The gut microbiota is therefore often referred to as the forgotten organ. The estimated number of species in the gut microbiota varies greatly, but it is generally accepted that the adult microbiota consists of more than 1,000 species which are belong to a few bacterial phyla [33], and more than 7,000 strains [32,34,35]. Interestingly, the gut microbiota modulated the expression of genes involved in immunity, nutrient absorption, energy metabolism and intestinal barrier function in human or mouse intestine [15].

The microbiota and host have mutually beneficial symbiotic relationships, which assure balanced habitat [36]. The compositions of the microbiota play an important role in the maintenance of intestinal homeostasis and host health [37]. Through the cooperative action of different functional microbial groups, the gut microbiota synthesizes essential amino acids and vitamins. In addition, by deploying an array of glycosidehydrolases and polysaccharide lysases, the microbiota facilitates utilization of otherwise indigestible food compounds [34,38]. Fermentation of saccharides by gut microbiota is the main source of energy for intestinal epithelial cells [26]. Microbial de-polymerization of complex carbohydrates and proteins gives rise to mono- and oligomeric compounds that are subsequently fermented into short-chain fatty acids (SCFAs) as well as to carbon dioxide and molecular hydrogen [39]. Carbohydrate fermentation and short-chain fatty acid production significantly improve the absorption of calcium, magnesium, and phosphorus [40].

For more than 50 years we have known that the administration of low doses of antibacterial agents promotes the growth of farm animals, consequently, in the United States, the largest use of antibiotics and related antimicrobial substances is within farms, with low doses fed to large numbers of animals used for food production to increase weight gain [41]. There are two main mechanisms by which it can maximize nutrient availability, either by the release of calories from otherwise unavailable oligosaccharides or by modulating absorption [42]. Alteration of gut microbiota can cause number of diseases for example, it has been shown that an increased ratio of the phylum Firmicutes to the genus Bacteroides is linked to obesity [43].

As might be expected given the importance of the microbiota in supporting host digestion and metabolism, obesity has been considered as an illness with a potential microbial basis [44]. Till 2004, there is over 138 data publications and 60 reviews for obesity and microbiota [45]. A perturbation of the resident flora in the accumulation of excess fat, microbial influences should not be considered in isolation because obesity is a multifactorial condition that also involves strong genetic factors, hypothalamic dysfunction, and an increase in the consumption of energy-dense food [46]. A significant energy source for humans is the bacterial metabolism of dietary fiber to short-chain fatty acids (SCFAs) [47]. SCFAs can modulate the host energy balance through Gpr41, a G protein coupled receptor that binds SCFA, and is dependent upon the gut microbiome. It is thought that interaction between SCFAs produced by the gut bacteria, and Gpr41 increases circulating levels of PYY, an enteroendocrine hormone that reduces gut motility and thus increases absorption of SCFAs [48]. A pictorial representation of Microbiota host metabolism is depicted in Figure 1.

Several nutrients, including L-glutamine, L-glutamate, glucose, and sucrose, have physiological effects such as protecting the gastric mucosa, improving emotional state, and supplying energy in the subconscious state. These nutrients can also modulate subsequent behavior, such as brain activation and behavioral modulation resulting from internal signaling through the gut-brain axis [49]. Ingested nutrients are digested and absorbed in the gastrointestinal tract. The afferent vagus nerve, which innervates the entire gastrointestinal tract and projects to the nucleus of the solitary tract, is then activated, or peripheral humoral factors such as insulin and glucagon like peptide-1 (GLP-1) are released. In addition to absorption and metabolism, recent studies have indicated that the stomach, duodenum, and intestine contain chemosensing taste receptors and some kind of the G-protein coupling receptors (GPRs). The T1R receptor, which is related to the chemoreception of the sweet and the umami taste, and the T2R receptor, which is related to the chemoreception of the bitter taste, are both expressed in the gut [50,51]. In addition, GPR120 exists in both the oral cavity and the gastroinestinal tract in rodents. Fatty acids interact with GPR120 to induce the release of circulating GLP-1 [52]. Free fatty acids also interact with GPR40 in the gastrointestinal tract and promote the secretion of GLP-1 [53], and CCK [54]. GLP-1 and CCK evoke c-fos positive immunoreactivity in several brain regions, including the amygdala and the periaqueductal gray matter [55-57]. Intragastric infusion of glucose solution increases blood glucose, GLP-1, and insulin, and circulating GLP-1 acts on neurons in the nucleus of the solitary tract. Recently, it has been demonstrated that fluctuations in insulin following the intragastric administration of glucose correlate with the blood oxygenation level-dependent response in the amygdala, ventromedial hypothalamus, and nucleus accumbens [49,58].

