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Does Gut Microbiome Modulates the Psychiatric Face of Covid-19? Implications for Probiotics

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Abstract

In COVID-19 patient's cytokine interaction in various brain areas through different neuronal pathways leads to disturbance in emotional behaviour, low mood or loss of interest, and changes in appetite and sleep. COVID-19 activates various cascades of inflammation, resulting in an increased level of IL-1β, TNF-α, IL-6, and interferon-γ with a parallel decrease in the anti-inflammatory factors IL-10 and transforming growth factor β-1, similarly seen in the manic phase of bipolar disorder. In the last decade, neuro-gastroenterology research has revealed a significant direct biochemical neurotransmitter signaling between the gastrointestinal (GI) and central nervous system (CNS) called as "gut-brain axis." Commercially available probiotics when given in adequate amounts emerged as a compelling candidate in addition to other antipsychotic drugs for the regulation of mental health. Probiotics and prebiotics are shown to reduce cortisol stress response and directly produce neurotransmitters like GABA, serotonin, noradrenaline, acetylcholine and dopamine in the sensory brain network area of the brain, controlling central processing for emotions and sensation In the light of current shreds of evidence, probiotics can improve the psychiatric face of COVID-19 and can be potentially used as a novel treatment in combination with other antidepressants treatment.

Keywords: COVID-19; Psychiatric Illness; Gut-Brain Axis; Probiotics

Abbreviations: CNS: Central Nervous Syste; CSF: Cerebral Spinal Fluid; ANS: Autonomic Nervous System; GABA: Gamma-Aminobutyric Acid; HPA: Hypothalamic Pituitary Adrenal; MDD: Major Depressive Disorders.

Introduction

Coronavirus-2 (SARS CoV-2) belongs to group 2B of β-coronavirus family. It is recognized as the seventh component of the coronavirus family and included in the orthocoronavirinae subfamily [1]. In mild cases, SARS-CoV-2 pneumonia causes hypoxia, which triggers or exacerbates the inflammatory response of the central nervous system (CNS) via NF-κB which stimulates the overproduction of pro-inflammatory messengers [2]. During COVID-19, throughout 2020, the pandemic led to a 27•6% increase in cases of major depressive disorders and a 25•6% increase in cases of anxiety disorders globally. Severe cases of covid-19 are accompanied by excessive host immune response. Systemic and cellular immune response in covid-19 is characterized by a massive increase in plasma and cerebral spinal fluid levels of IL-6, TNF-α and IL-1β and results in changes in the neurochemical environment and synaptic transmission, synthesis of neurotrophic factors, and neurogenesis [3,4]. Similarly, an abnormally high concentration of IL-6 was also detected in the cerebral spinal fluid (CSF) of patients with bipolar disorder with major depression [5], suicide attempters [6], post-traumatic stress disorder,

and schizophrenia [7]. In COVID-19 patient's cytokine interaction in various brain areas through different neuronal pathways leads to disturbance in emotional behaviour, low mood or loss of interest, and changes in appetite and sleep [8]. The COVID-19 pandemic has resulted in a significant impact on interpersonal relationships between people, and the inability to control and modulate human emotions [9]. A study by Troyer et al. on patients with SARS-COV-1 after 30-50 months of infections demonstrated the presence of post-traumatic stress disorder in 40%, depression in 15.6% and obsessive-convulsive disorder in 15.6% of patients [10]. Evidence is there that psychological stress may increase the permeability of the gastrointestinal lining and the microbiome can modulate and influence emotional behaviour [11].

In the last decade, neuro-gastroenterology research has revealed that the gut microbiota modulates a significant direct biochemical neurotransmitter signaling between the gastrointestinal (GI) and central nervous system (CNS) called as "gut-brain axis." It's a bidirectional communication network and occurs through the autonomic nervous system (ANS), enteric nervous system, neuroendocrine system and immune system [12]. Use of broad-spectrum antibiotics in the treatment of patients with COVID-19 results in an imbalance of the makeup of gut Microbiome.

