Can the gastrointestinal system alter liver damage caused by COVID-19?

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Abstract

Our gastrointestinal system, often referred to as our "second brain," is grappling with the devastating effects of COVID-19, a disease that has plagued recent years. Researchers are investigating how bacteria in the intestinal microflora may contribute to or mitigate liver damage caused by COVID-19. Despite the limited number of studies, the fight against liver organ damage by the gastrointestinal system, which is our second brain is important. All original articles published in English until March 01, 2020, were retrieved via a library-assisted literature search from PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science. A total of nine articles (2.188 patients) were found eligible for inclusion. Effect size and 95% confidence interval were evaluated in this study. The randomized trials exhibit a noteworthy level of heterogeneity (p<0.05), and upon scrutinizing the funnel plot, there is no discernible indication of publication bias. According to the meta-analysis tree graph, the weights of the studies are significantly to the right of the 2 vertical lines. The confidence interval of each study has significant weights. According to the study findings, the interaction of the intestinal flora and the immune system showed us that there is an area that we need to investigate against the COVID-19 disease. For many years, research has tried to explain how the signaling pathways in the intestinal tract are related to the brain. The study revealed that our digestive system plays a crucial role as an auxiliary component of our brain. Future studies should uncover the main ways of this communication.

Keywords: second brain, gut brain axis, COVID-19 and microbiome, COVID-19 liver effect

1. Introduction

The gastrointestinal tract includes life forms consisting of bacteria, viruses, fungi, and protozoa in its natural flora (1,2,3). This flora is different in every person like a fingerprint and is necessary for the protection of intestinal health and has an important place in the fight against various diseases (4,5,6,7). Our microbial flora, which is the basic defence element of our immune system, starts in the mother's womb and begins to colonize with birth. The commensal microorganisms residing in the gastrointestinal tract play a pivotal role in facilitating the metabolic processing of orally ingested nutrients through the process of fermentation. If the beneficial microbial flora develops in sufficient amounts, it prevents the reproduction of harmful microorganisms (8,9). The intestinal flora survives through the utilization of by-products resulting from the breakdown of fermentation products within the digestive tract (10,11,12). In addition, microscopic creatures in the digestive tract fight harmful organisms by triggering an immune response and directly affecting the health of vital organs such as the liver (13,14,15).

Recent studies show that liver transplant patients are at high risk for COVID-19 mortality (16,17,18). Researchers have proven that patients who drink alcohol and have advanced liver cirrhosis experience the disease severely. These patients should continue treatment with mechanical ventilation. Covid 19 disease creates a disorder in liver metabolism and mortality occurs (19,20). Metabolic disorder due to elevated liver enzyme values, combined with inflammation caused by COVID-19 infection, can accelerate cytokine storms and increase immune system dysregulation. Therefore, it has been reported that transaminase values were found to be high in patients who died as a result of COVID-19 disease (21,22,23).

The intestinal microbiota exerts influence on the immune system, thereby impacting the liver via systemic circulation (24,25,26). The function of our body's microbiome mechanism affects the health of our physiological nervous system and the perfection of our sensory perceptions. The microbiome, brain, central nervous system, endocrine glands, and lymphoid organs all communicate with one another through the living body (27,28,29,30,31). Studies on the relationship between the gut microbiome and the central nervous system have revealed that changes in the gut flora increase intestinal permeability, which makes it possible for neuroactive substances to enter the

bloodstream (32). The extant body of scientific literature substantiates the proposition that various microbiota exhibits the capacity to synthesize bioactive compounds with discernible impacts on gene expression within the neurological milieu. Empirical investigations have delineated a nexus between alterations in microbiota composition and the manifestation of depressive states, modulation of social responsiveness, and the fortification of the immune system against deleterious modifications induced by stressors. These findings underscore the intricate interplay between the microbiome and neurobiological processes, thereby advancing our comprehension of the multifaceted influences exerted by microbial communities on mental health and physiological resilience (33). In certain scholarly investigations, findings have been documented suggesting that alterations in the microbiome can precipitate neurological modifications, demonstrating a transferability that extends beyond conspecifics and encompasses inter-species dynamics, notably observed in subjects undergoing faecal transplant procedures (34,35). The reciprocal interaction between the microbiome and the nervous system is characterized by a bidirectional relationship, indicating that their influence on each other is not unidirectional. The microbiome can affect how we think, but also our nervous system and lifestyle have a major effect on the composition of our microbiome (36). The struggle to protect immunity lasts until the death of the person and explains why the flora in the digestive system fights for us like gladiators (37). The brain alters intestinal permeability and secretions, and the digestive tract microbiome is normal unless there is intestinal disease. Moreover, the endocrine secretions of the cerebral system, with consequential implications for microbial gene expression, possess the capacity to induce alterations in the constitution of the intestinal microbiota (38). Hormonal changes can cause disruptions in the flora of the digestive tract (39,40,41). According to recent studies the administration of antibiotics results in a depletion of the indigenous gut microbiota, affording an advantageous milieu for the colonization of the gut epithelium by pathogenic microbiota. (42,43,44). There have been studies on the signal pathways used by the gastrointestinal system to communicate with the brain (45,46). A neural network of more than 500 million neurons that controls the digestive system is intertwined with the enteric nervous system (47,48). This number of neurons is roughly five times that of the spinal cord's neurons. The enteric nervous system can be referred to as our second brain because of this (49). Some researchers are looking into the possibility of autonomous activation of this system. Additionally, they get signals from the prevertebral ganglia, the enteric nervous system, and the central nervous system via the vagus nerve (48). The nomenclature "intestinal axis" is employed to delineate the complex network of biochemical signalling that transpires between the digestive system and the central nervous system (50). Nevertheless, the comprehensive impact of the microbiome on cerebral function is currently emerging, prompting the characterization of the reciprocal interplay