The GI tract also is a locus of hormone production, including those involved in energy homeostasis (such as insulin, glucagon, leptin and ghrelin) and growth (for example, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) [59]. Scientists working in this field develop a model of obesity by treating mice at their early life time by administering mid-range of US FDA-approved sub-therapeutic

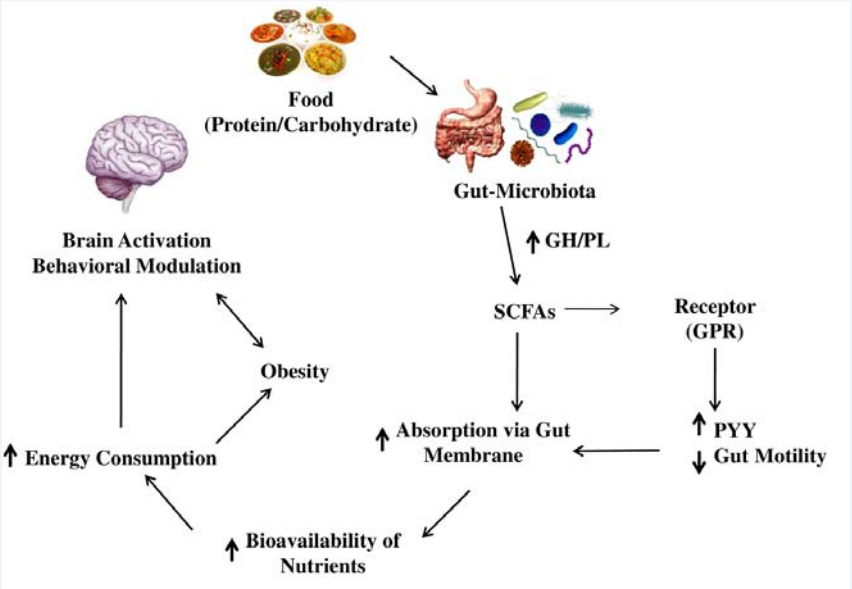

Figure 1 Microbial-host metabolism and the effect on behavioral function of brain. GH- Glycoside Hydrolases; PL- Polysaccharide Lysases; SCFAs-Short-Chain Fatty Acids; GPR- G-Protein Coupling Receptors; PYY- Peptide YY.

level of various antibiotics in their drinking water, and reported that subtherapeutic antibiotic treatment (STAT) in early life growth mice results in significant increase in adiposity, bone mineral density and GIP level. The increase GIP level was in supports with other existing models of obesity. But no significant differences for fasting insulin-like growth factor (IGF)-I, insulin, peptide YY, leptin, or ghrelin levels between control and STAT mice. Various dynamic phases of growth in young animals, STAT alterations of the microbiome may affect pluripotent cells that can become osteoblasts, adipocytes, or myocytes. Postulated that STAT exposures selected for microbiota with increased metabolic activity that were able to extract a higher proportion of calories from dietary complex carbohydrates that were relatively indigestible in the control mice. The increased SCFA concentrations are the metabolic products of this activity, which then may be delivered in increased quantities through the portal circulation to the liver, enabling enhanced lipogenesis. Enhanced caloric absorption has been implicated as a mechanism for increased weight gain in other murine obesity models [41].

Microbiota-gut-brain axis

In general the brain–gut–enteric microbiota axis includes the CNS, the neuroendocrine and neuroimmune systems, the sympathetic and parasympathetic arms of the autonomic nervous system (ANS), the enteric nervous system (ENS), and of course the intestinal microbiota. During the feeding, the gut released peptides which are affecting hypothalamic pathways, and especially arcuate nucleus involved in the regulation of satiety and metabolism. Put simply, through this bidirectional communication network, signals from the brain can influence the motor, sensory, and secretory modalities of the GIT and conversely, visceral messages from the GIT can influence brain function [60]. The vagus nerve is the direct communication observed between the bacteria and the brain [61]. A pictorial representation of the bidirectional communication represented in Figure 2. The cross talk between gut microbiota, the immune system and the brain-gut axis plays an important role in the modulation of the stress response of the gut in the context of the development of different gut disorders as microbiota communicate with the gut-brain axis through different mechanisms viz. direct interaction with mucosal cells (endocrine message), via immune cells (immune message), and via contact to neural endings (neuronal message) [2].

Microbiota also interacts with host gut-brain axis through neurohumoral communication to influence brain development and behavior [62]. For example, alteration in gastrointestinal function is communicated to the brain bringing about the perception of visceral events such as nausea, satiety, and pain or when, in turn, stressful experiences lead to altered gastrointestinal secretions and motility [63]. The neuroendocrine, neuroimmune, the sympathetic and parasympathetic arms of the autonomic nervous system and the enteric nervous system are the key pathways through which they communicate with each other [64]. This might influence a broad spectrum of diseases, psychiatric conditions and other disorders [65]. Putative mechanisms by which microbes access the brain and influence behavior include microbial products that gain access to the brain, via cytokine release from the mucosal immune cells, via the release of gut hormones such as 5-HT from endocrine cells, or via afferent neural pathways, including the vagus nerve. Stress and emotions can also influence the microbial composition of the gut through the release of stress hormones or sympathetic neurotransmitters (GABA, 5-HT precursors etc.) that influence gut physiology and alter the habitat of the microbiota and also these catecholamine alter the growth, motility and virulence of pathogenic and commensally bacteria. Alternatively, host stress hormones such as noradrenalin might influence bacterial gene expression or signaling between bacteria, and this might change the microbial composition and activity of the microbiota [66].

