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Review Article

GUT-BRAIN AXIS AND MANAS VIKARA: ROLE OF PROBIOTICS AND SATTVA ENHANCEMENT

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ABSTRACT

The gut-brain axis (GBA) consists of bidirectional communication between the central and the enteric nervous system, linking emotional and cognitive centres of the brain with peripheral intestinal functions. Recent advances in research have described the importance of gut microbiota in influencing these interactions. GBM science based largely on preclinical studies has suggested that the gut microbiome play a role in the pathophysiology of functional GI disorders as well certain psychiatric and neurological disorders (e.g. Depression, anxiety). Mental health conditions have been linked closely to an imbalance of microbiota in the gut, leading to disruption of the microbiome (dysbiosis). Several neurotransmitters, such as GABA (gamma-aminobutyric acid), serotonin, and glutamate, are produced in the gut, which are associated with anxiety and depressive symptoms.

Mental health and the gut have been linked closely, and many mental illnesses have been associated with gut dysbiosis. Probiotics are marketed to improve gut health, act as mood enhancers, and be effective in reducing stress and improvement in gut health. Alternatively, Satvavajaya Chikitsa, which emphasizes cognitive and behavioural regulation, has therapeutic potential in the treatment of various psychiatric conditions. This review aims to appraise the literature on probiotics for the prevention and treatment of mental and GI disorders. And assessing the satvavjya chikitsa in manas vikara.

KEYWORDS: Gut-brain axis, Gut microbiota, ANS, CNS, Probiotics, Manas vikara, Satvavajya chikitsa.

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GUT-BRAIN AXIS AND THE MICROBIOTA

Gastrointestinal motor and sensory components send messages to the central nervous system (CNS), and the return response to the intestine is the definition of the GBA.^[1] Nutrition affects microbiota colonization and gut metabolites, which can influence brain development and function through neural, immunological, and endocrine pathways.^[2] The brain is the central component of the GBA and includes connections between the cerebral cortex, the limbic system, the hypothalamic-pituitary axis, and the brain system. The limbic system receives input from other brain regions including the hippocampus, which is responsible for a range of behaviours.^[3] Growing evidence reports that gut microbiota has been shown to play a preeminent role in the gut–brain axis. Therefore, the interaction between the microbiota and brain is often called as microbiota/gut–brain axis.^[6]

GUT MICROBIOTA

The terms "microbiota" and microbiome refer, respectively, to the collection of bacteria, viruses and fungi colonising different parts of the body, and to the complete genetic material encoded by the microbiota. The gut microbiota, i.e., the commensal microorganisms within the gut, performs essential tasks for the normal functioning of the organism, such as the fermentation and digestion of carbohydrates, development of lymphoid tissues associated with the mucous membranes, production of vitamins, prevention of colonisation by pathogenic microorganisms and stimulation of the immune system. [4,7,8,9]

The gut microbiota represents an excellent example of this integrated system, as it is an important link between our body and the environment. Again, given that it engages in two-way communication with the CNS, it outlines a fascinating model of the connection between central and peripheral systems. ^[3] In the human body, trillions of microbes reside that are assumed to influence and regulate the physiology of the host. Most microbes are inhabitants in the gastrointestinal tract of the humans and are known as gut microbiota (GM). Several factors affect the inhabitants and the composition of the GM. Therefore, it can be varied depending on the host nature. The GM is comprised of four major (Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria) and two minor phyla (Verrucomicrobia and Fusobacteria)^[4] These commensal bacteria not only communicate with each other but also with host gut epithelium, to maintain the gut homeostasis and improve the host immunity. The gut-residing microbes exhibit several beneficial effects on the host at healthy state, but in the disease or disruption state, it has been reported to be involved in the progression of

several diseases, including neurological disorders.^[5] Growing evidence suggests that the gut has strong bidirectional communication with the brain, which is vital for maintaining the brain functions and gut homeostasis. Neurological disorders, such as Parkinson's disease (PD), Alzheimer's disease (AD), multiple sclerosis (MS), autism spectrum disorder (ASD), and stress are believed to induce changes in the bidirectional relationship, which results in the induction of brain–gut disorders, such as irritable bowel syndrome (IBS) and others.^[6,7]