Human gut microbiota consists of 1014 resident micro-organisms, including bacteria, protozoa, archaea viruses and fungi. The most prominent are phyla Actinobacteria, Firmicutes, Proteobacteria, and Bacteroidetes [13], while the colon harbours a high density of bacteria from the family Bacteroidaceae, Prevotellaceae, Rikenellaceae, Lachnospiraceae and Ruminococcaceae [14]. This commensal microbiota plays a key role in various host physiological functions, including dietary digestion, and modulates the immune response by inflammatory cytokines. This result in the colonization of specific bacterial species (lipopolysaccharide containing *B. fragilis* and *S. aureus*) and genera that are predicted to influence the production of cytokine, and have putative interactions between microbial metabolism and tumour necrosis factor-alpha (TNFα) and interferon-gamma (IFNγ) [15].

Most of the pharmacological treatments for psychiatric disorders, mainly focus on neurotransmitter activity alteration in the central nervous system and often miss out on the restoration of the altered gut milieu. These psychiatric medications have delayed action onset and have various side effects like headaches, sedation, agitation, tremors, nausea, metabolic disorders, loss of appetite and sexual dysfunction [16]. Several studies reported the alpha diversity of patients' gut microbiota compared with that of a healthy population. Based on basic research results showed that antipsychotic drugs particularly atypical antipsychotics and serotonin-specific reuptake inhibitors (SSRI) antidepressants have antibacterial effects in vitro and the potential to alter the composition of gut microbiomes [10,17]. When looking at the gut microbiome, it is important to consider medication usage in psychiatric disorders patients. Commercially available probiotics when given in adequate amounts emerged as a compelling candidate in addition to other antipsychotic drugs for the regulation of mental health [18]. Most probiotics do not colonize the GI tract due to the direct and indirect "colonization resistance" phenomenon. In direct colonization resistance, the gut microbiota inhibits exogenous microbial colonization via competition for resources [19]. Indirect colonization resistance is the result of host-derived factors, which include antimicrobial peptide production, epithelial barrier maintenance, and bile acid modulation of the host [20]. Probiotics are adversely affected by the colonization resistance exerted by the commensal gut microbiota. They reside in the GI tract and influence various GI disorders and neurotransmitter pathways in CNS.

In the present review, three main domains have been reviewed in context with post-COVID- 19 associated inflammation, neurotransmitters (serotonin (5-HT), dopamine (DA), noradrenaline (NE), gamma-Aminobutyric acid (GABA)), and the hypothalamic-pituitary-adrenal (HPA) axis. We aim to explore the potential role of probiotics, and their basic mechanism of action on various neurotransmitter pathways in post-COVID-19 mental health, and major depressive disorders (MDD).

Inflammatory Cascades and Psychiatric Disorders

Low-grade neuroinflammation has been suggested as one of the mechanisms of many psychiatric diseases and cognitive disorders. IL-6 and IL-8 are pro-inflammatory cytokines produced by many cell types including macrophages and microglia. During acute manic or depressive phases of BPAD, there is an activation of the inflammatory cascade resulting in an increase in the level of IL-1β, TNF-α, IL-6, and interferon-γ with a parallel decrease in the anti-inflammatory factors IL-10 and transforming growth factor β-1, especially in maniac phase of BPAD [21,22]. IL-6 and cytokines decrease the synthesis of monoamine and may increase the activity of indoleamine-2,3-dioxygenase (IDO), responsible for tryptophan catalysis, and activation of kynurenine pathway activation and decreasing availability of central serotonin [23]. As a result, there is a synthesis of neurotoxic N-methyl-d-aspartate glutamate (NMDA) agonist quinolinic acid and 3-hydroxykyneurine, which enhance oxidative stress and contribute to neurodegeneration [24].

Neurotransmitters (Serotonin (5-Ht), Dopamine (Da), Noradrenaline (Ne), Gamma-Aminobutyric Acid (Gaba)

The neurotransmitters (5-HT), DA, NE and GABA, are monoamine neurotransmitters. These neurotransmitters are either gut-derived or brain-derived, which plays a major role in the aetiology and pathophysiology of MDD by maintaining systemic homeostasis or regulation and development of various neurogenic pathways. Their depletion results in the development of various neuropsychiatric disorders including MDD [25].