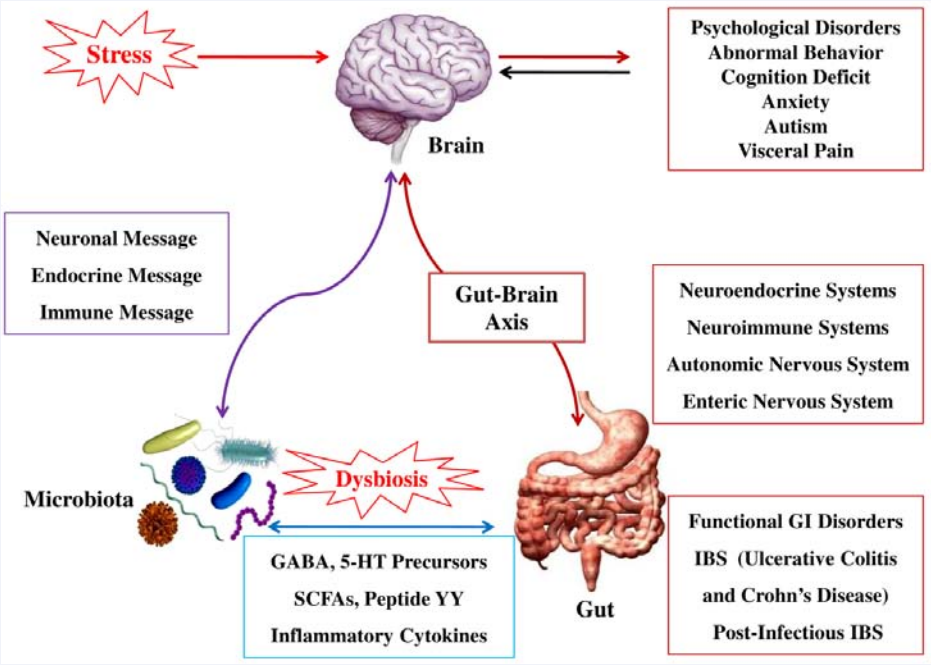

Figure 2 Bidirectional communications between Gut-Microbiota and Gut-Brain Axis (GBA) in the modulation of the stress response. Microbiota communicate with the gut-brain-axis through different mechanisms viz. direct interaction with mucosal cells (endocrine message), via immune cells (immune message), and via contact to neural endings (neuronal message) to influence brain development and behavior. Stress through GBA effect on Gut-Microbiota which is responsible for functional GI disorders and dysbiosis. Similarly dysbiosis effect synthesis of several microbial by-product and precursor that gain access to the brain via the bloodstream and the area postrema, via cytokine release from mucosal immune cells, via the release of gut hormones such as 5-hydroxytryptamine (5-HT) from entero-endocrine cells, or via afferent neural pathways, including the enteric nervous system.

Some of the earliest indications of a critical role of the gut microbiota in stress responses are well recognized. Germ-free animals were identified as having exaggerated hypothalamic–pituitary–adrenal (HPA) axis activation in response to stress. This hyper responsiveness was reversed by reconstitution with feces from animals kept in a pathogen- free environment or with a single bacterial strain, *Bifidobacterium infantis* [67]. More recently, two studies have indicated that germ-free conditions during early growth of mice results in decreased anxiety-like behavior compared to conventional animals [68,69]. Addressing neural correlates of reduced anxiety in germ-free animals, Diaz et al. demonstrated that NGFI-A mRNA expression was significantly lower in various sub-regions of the prefrontal cortex, including the orbital frontal cortex and the striatum, hippocampus dentate gyrus, and amygdala, compared with specific pathogen-free mice [68]. Germ-free mice also had significantly lower BDNF mRNA expression in the hippocampus, amygdala, and cingulate cortex, which are important components of the neural circuitry underlying anxiety and fear [70, 71]. In addition to altered neurotrophin levels, changes have been reported in NMDA receptor subunit expression with decreased NR1 and NR2A in the hippocampus, decreased NR2A in the cortex, and decreased NR2B in the amygdala, but not in the hippocampus [67,69]. Enhanced turnover rate of noradrenaline, dopamine, and 5-HT has also been demonstrated in the striatum of germ-free mice compared with specific pathogen-free mice [68].

Gut microbiota and neurotransmission

Gut microbiota influences the release of some of the major brain neurotransmitters which act in the gut-brain axis and modulate food intake and energy balance [72] i.e., short chain fatty acids (SCFAs), Peptide YY (PYY), tryptophan, serotonin, endocannabinoid ligands, cholecystokinin, and ghrelin. The gut hormones affect glucose metabolism by altering food intake, body weight, insulin sensitivity, gastric delay, gut motility, glucose levels and plasma glucose levels. It has been shown that low doses of PYY3-36 and GLP-1 can additively reduce food intake in rodents and man [73]. The interaction between SCFAs produced by the gut bacteria, and Gpr41 increases circulating levels of PYY, a potent orexigenic agent [48]. Conventionalized germ-free mice present with a 2.8-fold increase in plasma serotonin levels respect to control animals [74]. Administration of *Bifidobacterium infantis* 35624 to Sprague-Dawley rats, for example, has been shown to induce an elevation in plasma tryptophan levels, a precursor to serotonin [75].