MICROBIOME GUT-BRAIN AXIS STRUCTURE

Interaction of Gut and Nervous System: Gut-Brain Axis

Anatomically, the gut has a complex and bidirectional relationship with the CNS, which is termed as the gut–brain axis that crosstalk each other in the context of both health and diseases ^{6]} This crosstalk allows the gut sensory visceral signals that travel through the vagus nerve to influence the CNS to regulate the reflex and mind/moods changes; in turn, the brain directs the signals to modulate the gut physiology and other functions (Figure 1). Afferent (A neuron that brings signals in) and efferent (A neuron that carries signals out) neurons are involved in the connecting neuronal pathways and transferring the signals through different pathways, including the autonomic nervous system (ANS), enteric nervous system(ENS), hypothalamic–pituitary–adrenal (HPA) axis, sympatho-adrenal axis, and descending monoaminergic pathways. ^[6,8]

MANAS VIKARA

Ayurveda is a branch of medicine that primarily focuses on two areas of disease analysis, understanding, and treatment: *Manasika* and *Shaaririka*.^[10] The essential ideas of *Ayurveda*, which holds that the Shareera is closely linked with *Manas*. *Manas*, said to be located between *Shiras* (Head) and *Talu* (Hard Palate) ^[11] According to *Charaka*, The entity which is responsible for thinking is called *Manas*.^[12]

According to *Acharya Charaka*, *Mansik vikara* result due to accrual of undesired objects and loss of desired objects. In this reference *Sushruta* has identified emotions like *krodha*, *shoka*, *bhaya*, *kama*, etc as cause of *manovikara*. Manasa vikara usually runs a sequential process from minor unnoticed general behavioural symptoms to the marked alteration of buddhi, Dhriti and Smriti. Usually, these symptoms act as *Nidanarthakara roga* (primary disease acting as aetiology of the secondary one). Regarding *samprapti* of Manasa *roga* our classics hold that the disturbance of equilibrium of Manasa gunas leads to the origin of mental disorders along with disequilibrium of *Sharirika dosha*. [13]

For all manasika vikaras Alpa satwa is the most important part, excited vata depresses the mind and gives rise to feelings of helplessness, delirium, fear, etc. This suggests Ayurveda is perhaps the earliest Medicare system to have an understandable concept about psychosomatic approach. A psychosomatic disorder, by definition, is a stress disorder whose principal cause is psychological in origin, but its manifestations are mostly observed in the body. [14,15]

IDIOPATHIC ORIGIN

Agantuja, Unmada, Graha Badha, Bhuta Graha, Pisacha Graha.

Common etiological factors

- a) Asatmendriyartha Sannikarsha. b) Prajnaparadha
- c) Parinama d) Sadvritta Apalana
- e) Vegavarodha f) Vegodhirana

GUT-BRAIN-MICROBIOME DISORDERS

GBM science based largely on preclinical studies has suggested that the gut microbiome play a role in the pathophysiology of functional GI disorders as well certain psychiatric and neurological disorders.[16]

IRRITABLE BOWEL SYNDROME

Altered Gut-Brain Interactions

IBS affects 9-11% of the world population and is characterized by chronically recurrent abdominal pain associated with alterations in bowel habits. [17] The majority of patients exhibit increased stress responsiveness, increased anxiety and comorbidities with other chronic pain syndromes. An extensive body of research has led to the new definition of IBS as a disorder of altered GB interactions. [18]

According to ayurveda Grahani Roga has strong Psycho-somatic base. And Manasik Bhavas such as Krodha, Shoka, Bhaya, Kama etc. results in Agnidushti causing Grahanidosha. [19] IBS is a condition caused by a disturbance of Vata in Pakvashaya, particularly of Apana Vayu, which manifests as abdominal pain and irregular bowel movements. The disturbance of Agni is the main cause of almost all disorders. Dosha Prakopa is reached via Mandagni. The Agni is impacted differently by the emotions such as Krodha, Bhaya, and Shoka, among others. Indigestion is caused by Mana or Agni Dusti, while Vata Prakopa is brought on by Shoka, Bhaya, etc. Both Ayurveda and contemporary science acknowledge that psychological factors play a crucial part in the treatment and prevention of *Grahani Roga* (IBS). [20]