between the microbiome and the central nervous system as the "microbiome-gut-brain axis." Notably, the absence of a typical gut microbiome during early developmental stages markedly influences an individual's stress response in adulthood (51). One of the first studies that turned the microbiome gut brain access into a hot research topic was a study in 2004 that showed differences in behaviour between germ free and non-germ free laboratory mice (52). The mice lacking a microbiome showed an exaggerated stress response. This was reversed when their gut was colonized by a bifidobacterium species. Elimination of the gut microbiome and mice resulted in problems with spatial and working memory (53). In other studies, dietary modifications also altered the performance of mice on memory tasks. One potential mechanism for these changes is the nerve growth factor BDNF, which is short for brain derived neurotrophic factor (54,55). This substance influences neuronal development, protects against stress induced damage, and is important in determining stress tolerance, mood, and cognitive function. Mice with healthy microbiomes have higher expression of BDNF in their brains, which might be why they have better memories. Another study showed that even in the absence of obesity, the microbiome associated with obesity can cause neurophysiological changes (3). Researchers use donor mice for the development of two different types of microbiomes. One group was fed a diet with 13% fat calories, while the other was fed a diet with 60% fat calories. 10 weeks after the diets commenced, the researchers harvested their microbiomes. At this time, mice from the leaner group weighed an average of 24.5 grams, while mice from the high fat diet group weighed an average of 37 grams. Next, another group of mice, the microbiota recipients, were given antibiotics daily for two weeks to eliminate their original microbiomes. Three days after the end of the two-week course of antibiotics, the mice were recolonized by donor microbiota from either the group that had been found, the high fat diet or from the group that had been fed the control diet (56). Behavioural assessments were systematically executed, revealing a discernible reduction in exploratory behaviour and a concurrent elevation in anxiety-related behaviours among recipients exposed to high-fat microbiota. Notwithstanding, locomotor activity and overall behavioural metrics remained within comparable ranges. Distance travelled was the same for both groups of recipient mice, indicating no effect of the different microbiomes on motor function (57). The mice which received the high fat diet microbiota also had increased intestinal permeability. The authors also examined markers for brain injury and inflammation and found that the high fat diet microbiota receiving mice had higher numbers for these markers. It is, of course, much more difficult to conduct studies regarding the relationship of the brain and the microbiome in humans. Interesting link that is still being investigated is the correlation between autism and high levels of Clostridium bacteria in children's stools (58). Around 70% of people with autism suffer from gastrointestinal problems (59). The gastrointestinal maladies in question may potentially correlate with a modified

gut microbiome, leading to heightened intestinal permeability; however, it is imperative to acknowledge that substantial further inquiry is requisite before definitive conclusions can be drawn. It is possible that certain developments in gut flora may trigger autism, or that the two develop concurrently. Upon traversing the birth canal, neonates encounter constituents of their maternal microbiome, constituting their inaugural exposure to bacteria that subsequently assume a pivotal role in the establishment and maturation of their indigenous microbiota (60). Alterations in dietary patterns have been demonstrated to exert substantial and expeditious impacts on the compositional framework of the gut microbiome in both human subjects and murine models. Notably, such modifications have been observed to exert discernible influences on cognitive processes, specifically memory and learning. Further exploration of the ramifications of the gut-brain axis microbiome interrelation on visceral organs, such as the liver, holds promise for enhancing our understanding of the pathophysiological sequelae induced by COVID-19. The principal emphasis of this systematic review cantered on a research article and meta-analysis, aimed at providing a comprehensive synthesis of data elucidating the impact of gut microbiota on COVID-19 comorbidities, specifically with regard to hepatic injuries.

2. Materials And Methods

The checklist's meta-analyses and observational PRISMA 2009 guidelines were followed in gathering the data for this study.