Serotonergic neurotransmission modulates many brain functions including emotion, cognition, motor function, pain as well as neuroendocrine functions such as food intake, circadian rhythms and reproductive activity [76]. 5-HT is an important signaling molecule in the brain-gut axis and the 5-HT released from enterochromaffin cells modulates peristaltic, secretory, vasodilatory, vagal and nociceptive reflexes [77]. A high incidence of specific psychological features, including anxiety and obsessive compulsive behavior was observed in irritable bowel syndrome (IBS) patients. A positive correlation between neuropeptide Y and state anxiety and simulation/social ingenuity was found in these patients. In diarrhea-predominant IBS, plasma cortisol was linearly related to plasma serotonin [78].

Diet supplementation with prebiotic fiber has been associated with alterations in the expression or content of various gut hormones linked to the regulation of energy balance, notably increasing the satiety hormone PYY and reducing the expression of the orexigenic peptide ghrelin [79]. It has been demonstrated that prebiotic treatment was increasing plasma levels of GLP-1 and PYY [80]. Probiotics are capable of producing and delivering neuroactive substances such as gamma-aminobutyric acid and serotonin, which act on the brain-gut axis. Preclinical evaluation of probiotics in rodents suggests that certain probiotics possess antidepressant or anxiolytic activity and therefore, better called as psychobiotics [81].

A potential role for the microbiota in the development of autism, a developmental disorder that appears in the first 3 years of life and affects the brain's normal development of social and communication skills [82]. Interestingly in a study of 58 autism patients >90% had gastrointestinal problems compared to none in the control group [83]. There is evidence to support alterations of the fecal microbiota in patients with autism, with an increase in several subtypes of Clostridium [84,85], pathogens from the family Alcaligenaceae and Sutterella, which may contribute to the pathogenesis of GI disturbances in children with autism [86]. Metagenomic analyses demonstrate a dysbiosis with reductions in Bacteroidetes and increase in the ratio of Firmicutes to Bacteroidetes, as well as in Betaproteobacteria [87]. In case of Clostridium, the majority of cases treatment with vancomycin, an antibiotic that targets gram positive anaerobes and is minimally absorbed by the GIT, can improve symptoms [88]. The possibility of microbiota involvement in development of Parkinson disease and cerebrum metabolic changes has been discussed [89]. It has been shown that increased peptidoglycan production by the gut metagenome may contribute to symptomatic atherosclerosis. Because atherosclerosis is associated with lipid accumulation and inflammation in the arterial wall, enriched presence of Collinsella bacteria in gut microbiota have been suggested as a causative agent of this disease [90,91]. Also, it has been found that decrease in Clostridium in gut microbiota content is associated with an increased inflammatory response and liver injury progress and induction of experimental cirrhosis in CCl4-treated mice [92,93], as well as fat deposition in the liver [94,95]. There is also a number of publications on the potential role of microbiota's misbalance in case of perinatal programmed asthma [96], allergy [97], and Crohn's disease [98].

Bercik et al. reported that alteration in the brain-derived neurotrophic factor (BDNF) mRNA and protein level in hippocampus and amygdala in mice of antibiotic-induced dysbiosis [99]. Oral administration of non-absorbable antimicrobials to SPF mice transiently altered the composition of the microbiota and increased exploratory behavior and hippocampal BDNF expression. BDNF levels in antimicrobial treated mice were greatly higher in the hippocampus and lower in the amygdala compared with control mice [99]. Alterations in the BDNF level were consistent with the behavioral changes observed in that study. On the other hand, changes in BDNF level have also been implicated in the pathogenesis and treatment of depression. There are ample evidences which suggest that BDNF and its mediated signaling may participate in the pathophysiology of depression [100]. Antidepressant-like property of BDNF has been reported in animal models of depression [101] and it is now established that BDNF contributes to the therapeutic action of antidepressant treatment [102]. Hence, BDNF might be the common substrate through which alteration in the gut microbiota mediate the behavioral effect.

Gut-mirobiota and immune system

Series of studies summarized in recently published reviews indicate a critical role of intestinal commensally microbiota in the development of autoimmune diseases including inflammatory bowel diseases, rheumatoid arthritis and multiple sclerosis [103,104]. The vertebrate GI tract contains an exceptionally complex and dense microbial environment, with bacterial constituents that affect the immune responses of populations of reactive host cells [105], and stimulate a rich matrix of effector mechanisms involved in innate and adaptive immune responses [32].