THE INFLUENCE OF THE GUT-MICROBIOTA ON MENTAL HEALTH

Healthy gut function has been linked to normal central nervous system (CNS) function.^[21] Hormones, neurotransmitters and immunological factors released from the gut are known to send signals to the brain either directly or via autonomic neurons. Recently, studies have emerged focusing on variations in the microbiome and the effect on various CNS disorders, including anxiety, depressive disorders, schizophrenia, and autism.^[22, 23,24]

DEPRESSION

Depression is a common chronic condition marked by a depressed state of mind, lack of energy, melancholy, insomnia, and an inability to enjoy life. It can influence thoughts, mood, and physical health.^[25]

According to recent estimates, there are 350 million depressed persons in the world today, and according to the disability-adjusted life years (DALY), depression is the third most common condition and a significant contributor to non-life-threatening disorders.^[26]

ANXIETY

Anxiety is a mental condition brought on by a threat or perceive threat; although it is a standard component of life, excessive or improper anxiety can lead to sickness. [27] Among the most common psychiatric disorders, anxiety disorders such as generalized anxiety disorder (GAD), panic disorder/agoraphobia, social anxiety disorder, and others are frequently underreported and undertreated. Treatment is only necessary when a patient exhibits considerable suffering or has problems related to the disease. [28] The PFC (Prefrontal Cortex) inhibits the amygdala's activity under physiological circumstances, reducing its output and preventing the manifestation of improper emotions. Prefrontal control, however, degenerates under adverse events, such as prolonged exposure to unavoidable stress that may trigger the onset of psychiatric conditions (such as anxiety disorders and depression), leading to aberrant amygdala activation and deficits in emotion and behaviour. [29] In more detail, during anxiety states, these regions show structural and functional changes potentially triggered by altered glutamatergic and gamma-aminobutyric acid (GABA)transmission. [30]

THE ROLE OF THE GUT-BRAIN AXIS IN MOOD REGULATION

The vagus nerve, the immune system, metabolites, and bacterial products are parts of the gutbrain axis, a two-way network of signalling channels facilitating communication between the neurological and gastrointestinal tract^[27] The gastrointestinal tract contains a variety of

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bacteria and their metabolites, which can have a major impact on various biological processes in the organism.^[28]

The brain-gut-microbiota axis is regulated by several mechanisms, including the hypothalamic-pituitary-adrenal (HPA) axis. The hypothalamus releases corticotropinreleasing hormone (CRH) in a humoral manner in response to stress. [29] CRH then travels through the bloodstream to the pituitary gland, where it stimulates the creation of adrenocorticotropic hormone (ACTH), which in turn causes the adrenal glands to release glucocorticoid steroid hormones (stress hormones) like cortisol or corticosterone. [30] Stress hormones promote the disintegration of tight junctions, thereby enhancing intestinal barrier permeability at the systemic level. [31]

The HPA axis and immune system are subsequently activated due to bacterial translocation. [29] As a result, it is possible to pinpoint the human microbiota's critical function in controlling the body's homeostasis.

DYSBIOSIS OF HUMAN INTESTINAL MICROBIOTA

Dysbiosis is defined as an imbalance in the composition and operation of the resident microbial community of the enteric tract several studies have associated with several diseases of gastrointestinal tract like inflammatory bowel disease (IBD), irritable bowel syndrome (IBS). Although it is still unclear whether intestinal microbial dysbiosis directly causes inflammation in IBD or merely contributes to it by establishing an unfavourable environment in the gastrointestinal tract, there is growing evidence that it plays a role in the pathophysiology of the illness.^[32] dysbiosis alters the intracellular tight junctions that protect the intestinal mucosa's integrity and permeability, which is required to thwart pathogen infiltration at the systemic level. [33] In addition, the gut microbiota has a regulatory role in oxidative stress (OS). When nitric oxide (NO) and nitrite concentrations have risen due to high nitrate intake, Lactobacilli and intestinal bifidobacteria can transform nitrate and nitrite into NO while enhancing its release by host epithelial cells. Through their NO synthetase (NOS), intestinal Bacilli and Streptomycetes also create NO in addition to nitrates. Even though NO has a role in signalling and apoptosis at nanomolar concentrations, excessive NO synthesis is dangerous since it is connected to neuroinflammation, cellular harm, and neurodegenerative disorders.^[34] The gut microbiome is, in turn, affected by a diverse range of metabolites, including gaseous mediators such as hydrogen sulphide (H2S) that bacteria use as an energy source in the gut. [35]