During COVID-19, cytokines and their signal pathways including p38 mitogen activates protein kinase and shows significant effects on the metabolism of various neurotransmitters like serotonin, glutamate and dopamine by inhibiting their synthesis, release and reuptake [26]. IL-6 and cytokines decrease the synthesis of monoamine and may increase the activity of IDO which release kynurenine and potentially decreases the availability of serotonin in the brain. The second mechanism by which inflammatory cytokines inhibit the synthesis of serotonin is by disruption of tetrahydrobiopterin (BH4). BH4 is a rate-limiting essential enzyme cofactor for tryptophan and tyrosine hydroxylase. It is also required for the activity of phenylalanine hydroxylase which converts phenylalanine to tyrosine [27].

Cytokinin further activates the mitogen-activated protein kinase (p38 MAPK) pathway which increases the function of the reuptake pumps for serotonin and dopamine transporters [28]. Inflammatory cytokinin also stimulates the release of glutamate from astrocytes and reduces the astrocytic expression of glutamate transporters, leading to glutamate excitotoxicity. Glutamate results in access to extra-synaptic NMDA receptors which leads to a decrease in neurotrophic factors, important in neurogenesis [29].

Hypothalamic Pituitary Adrenal (HPA) Axis

The HPA axis causes the release of glucocorticoids (cortisol in humans), from the adrenal cortex in response to adrenocorticotrophic hormone (ACTH) from the anterior pituitary gland. Increased circulatory glucocorticoids, establish a negative feedback mechanism and inhibits corticotrophin-releasing hormone (CRH) and vasopressin from the hypothalamus. Chronic stress leads the immune system to become insensitive to the inhibitory signals of glucocorticoids and disturbs the negative feedback mechanism. Increased circulatory glucocorticoids and pro-inflammatory cytokines further desensitize and downregulate the central neurotransmitter circuits causing elevation of cortisol, CRH and ACTH levels in MDD patients.

Probiotics and Brain Functions

There is much substantial evidence that the gut microbiome is the key regulator of the stress pathway, and has potential antidepressant properties by regulating inflammatory markers and neurotransmission of monoamine neurotransmitters. Many microorganisms have been proposed as potential psychotropic agents, including *Streptococcus thermophiles, Bifidobacterium animalis, Bifidobacterium bifidum, Bifidobacterium longum, Streptococcus thermophiles, Lactobacillus bulgaricus, Lactococcus lactis, Lactobacillus acidophilus, Lactobacillus Plantarum, Lactobacillus reuteri, Lactobacillus paracasei, Lactobacillus helveticus, Lactobacillus rhamnosus, Bacillus coagulans, Clostridium butyricum*, and others [30-32] (Table 1).

Nation	Probiotic	Dosage	Duration	Sample size	Diagnosis criteria	Conclusion	References
Canada	Contained freeze-dried L. helveticus R0052 and B. longum R0175 bacteria	Three billion colony-forming units (≥3 × 109 CFU) per 1.5 g	8 weeks	74 patients with MDD (18-50 years)	BDI	Result in the improvement of BDI score	Kazaemi, et al.
Iran	CFU Bifidobacterium longum, Bifidobacterium bifidum, Bifidobacterium lactis, and Lactobacillus acidophilus bacteria) or placebo in addition to 25 mg of sertraline	One capsule 18 X 109	8 weeks	48 patients, (18-65 years old)	DSM-V criteria	Probiotics with a sertraline combination was superior to sertraline alone	Eskandarzadeh, et al.

Poland	Lactobacillus plantarum 299v	1 capsule (contained 10 × 109 CFU	8 weeks	79 patients with MDD	HAM	Lactobacillus Plantarum 299v improved cognitive performance and decrease KYB concentration in Patients with MDD	Rudzki, et al.
Ireland	L. rhamnosus (JB-1)	capsules were 1 × 109 colony-forming units (CFU).	8 weeks	29 patients, (20-33 years)	BDI;BAI	No significant effect on BDI Scores, but reduced stress-related behaviour and corticosterone release	Kelly, et al.
Japan	CP2305	1 × 1010 bacterial cells per 2 tablets)	24 weeks	74 Japanese medical students (average 25 years of age)	STAI; HADS	CP2305 on long-term use improve the mental state, sleep quality and gut microbiota of healthy adults under stressful condition	Nishida, et al.
	Lactobacillus acidophilus, L. casei, and Bifidobacterium bifidum		8 weeks	40 patients with MDD (20-55 years)	BDI	Improved BDI Score	Akkasheh, et al.
	lactobacillus. acidophilus and Bifidobacterium. bifidum and longum		6 months	34 patients with stress or exhaustion (average age 44 years	PNQ, EWL	General condition improved by 40.7%. 70 % participants rated the treatment effect as good and very good.	Grunewald, et al.