More recent studies substantiate these assertions with demonstrations that commensally flora recognition by toll-like receptors (TLRs) is necessary to induce increased epithelial cell proliferation thus accelerating repair of the epithelial surface following injury and to inhibit inflammation [106]. TLR signaling is vitally important not only for protection from pathogenic infection, but also for inducing tolerant responses to commensalism. The activation of the TLR2 signaling pathway directly enhances intestinal epithelial integrity through translocation of the tight junction protein zonula occludens-1 (ZO-1) [107,108]. The basic mechanism of the mucosal immune system is innate immunity and its characteristic ability to distinguish potentially pathogenic microbes from harmless antigens is achieved through pattern recognition receptors. TLRs are present on cells of the innate immune system and recognize characteristic molecules called pathogen associated molecular patterns [109]. Pathogen recognition by a particular TLR results in a cascade of events starting with the activation of the NF-κB signaling system and resulting in increased cytokine production and T cell activation [110]. A mechanistic perspective has been provided by a number of studies which found a persistent elevation in rectal mucosal enteroendocrine cells, T-lymphocytes and gut permeability following the infectious insult in subjects who went on to develop IBS [111,112]. Microbiota's inflammation-suppressing fractions may simultaneously counteract with inflammation-aggravating bacteria, improve the barrier effect of the GI mucosa and more directly interact with inflammation-driving components of the immune system [113]. Multiple studies are regarded as important indicators of a link between alterations in the microbiota and mucosal inflammation in IBS [114-116]. Persistent low grade inflammation is a characteristic of post-infectious IBS (PI-IBS) [17] and these patients exhibit greater IL-1β mRNA expression, both during and after the infection, compared with individuals who do not develop PI-IBS [117]. IBS patients with normal histology had increased intraepithelial lymphocytes and CD3+ and CD25+ cells in the lamina propria [118]. Increased CD25+ cells in IBS suggests an antigen challenge and these cells are preventing "a more florid inflammatory response" [65].

It has been hypothesized that changing diets are altering the gut microbiota towards dysbiosis and may thus be driving an increase in the incidence of inflammatory diseases. Dietary

factors apparently associated with dysbiosis in animal models include high-fat, high-carbohydrate, and low-fibre diets. These diets are associated with lower levels of short-chain fatty acids (SCFAs), produced by the microbiota, leading to inflammation [119]. Obesity is regarded as a chronic low-grade inflammatory state, and inflammatory cytokines secreted from adipose tissue are associated with rheumatoid arthritis [120]. Increased bacterial lipopolysaccharide (LPS) uptake through the gut lumen to other tissues occurs in obese murine models as a response to fat feeding [121], and enhanced systemic exposure to LPS could increase the risk of such inflammatory disorders as rheumatoid arthritis. Rheumatoid arthritis patients are prone to a higher ratio of fat to muscle mass, so-called sarcopaenic obesity [122], but debate continues about whether sarcopaenia is a cause or an effect of rheumatoid arthritis.

Microbial infections were thought to trigger multiple sclerosis (MS). Although there is no clear epidemiological evidence, which suggests that commensal bacteria contribute to MS pathogenesis, the effects of diet on MS development provide some indirect evidence [123]. Recently a review by Berer and Krishnamoorthy, clearly summarized the role of commensal gut flora and brain autoimmunity [124]. Experimental autoimmune encephalomyelitis (EAE), an animal model of MS, suggests that the gut flora contribute to the development of this disease and therapeutic administration of probiotics (live beneficial bacteria) or prebiotics (compounds that stimulate the growth of beneficial bacteria) have been studied in various autoimmune disease models including MS [125,126]. EAE is typically induced in experimental animals via immunization with myelin antigens in combination with a strong adjuvant. In contrast, sterilization of the gut by treatment with a mixture of antibiotics reduced the severity of EAE [127,128]. The reduced severity of demyelinating disease is thought to be due to the attenuation of pro-inflammatory T_H1/T_H17 responses. Lee and colleagues showed that disease protection in germ free mice coincided with reduced levels of the pro-inflammatory cytokines IL-17 and IFN-c and increased numbers of Forkhead box $P3^+$ ($Foxp3^+$) regulatory T (TReg) cells in peripheral lymphoid tissues and the CNS [129]. Moreover, IL-10-producing, $Foxp3^+$ TReg cells accumulated in the cervical LNs (cLNs) of antibiotic-treated mice and were able to protect naive recipients against the transfer of EAE [127].

Stress and gut microbiota

The core neuroendocrine pathway in human is the hypothalamic-pituitary-adrenal (HPA) axis and activation of this axis takes place in response to a variety of physical and psychological stressors [130]. After much initial speculation, an elegant study by Sudo et al. provided some insight into the role of the intestinal microbiota in the development of the HPA axis [67].

Signaling molecules released into the gut lumen from cells in the lamina propria that are under the control of the CNS can result in changes in gastrointestinal motility and secretion as well as intestinal permeability, thus altering the GIT environment in which the bacteria reside [2].

Stress affects our Brain and GI tract both ways:

(a) from up to down, when our CNS triggers response through hypothalamic-pituatary-adrenal pathway and the autonomic nervous system (ANS) resulting in increase of cortisol, adrenaline and noradrenaline secretion, and corticotropin-releasing-factor (CRF) as well, increases anxiety-like behavior, abdominal pain, colon secretions, muscle contractions (motility) and increased permeability within the lining of the bowel.

(b) from down to up, when under the stress GI inflammation triggers intense firing of the gut's sensory neurons, culminating in a kind of sensory hyperactivity.