GUT MICROBIOTA AND DEPRESSION

Reduced expression of tight junction is another sign of a changed dysbiosis. Multiple studies have documented a disparity in the levels of pro-inflammatory cytokines, including interleukin (IL) – 1, IL-6, IL-8, IL-12, and tumour necrosis factor α (TNF- α), and the levels of anti-inflammatory cytokines, such as transforming growth factor-beta (TGF-β) and IL-10, in individuals diagnosed with depression. [36] As previously stated, the biochemical activation of the inflammatory pathway is distinguished by an excessive generation of reactive oxygen species (ROS). The existence of OS is substantiated by identifying elevated levels of lipid peroxidation by-products, such as malondialdehyde and 4-hydroxynonenal, in individuals diagnosed with depression. [37] A changed microbiota has the potential to activate nicotinamide adenine dinucleotide phosphate oxidase (NADPH) and NO production, hence initiating OS. In typical circumstances, the intestinal epithelial barrier is safeguarded against OS and inflammation by a group of intracellular proteins known as heat shock proteins (HSPs), which are widely distributed. [38] In addition, individuals with chronic depression exhibits increased levels of IgA immunoglobulins and IgM antibodies against lipopolysaccharide (LPS) derived from Enterobacteriaceae in their plasma. This suggests that the microbiota may contribute to depression by potentially promoting a persistent state of inflammation.[40]

GUT MICROBIOTA AND ANXIETY DISORDER

There is a clear correlation between inflammation of the gastrointestinal system and the expression of anxiety. Several neuropeptides controlled by the microbiome, such as dopamine, NA, GABA and serotonin, among others, can influence brain function and modulate the composition and function of the gut microbiota, reflecting the complex bidirectional crosstalk between the gut and brain. Furthermore, a study revealed a significant decrease in the richness and diversity of the Microbia population in individuals diagnosed with GAD. This decrease was accompanied by a lower prevalence of bacteria that produce short-chain fatty acids (SCFA) and an increased prevalence of Escherichia-Shigella, Fusobacterium, and Ruminococcus gnavu. SCFA are typically present in the intestinal tract; nonetheless, they can enter the systemic circulation and traverse the blood-brain barrier via transporters situated on the vascular epithelial cells of the brain. Neuroglial cells play a significant role within the brain since they can influence many neurotransmitters, including glutamate, glutamine, GABA, and neurotrophic factors. [43]

Moreover, gut dysbiosis resulting from bacterial infection can intensify anxiety by affecting the immune and metabolic pathways within the gut-brain axis. Eventually, the available research has indicated a strong and reciprocal relationship between disruptions in the gut microbiome and psychiatric illnesses.^[44]

PROBIOTICS

Probiotics, are "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" and have been used to preserve person's immune function and to improve indigenous gut microflora properties (FAO/WHO 2002). As we all know that diet can modulate intestinal health and simultaneously, microflora of gut can be manipulated by taking probiotic supplements or prebiotics. Fermented foods, milk products, gut of some organism's microflora are the sources of probiotics. [45,46] Recent researches indicate that the gut microflora influences the brain function as well as psychological behaviour significantly.