Table 1: *MDD major depressive disorder, BDI Beck Depression Inventory, PNQ psychological-neurologic questionnaire, EWL list of adjectives, STAI state-trait anxiety inventory, HADS Hospital Anxiety Depression Scale, BAI Beck Anxiety Invento.

Table1. Depicts the group of various studies assessed the daily doses of commercially available probiotics, ranging from 6 billion to 12.5 billion bacteria every day, these seven studies included 204 patients with depression on probiotics. The met analysis reported significant differences in the clinical outcome when probiotics were consumed for a period of 8 weeks and more resulting in an improved Beck Depression Inventory score and reducing stress-related behavior [33]. Probiotics and prebiotics are shown to reduce cortisol stress response [34]. Secondly, gut bacteria directly produce neurotransmitters like GABA, serotonin, noradrenaline, acetylcholine and dopamine in several brain regions [35,36], but most notably in the sensory brain network area of the brain, controlling central processing for emotions and sensation when compared to a patient with no intervention [37,38]. These are the mediators of major interest in all psychiatric illnesses. Although it remains unclear whether the levels of microbe-derived neurotransmitters are sufficient to be clinically important, such a scenario is worth exploring. They also produce short-chain-fatty-acids (SCAFs) by bacterial fermentation of fiber in the colon like butyrate, which acts as a histone deacetylase inhibitor, functions as a ligand for a subset of G protein-coupled receptor and energy metabolite which plays a major role in brain health by showing antimanic and antidepressant effects [39].

Gut microbiota plays an important role in tryptophan metabolism via the kynurenine pathway, thus increasing the production of neuroactive kynurenic acid and quinolinic acid, while reducing the availability of tryptophan for serotonin synthesis. The kynurenine pathway plays a major role in the pathogenesis of depression [40,41].

Restoration of Healthy Gut Bacteria After COVID-19 Therapy

The evidence compiled in the presented review indicates that probiotics might improve the psychiatric face of COVID-19.

Probiotics can be potentially used as a novel treatment in combination with other antidepressants treatment. Probiotics and prebiotics (combinations called synbiotics) supplements are the most effective way to restore the healthy gut microbiome. Probiotics feed on prebiotics, so a diet rich in prebiotics can help ensure that the microbiome has the resources necessary to repopulate properly by providing nutrients that promote gut health and microbiome diversity. When recovering from COVID-19, food diversity and a balanced diet, with extra fibers and fermented food might be part of a diet to maintain the balance in the aftermath of antibiotics.

References

1. Gorbalenya AE, Susan CB, Baric RS, Groot RJ, Drosten C, et al. (2020) The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 5(4): 536-544.

2. Rao NAS, Melysia TMC, Moulos P, Francoijs LJ, Chatziioannou A, et al. (2011) Coactivation of GR and NFKB alters the repertoire of their binding sites and target genes. Genome Res 21(9): 1404-1416.

3. Vickers C, Hales P, Kaushik V, Dick L, Gavin J, et al. (2002) Hydrolysis of biological peptides by human angiotensin-converting enzyme-related carboxypeptidase. J Biol Chem 277: 14838-14843.

4. Enache D, Pariante CM, Mondelli V (2019) Markers of central inflammation in major depressive disorder: A systematic review and meta-analysis of studies examining cerebrospinal fluid, positron emission tomography and post-mortem brain tissue. Brain Behav Immun 81: 24-40.