Stress also induces permeability of the gut allowing bacteria and bacterial antigens to cross the epithelial barrier and this can activate a mucosal immune response which in turn alters the composition of the microbiome [131]. Acute stress was shown to cause an increase in colonic paracellular permeability which involved mast cells and overproduction of IFN-γ with decreased expression of ZO-2 and occludin mRNA [132].

Recently, some studies indicate a positive effect of probiotics on stress related pathology in upper GI tract, however the effects need to be further evaluated [133]. There is also evidence that stress may have a profound effect on bacterial flora leading to increased adhesion and translocation of bacteria due to increased barrier permeability. Chronic stress disrupts the intestinal barrier, making it leaky and increasing the circulating levels of immune modulator bacterial cell wall components such as lipopolysaccharide [134]. Stress may be an important factor leading to the activation of the immune system resulting in the exacerbation or induction of acute colitis [135,136]. The modulator role of stress-related brain-gut interactions in the IBS pathophysiology, in particular neuroimmune modulation associated with psychological factors and emotional state [6,8,137] has been confirmed by the encouraging outcome of non-pharmacologic and pharmacologic treatment modalities aimed at reducing stress perception [138-140]. Recent developments showing the critical interdependence between the composition and stability of the microbiota and GI sensory-motor function indicate a novel approach to IBS treatment with a use of probiotics, prebiotics and antibiotics [2,141]. Specific modulation of the enteric microbiota in the context of neuroimmune interactions within the brain-gut axis opens a new promising strategy for stress-related disorders, particularly in the aspects of comorbidity in functional GI disorders such as IBS [1,142]. Experimental findings suggest that minor irritation of the gut in neonatal animals leading to features of depression and anxiety that persist into adulthood [143].

An early study conducted in a gastroenterology clinic reported a very high lifetime prevalence of generalized anxiety disorder of 34% in newly referred IBS patients [144]. Talley et al. reported that dyspepsia patients who present for investigation were more likely to be neurotic, anxious, and depressed than non-dyspepsia controls [145]. Using the gold standard diagnostic method with psychiatrist-conducted structured Clinical Interview for Diagnostic Statistical Manual of Mental Disorders-IV Axis I Disorders, reported that anxiety disorders are diagnosed in 38% of patients with functional dyspepsia compared with 4% in the general population [146]. It has been shown that stress or bacterial-mediated disruption of epithelial barrier function in IBS result in malfunctioning of inflammation

tuning-down mechanisms may lead to longstanding increase of gut permeability and hypersensitivity [147].

It has also been observed that IBS patients with psychiatric morbidity are characterized by low rectal distension pain thresholds, high rates of healthcare consultations, interpersonal problems and sexual abuse [148]. In a population based study in Hong Kong, the prevalence of generalized anxiety disorder is significantly higher in subjects reporting IBS symptoms compared to those reporting these symptoms (16.5% vs. 3.3%, P<0.001), and IBS is associated with 6-fold increase in the likelihood of having generalized anxiety disorder [149]. Yet, there are cumulating evidence showing that the pathophysiology of functional gastrointestinal disorders (FGID) involves abnormal processing of visceral nociceptive signals in the brain-gut axis, which leads to visceral hypersensitivity and hyperalgesia [150]. Furthermore, FGID patients are also characterized by abnormalities in autonomic, neuroendocrine and immune functions. This neural network involves corticotrophin releasing factor (CRF) containing neuronal projections that activate both the autonomic nervous system and hypothalamus-pituitary-adrenal axis. The alterations in CRF secretion and expression of its receptor, CRF1, involved in the pathophysiology of stress-related, which includes anxiety, depression, and changes in gastrointestinal motility and visceral sensation [147].

The system is involved in a wide spectrum of physiological activities such as arousal, vigilance and pain modulation. Hyperactivity of the neuroendocrine and visceral perceptual response to physiological (e.g. meal) or psychological stimuli may account for the stress-induced flare of bowel symptoms in IBS patients [151,152], and administration of CRF alleviates visceral hyperalgesia and negative affective response to bowel stimulation in IBS patients [153]. Increased β-adrenergic activity is significantly correlated with visceral hypersensitivity and symptoms of hard or lumpy stools in constipation- predominant IBS [153,154]. It has also been reported that anxiety induces gastric sensorimotor dysfunction and postprandial symptoms in patients with functional dyspepsia [155]. Psychological disorders and FGID also share common genetic predispositions particularly the genes that are involved in serotonergic activities. It has been reported that the polymorphism of serotonin reuptake transporter (SERT) genes is associated with the subtypes of IBS [156]. Polymorphisms in the promoter for synthesis of SERT influence response to serotonergic medications in depression as well as colonic transit response to alosetron, a serotonin receptor-3 (5-HT3) antagonist, in patients with diarrhea predominant IBS [157]. Early life adversity, particularly psychological stress, has been speculated to play an important role of pathogenesis of FGID. Other social and environmental factors, such as exposure to war time conditions, infantile and childhood trauma and social learning of illness behavior are predictors of the IBS in adulthood [158,159]. In recent years, a positive association between psychological stress and abnormal immunity has also been implicated in the pathophysiological mechanism of IBS. IBS patients have coexisting hyperactivity of the hypothalamic-pituitary-adrenal axis and increase in pro-inflammatory cytokine levels [130]. Chronic psychological stress leads to maladaptive increase in mucosal permeability and decrease in secretory response of intestinal epithelium to luminal stimuli [160]. It has been shown that the change in intestinal mucosal permeability is mediated by CRF [161,162].