PROBIOTIC BACTERIA

Lactobacillus spp., Bifidobacterium spp., and Enterococcus spp. are the most used probiotic microorganisms in human nutrition; whereas in ruminants, yeast, particularly Saccharomyces cerevisiae, plays a significant role; whereas in pigs and poultry, Bacillus spp., Enterococcus spp., and Lactobacillus spp. [47]

SOURCES OF PROBIOTICS

Probiotics are usually found in fermented dairy products such as yogurt, cultured buttermilk, and cheese. Additional sources of bacterial fermentation include Japanese miso, tempeh, sauerkraut, beer, sourdough, bread, chocolate, kimchi, kefir, olives, and pickles. However, yogurts and fermented milk remain probiotics' most prevalent food transporter, as it has been demonstrated that non-dairy fermented substrates, such as soy-based products, cereals, legumes, cabbage, maize, pearl millet, and sorghum, contain probiotic bacteria. [48]

APPROACH OF PROBIOTICS IN MENTAL HEALTH AS A PSYCHOBIOTICS

The term "Psychobiotics" was defined by Dinan and colleagues in 2013, as that novel group of probiotics that indicate a potential approach in the therapeutics of psychiatric disease (Timothy et al. 2013). They may modulate the neurotransmitters and some proteins, including glutamate, serotonin, and gamma-aminobutyric acid (GABA) that plays vital function in regulating the neural inhibitory and excitatory balance, memory process and cognitive functions (Marti-now ich and Lu 2008). Lactobacilli such as Lactobacillus odontolyticus and

L. plantarum produce acetylcholine (Roshchina 2016). Recently, it has been discovered that microbes can regulate the synthesis of serotonin in the gut. For instance, it has been found that some strains of gut can persuade biosynthesis of serotonin from enterochromaffin cells and gut. These probiotics are therefore worth studying to explain their potential as Psychobiotics (Yanoet al. 2015). So, in this study, we have sum up the impact of Psychobiotics in various psychological disorders.

SOME POTENTIAL STRAINS OF PSYCHOBIOTICS MICROORGANISMS

- **1. Lactobacillus Helveticas** It is a lactic-acid producing bacteria (LAB) which is rod-shaped. It can treat visceral pain caused by stress represent (Ait-Belgnaoui et al. 2018). Moreover, the effects of anxiety and depression can be decreased or reduced with a combination of L. Helveticas as well as Bifidobacterium longum.
- **2. Clostridium butyricum** It is a Gram positive and endospore forming Firmicutes species that mostly inhabit in the human's and animal's intestine. It acts as probiotic that exerts beneficial effects by modulating gut-microbiota (Roh and Seki 2013).

ROLE OF TAKRA (AYURVEDIC PROBIOTIC) IN THE MANAGEMENT OF GASTROINTESTINAL DISORDERS

An ancient medical science known as *Ayurveda* also considered as the science of life or the holistic science has a vast treasure of knowledge regarding *Pathya apathya*, *lifestyle*, *Dinacharya*, *Ritucharya* etc., with the objective of both prevention and treatment of the mankind. Its distinguished nature lies in the unique perspective of disease management by uprooting. *Ayurveda* mentions buttermilk as *Takra*. *Samhitas* like *Susrutha samhita*, *Charaka samhita* and *ashtanga hridaya* of *Ayurveda* describes the advantages of *Takra* in *Grahani*.

Ayurveda explains three types of buttermilk with their properties based on fat content such as fat-free, half fat and full fat which are to be consumed according to individual's power of digestion or based on the *Agni*.^[49]

Researches show that probiotics have been extensively studied in infectious gastroenteritis, antibiotic-associated diarrhoea (including CDAD), IBD and IBS etc., gastrointestinal diseases. [50] *Takra* as a probiotic contains several important vitamins and minerals, such as vitamin B12, riboflavin, calcium and phosphorus and is also low in fat and calories.

The gut microbiota has a significant role in human health and diseases. Certain illnesses can be reversed by favourable alterations of probiotics that contributes to the development of the dysbiosis of the intestinal ecosystem. This involves the three general mechanisms by which probiotics appear to exert their beneficial effects with important differences seen between probiotic species and strains such as Anti-microbial effects, Enhancement of mucosal barrier integrity and Immuno-modulation. [56] In additional, probiotics relieves constipation by regulating bowel movements, improves energy levels by enhancing B - complex synthesis, protects the vital organs like heart, kidney, lungs and liver with its antioxidant properties and ensures faster clinical response since it enhances drug absorption. Probiotics supports the immune system to battle infection, protects the urinary tract from infection, helps to heal peptic ulcer and prevents diarrhoea, gastroenteritis and other bowel problems. In the present study, an effort has been made to evaluate the effect of an *Ayurvedic* probiotic, *Takra* the buttermilk and its effectiveness in the management of gastrointestinal disorders.