5. Kern S, Skoog I, Borjesson HA, Blennow K, Zetterberg H, et al. (2014) Higher CSF interleukin-6 and CSF interleukin-8 in current depression in older women. Results from a population-based sample. Brain Behav Immun 41: 55-58.

6. Lindqvist D, Janelidze S, Hagell P, Erhardt S, Samuelsson M, et al. (2009) Interleukin-6 is elevated in the cerebrospinal fluid of suicide attempters and related to symptom severity. Biol Psychiatry 66: 287-292.

7. Hsu MP, Frausto R, Rose JS, Campbell IL (2015) Analysis of IL-6/gp130 family receptor expression reveals that in contrast to astroglia, microglia lack the oncostatin M receptor and functional responses to oncostatin M. Glia 63(1): 132-141.

8. Spooren A, Kolmus K, Laureys G, Clinckers R, De Keyser J, et al. (2011) Interleukin-6, a mental cytokine. Brain Res Rev 67: 157-183.

9. Sasayama D, Hattori K, Wakabayashi C, Teraishi T, Hori H, et al. (2013) Increased cerebrospinal fluid interleukin-6 levels in patients with schizophrenia and those with major depressive disorder. J Psychiatr Res 47: 401-406.

10. Troyer EA, Kohn JN, Hong S (2020) Are we facing a crashing wave of neuropsychiatric sequelae of COVID-19? Neuropsychiatric symptoms and potential immunologic mechanisms. Brain Behav Immun 87: 34-39.

11. Madison A, Kiecolt GJK (2019) Stress, depression, diet, and the gut microbiota: human-bacteria interactions at the core of psychoneuroimmunology and nutrition. Curr Opin Behav Sci 28: 105-110.

12. Martin CR, Osadchiy V, Kalani A, Mayer EA (2018) The Brain-Gut-Microbiome Axis. Cell Mol Gastroenterol Hepatol 6(2): 133-148.

13. Villanueva MMJ, Perez MP, Oteo JA (2015) Gut microbiota: a key player in health and disease. A review focused on obesity. J Physiol Biochem 71(3): 509-525.

14. Hall AB, Tolonen AC, Xavier RJ (2017) Human genetic variation and the gut microbiome in disease. Nat Rev Genet 18(11): 690-699.

15. Leonard BE (2018) Inflammation and depression: a causal or coincidental link to the pathophysiology? Acta Neuropsychiatr 30(1): 1-16.

16. Guina J, Merrill B (2018) Benzodiazepines I: Upping the Care on Downers: The Evidence of Risks, Benefits and Alternatives. J Clin Med 7(2): 17.

17. Munhoz RP, Bertucci FD, Teive HA (2017) Not all drug-induced parkinsonism are the same: the effect of drug class on motor phenotype. Neurol Sci 38: 319-324.

18. de Araujo FF, Farias DP (2020) Psychobiotics: An emerging alternative to ensure mental health amid the COVID-19 outbreak? Trends Food Sci Technol 103: 386-387.

19. Pickard JM, Zeng MY, Caruso R, Nunez G (2017) Gut microbiota: Role in pathogen colonization, immune responses, and inflammatory disease. Immunol Rev 279 (1): 70-89.

20. Gibson GR, Hutkins R, Sanders ME, Prescott SL, Reimer RA, et al. (2017) The International Scientific Association for Probiotics and Prebiotics (ISAPP) consensus statement on the definition and scope of prebiotics. Nat Rev Gastroenterol Hepatol 14 (8): 491-502.

21. Li Y, Oosting M, Smeekens SP, Jaeger M, Aguirre GR, et al. (2016) A Functional Genomics Approach to Understand Variation in Cytokine Production in Humans. Cell 167(4): 1099-1110.

22. Ter Horst R, Jaeger M, Smeekens SP, Oosting M, Swertz MA, et al. (2016) Host and environmental factors influencing individual human cytokine responses. Cell 167(4): 1111-1124.

23. Maes M, Bosmans E, Suy E, Vandervorst C, DeJonckheere C, et al. (1991) Depression-related disturbances in mitogen-induced lymphocyte responses and interleukin-1 beta and soluble interleukin-2 receptor production. Acta Psychiatr Scand 84(4): 379-386.