Within the realm of gastrointestinal disorders, inflammatory bowel disease (IBD), which includes the two distinct disease patterns of ulcerative colitis (UC) and Crohn's disease (CD) has attracted attention as a disorder with an aberrant GIT microbial signature [163-167]. Altered microbiota is also evident in animal models of inflammation relevant to IBD with a dramatic increase in the Proteobacteria classes of bacteria evident [168]. Furthermore, in terms of exogenous microbial threats, the frequency of *Clostridium difficile* has been shown to be higher in IBD and may trigger relapse where the disease is established but in remission [169]. It is well recognized that psychological stress, a factor which can perturb the microbiota, exacerbates the condition [170,171]. A number of strands of evidence support a role for the microbiota in the pathophysiology of IBS and chief among these is the supporting data for PI-IBS, a term which describes the development of IBS following an episode of bacteriologically confirmed gastroenteritis [115,172].

Microbiota-gut-brain axis and role of probiotics

The idea of connection between gut-microbiota and onset of mental illness based on 'autointoxication' and 'intestinal toxemia' theory and toxemia were used to describe a process where toxins influence systemic health [173]. Later on, brilliant work of British surgeon Sir Arbuthnot Lane and Nobel-Prize-winning microbiologist Ilya Metchnikoff added great explanation for mental health disorders, which development could be connected to autointoxication, when systemic toxin load would influence nervous system function [174]. A New Jersey physician, Henry Cotton, believed that gut infections are the initiator of all forms of behavioral and mood disorders, and psychosis as well [175]. In 1926, Kopeloff proposed to use the *Lactobacillus acidophilus* as a potential treatment for different health conditions, because "... acidophilus, the twin brother of *Bulgarian bacillus*, is much more desirable" [176]. Great proposal made by a brilliant scientist Elie Metchnikoff, that orally consumed lactic acid bacteria could combat the dangers of autointoxication, could slow the aging via to slowing arteriosclerosis and improve the quality of life [177,178]. This great work was also supported by Albert Abrams [179], Frederick Forchheimer [180] and was carried out through the early 1930s. In 1945 Danish scientists found that older adults with dementia had the highest level of clostridia species [181]. The first practical suggestion to use probiotics for treatment of mental illness was proposed by Scottish physician Hubert J. Norman [182], but it took over 70 years to combine these ideas with research results. However, for any firm conclusions, properly powered studies are required before using probiotics in treatment of depression [183].

Now, the evidence of the gut-microbiota influence on behavior and brain chemistry is well documented [67,184]. It is also known, that normal healthy microbiota influences the development and function of CNS, via behavioral and molecular changes [68]. It is known that cerebral dopamine (DA) synthesis is induced by DA-producing enzymes, inhibited by stimulation of intestinal microbiota through the "microbiota-gut-brain axis" (MGB). The oral treatment of rats with *Lactobacillus reuteri* which activated calcium dependent potassium channels in

enteric neurons in the colonic myenteric plexus, proves that that gut microbiota may affect brain via autonomic nervous system [185,186]. Anxiety and depression are common in patients with chronic GI disorders [187]. Recent research supporting a role for the microbiota in maintaining normal brain function offers the intriguing possibility that the therapeutic targeting of the gut microbiome might be a viable strategy in the treatment of CNS disorders [84]. Around 4 million people in USA are suffering from chronic fatigue syndrome, which is a result of prolong IBS which is characterized by neuropsychological and cognitive problems, as well memory loss, lack of concentration, bad sleep, moodiness, anxiety and depression [188, 189]. The results of a recent study which demonstrated beneficial psychological effects in healthy human volunteers following administration of a combination of *Lactobacillus helveticus* R0052 and *Bifidobacterium longum* R0175 [190]. *Bifidobacterium infantis* 35624 treatment, for example, was shown to normalize immune responses, reverse behavioral deficits in the forced swim test, and restore basal noradrenaline concentrations in the brainstem of adult rats subjected to the early life stress of maternal separation, an animal model of brain–gut axis dysfunction [60,191]. *Lactobacillus paracasei* NCC2461 administration has also shown efficacy in reducing visceral hypersensitivity in a mouse preclinical model of IBS [192]. Furthermore, a preclinical study using the same probiotic found that CRD-induced visceral pain behaviors were significantly reduced in the viscerally hypersensitive Wistar-Kyoto rat strain [165,193]. These reports raise the possibility that therapeutic targeting of the microbiome might be an effective treatment strategy for specific disorders of the CNS. In this context, supporting gut health through microbiota supplementation with a view toward positively influencing mental status represents a putative preventative strategy worth following [194]. In addition to consideration of the microbiome as a therapeutic target, we also need to direct more efforts toward mining its metabolites for putative drugs, a strategy that has already paid some dividends [195].