SATTAV ENHANCEMENGT

In support of its concepts on preservation and promotion of health and prevention of illnesses, *Ayurveda* lays due stress on various measures to be adopted in order to promote mental health and prevent mental disorders. These measures find lucid descriptions in the chapters devoted to *Dinacharya* (daily regimen) *Ritucharya* (seasonal regimen), *Sadvritta* (code of virtues), *Roganutpadana* (prevention of diseases) and *Anna-Pana vidhi* (rules pertaining to food and drinks), in the classics of *Ayurveda*.

In order to be free from mental disorders *Ayurveda* prescribes that one should not allow oneself to become a victim of impulses like greed, grief, fear, anger, jealousy, impudence, vanity etc. Further, it declares that one who speaks truth, refrains from overindulgence in alcohol and meat, hurts none, avoids overstrain, fair spoken, always compassionate and given to wholesome eating, would enjoy the benefits of sound mental health.

All these measures are aimed at bestowing relaxation and mental equipoise which are the basic prerequisites of a sound mind. They are particularly relevant to our times when we are forced to battle continuously against stress and strain for our very survival.

Summing up *Vagbhata* states that one who introspect daily once and react to fellow beings and surroundings dawn to dark would modify his behaviour, remain free from grief, and enjoy perennial happiness.^[58]

ADRAVYABHUTA CHIKITSA

S.N	Daiva Vyapashraya [60]	Satwavajaya [61]	Lifestyle Modifications
1	Mantra	Assurance	Nidana Parivarjana
2	Aushdi	Replacement of emotions	Satmya Kala – Buddhi – Indriya - Artha Sannikarsha
3	Manidharan	Regulation of thought process	Samyak Vega Dhaarana
4	Mangal	Retraining the ideas	Udeerana
5	Bali	Channelizing Presumptions	Ceiling on Desires (<i>Upadha</i>)
6	Upahar	Guidance	Practice of <i>Yoga</i>
7	Ноте	Advice in decision taking	Relaxation
8	Niyam	Control of Temperament	Sadvritta & Sadaachara (Achara Rasayana)
9	Upavasa	Shock Therapy	

CONCLUSION

The mounting evidence of connections between the brain and peripheral organs allowed for highlight the possible existence of fine-tuned reciprocal influences between the CNS and the gut microbiota. Given that the gut microbiota may affect brain functions through hormonal messengers and impact neurotransmitter metabolism and immune systems, it is not surprising that the gut microbiota was supposed to be involved in the pathophysiology of several neuropsychiatric disorders. And in the area of mental health, probiotics have proven advantages and promise. Supplemental probiotics, in particular, alter the gut-brain axis, creating neurotransmitters, an anti-inflammatory response, and epigenetic mechanisms. The regulation of the gut microbiota by probiotic supplementation may be advantageous since the multiple metabolic functions these supplements stimulate also coincide with the recovery of the pathophysiological pathways for depression.

Ayurveda in its Samhitha's stresses on the importance of Agni (Digestive Fire) and its disorders. As healthy Agni is required for the healthy body. Agni once deranged can lead to many gastrointestinal disorders. Acharyas have advised the consumption of Takra as a primary digestive aid in the diseases associated with the Agni. Takra can also be used as a Pathya Ahara to maintain healthy status of the body. As the Takra or the buttermilk confers the same benefits as of probiotics, Takra can be considered as an Ayurvedic probiotic. Consumption of Takra, an Ayurvedic probiotic in our daily diet helps to promote the

intestinal immunity, very effective in the management of gastrointestinal disorders and prevention of the same.

On the other hand, satvavajaya chikitsa is considered highly effective in managing various mental and psychosomatic disorders. The vitiation of Vata in Rajas (Dosha of mind) is a significant factor in the pathophysiology of manas Vikar. Psychological assistance and counselling, referred to in Ayurveda as Satvavajaya Chikita.

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