24. Myint AM, Kim YK, Verkerk R, Scharpe S, Steinbusch H, et al. (2007) Kynurenine pathway in major depression: evidence of impaired neuroprotection. J Affect Disord 98(1-2): 143-151.

25. Filatova EV, Shadrina MI, Slominsky PA (2021) Major Depression: One Brain, One Disease, One Set of Intertwined Processes. Cells 10(6): 1283.

26. Miller AH, Haroon E, Raison CL, Felger JC (2013) Cytokine targets in the brain: impact on neurotransmitters and neurocircuits. Depress Anxiety 30(4): 297-306.

27. Fanet H, Capuron L, Castanon N, Calon F, Vancassel S (2021) Tetrahydrobioterin (BH4) Pathway: From Metabolism to Neuropsychiatry. Curr Neuropharmacol 19(5): 591-609.

28. Quagliato LA, Nardi AE (2022) Cytokine profile in drug-naïve panic disorder patients. Transl Psychiatry 12(1): 75.

29. Mahmoud S, Gharagozloo M, Simard C, Amrani A, Gris D (2019) NLRX1 Enhances Glutamate Uptake and Inhibits Glutamate Release by Astrocytes. Cells 8(5): 400.

30. Cheng LH, Liu YW, Wu CC, Wang S, Tsai YC (2019) Psychobiotics in mental health, neurodegenerative and neurodevelopmental disorders. J Food Drug Anal 27(3): 632-648.

31. Gualtieri P, Marchetti M, Cioccoloni G, De Lorenzo A, Romano L, et al. (2020) Psychobiotics regulate the anxiety symptoms in carriers of allele A of IL-1β gene: A randomized, placebo-controlled clinical trial. Mediators Inflamm, pp: 1-11.

32. Vaghef ME, Maleki V, Behrooz M, Ranjbar F, Ebrahimi MM (2020) Can psychobiotics "mood" ify gut? An update systematic review of randomized controlled trials in healthy and clinical subjects, on anti-depressant effects of probiotics, prebiotics, and synbiotics. Clin Nutr 39(5): 1395-1410.

33. Chao L, Liu C, Sutthawongwadee S, Li Y, Lv W, et al. (2020) Effects of Probiotics on Depressive or Anxiety Variables in Healthy Participants Under Stress Conditions or With a Depressive or Anxiety Diagnosis: A Meta-Analysis of Randomized Controlled Trials. Front Neurol 11: 421.

34. Schmidt K, Cowen PJ, Harmer CJ, Tzortzis G, Errington S, et al. (2015) Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. Psychopharmacology (Berl) 232(10): 1793-1801.

35. Strandwitz P, Kim KH, Terekhova D, Liu JK, Sharma A, et al. (2019) GABA-modulating bacteria of the human gut microbiota. Nat Microbiol 4(3): 396-403.

36. Strandwitz P (2018) Neurotransmitter modulation by the gut microbiota. Brain Res 1693: 128-133.

37. Bagga D, Aigner CS, Reichert JL, Cecchetto C, Fischmeister FPS, et al. (2019) Influence of 4-week multi-strain probiotic administration on resting-state functional connectivity in healthy volunteers. Eur J Nutr 58: 1821-1827.

38. Roman P, Sanchez LN, Cardona D, Estevez AF, Canadas F, et al. (2018) A Pilot Randomized Controlled Trial to Explore Cognitive and Emotional Effects of Probiotics in Fibromyalgia. Sci Rep 8.

39. Bourassa MW, Alim I, Bultman SJ, Ratan RR (2016) Neuroepigenetics and the gut microbiome: can a high fibre diet improve brain health? Neurosci Lett 625: 56-63.

40. Dehhaghi M, KazemiShariat PH, Guillemin GJ (2019) Microorganisms, Tryptophan Metabolism, and Kynurenine Pathway: A Complex Interconnected Loop Influencing Human Health Status. Int J Tryptophan Res 12: 1-10.

41. Roth W, Zadeh K, Vekariya R, Ge Y, Mohamadzadeh M (2021) Tryptophan Metabolism and Gut-Brain Homeostasis. Int J Mol Sci 22(6): 2973.