The probiotic *Bifidobacterium longum* (Bl NCC3001) normalizes behavior and CNS biochemistry in mice with mild colitis, an effect also mediated via the vagus nerve. Bl NCC3001 produces an anxiolytic effect in two different models of anxiety-like behavior as assessed by light/dark preference and step-down tests [184,196,197]. Evidence that microbiota are linked to brain chemistry and behavior is well documented, an interestingly abnormal behavior was displayed before there was any significant immune response gut microbiota change, indicating that this behavior was not a consequence of cytokine-induced reactions, but a interaction between the gut microbiota and the neural system. Infestation of mouse with H. pylori infection has been shown to lead to change in behavioral pattern and changes in neural biochemistry accompanied with following dyspepsia [198]. Using of probiotics, for example administration of *Bifidobacterium longum* to DSS-treated mice reversed their altered behavior without affecting gut inflammation with possible effect of *Bifidobacterium longum* on enhancement of exploratory behavior [184]

In contrast, the effect of *Lactobacillus rhamnosus* (Lr JB-1) varies considerably depending on the experimental paradigmused, an anxiolytic-like effect observed in open field and elevated plus maze tests vs. an anxiogenic effect reported in the fear-conditioning model (increased emotional learning is an anxiety-like behavior) with no significant effect observed against stress-induced hyperthermia [61,199].

Gut-micobiota and ayurvedic biology

It is now well recognized, that most polyphenolics consumed with meals are extensively metabolized in the gastrointestinal tract. Phloroglucinol is a polyphenolic phytoconstituent, catabolized by gut microbiota to acetate, butyrate and CO_2 [200,201], and is also known to possess antibacterial activities [202]. Thus it can alter the gut microbiota ecology, which is well recognized to be an integral part of human physiology [203,204]. In a recent finding, it was suggested that the route of administration determines the biological activity of flavonoids and produced anxiolytic effect which was absent in intraperitoneal administered animal [205]. The gut microbiota ecology and the gut brain axis play important roles in altering central sensitivity of almost all inflammatory diseases [64]. Since antimicrobial, antifungal, and antiparasitic activities of *Andrographis paniculata* and Andrographolide are known, it could as well be that the reported therapeutic benefits and its ability to modulate stress triggered thermoregulatory mechanisms observed due to its effects on gut microbiota ecology [206,207].

Recently, probiotics are also reported to reverse the deteriorated brain functions and cognitive performance in diabetic rats [208]. Dietary manipulation is an emerging strategy for the management of type 2 diabetes [209]. A recent study reported that administration of probiotic *Lactobacillus reuteri* GMNL-263 (Lr-263) in high-fructose fed rats significantly reduced insulin resistance as well as hepatic steatosis formation [210].

Hypericum perforatum, a well known herb for CNS disorders such as anxiety and depression. Several reports including studies from our laboratory have confirmed the efficacy of *Hypericum perforatum* in anxiety, depression and stress related conditions [211-218]. Apart from its effect on central neurotransmission (e.g., inhibition of reuptake of serotonin), a number of studies are available regarding antibacterial activity of crude plant extracts of *Hypericum perforatum* [219,220]. Hyperforin, the major bioactive constituent of *Hypericum perforatum*, inhibited the growth of gram-positive bacteria such as *Corynebacterium diphtheriae* at concentrations as low as 0.1 μg/ml. Multiresistant *Staphylococcus aureus* strains were also susceptible to hyperforin [221]. Therefore, alteration of gut microbiota by oral administration of *Hypericum perforatum* extract may be partly responsible for its efficacy in stress and behavioral disorders. Studies in germ-free animals are required to clarify the role of *Hypericum perforatum* and its isolated bioactive constituents such as hyperforin in stress and related conditions.

Since last many years we have been working on holistic psychopharmacological approach to discover effective natural remedies for neurological disorders probably working through gut-microbiota theory [206,212-218,222-231].

Current and future perspective

It is now established that there is symbiotic interaction

between gut-microbiota and mental wellbeing and the integrity of both of these factors is essential to maintain the homeostasis. Alteration in the normal gut-microbiota mediates the functional and behavioral changes in animals as well as in clinical studies. Modulation of the gut-microbiota by therapeutic agents opens a new promising strategy for stress-related disorders, particularly in the aspects of functional GI disorders such as IBS. Probiotics have shown promising results in the management of anxiety and depression and there is a need to further explores the potential of probiotics as well as prebiotics for the management of metabolic disorders such as diabetes and obesity. Additionally concentrated efforts are required to explore the interaction of herbal medicine with gut-brain axis. Further, as the use of probiotics is growing exponentially, there is a need to determine the long-term safety of such therapeutic intervention.

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Cite this article

Thakur AK, Shakya A, Husain GM, Emerald M, Kumar V (2014) Gut-Microbiota and Mental Health: Current and Future Perspectives. J Pharmacol Clin Toxicol 2(1):1016.