2.1. Literature Search

A systematic inquiry was conducted utilizing reputable databases, namely PubMed/MEDLINE, Excerpta Medica Database (EMBASE), and Web of Science, with the objective of identifying pertinent cohort studies, case-control studies, or randomized controlled trials that furnished comprehensive data regarding the nexus between the gut microbiome and COVID-19. The search encompassed publications available up to September 1, 2022 (Table 1). The terms related to the microbiota, the relationship between the liver and COVID-19, and the function of the microbiome in COVID-19 were combined with or used as synonyms in the literature search method. To ascertain additional data sources within the obtained results, an exhaustive review of the reference lists from relevant research and review articles was systematically undertaken.

Table 1. Potential Gut Brain Axis Presence

Ref.	Study Design	Comparison Criteria	Total Sample	Gut Microbiome Culture	COVID-19 Presence	Potantiel Gut Brain Axis Presence
Yeoh et al.	CC	GIS probiotic formula	178	Performed	+	+
Zuo et al.	CC	Fecal sample	69	Performed	+	+
Maeda et al.	CC	Fecal sample	108	Performed	+	+
Castrellon et al.	CC	GIS probiotic formula	300	Performed	+	+
Newsome et al.	RCS	Observational cohort study	93	Performed	+	+
Schult et al.	CC	Saliva and fecal samples	130	Performed	+	+
Jin et al.	CC	Retrospective bioinformatic data	651	Performed	+	+
Nobel et al.	CC	Retrospective bioinformatic data	516	Performed	+	+
Ceccarelli et al.	RCS	Observational cohort study	143	Performed	+	+

Abbreviations: CC: Case Contrl, RCS: Randomise Case Control, GIS: Gastrointestinal System

2.2. Study Selection

A comprehensive literature review encompassing 80,891 records was conducted, culminating in the final inclusion of nine pertinent articles. The subsequent meta-analysis incorporated data derived from these nine selected studies. 2.188 patients with liver findings and COVID-19 disease were included in the studies that made up the meta-analysis in this study. Most of the data was collected prospectively for observational studies, all of which were case-control studies. The majority of assessment items had a low risk of bias in studies. Fig. 1 provides a summary of the chosen studies.
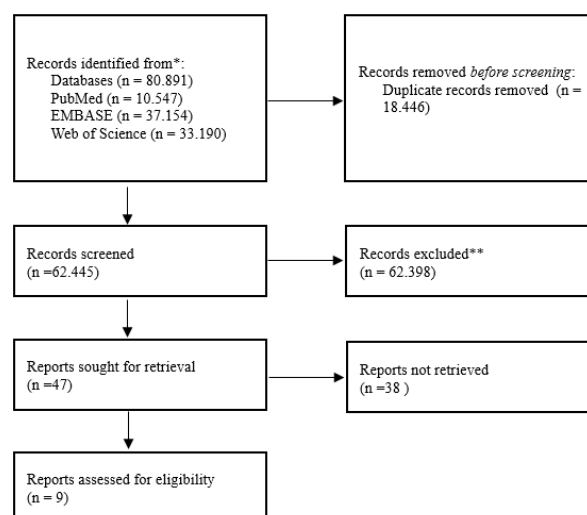
Fig. 1. PRISMA flow chart of study selection

This study incorporated retrospective cohort studies and case-control investigations involving a cohort size of 69 or more participants. Inclusion criteria encompassed studies that reported on the risk of gastrointestinal system symptoms associated with COVID-19, or studies providing empirically derived data suitable for the computation of said risk estimates. Studies that included patients undergoing non-COVID-19, lacked a clear definition of the recovery period after illness follow-up, and failed to report high priority data were excluded from the main analysis. We only included the one report with the largest sample size to avoid publishing the same group or cohort of patients twice. The same investigators individually retrieved and downloaded the full texts of articles that were thought to be potentially admissible for analogy inclusion. Each downloaded file received a file number and a password that was known to both researchers.

2.3. Data Extraction and Processing

One researcher extracted data using a common data abstraction form, and another researcher double-checked the results. Data retrieval encompassed pertinent information on the study's objectives, COVID-19 typology, the interplay between the microbiome and COVID-19, sample size, demographic characteristics such as mean or median age and sex ratio, prevalence of comorbid conditions (e.g., cirrhosis, immune-specificity), incidence of COVID-19 among participants, and the associated risk estimation accompanied by a 95% confidence interval (95% CI). Utilizing Comprehensive Meta-Analysis Software tools tailored for case-control studies and randomized controlled trials, a meticulous assessment of bias risk was undertaken.

2.4. Statistical Analysis

Analyses were conducted with Comprehensive Meta-Analysis Software (version 3.3.070, USA). Heterogeneity evaluation was conducted through the χ^2 test on Cochrane's Q statistic, with quantification facilitated by I² values. The I² values were interpreted as indicators of heterogeneity, acknowledging that higher I² values correspondingly denote greater heterogeneity in the data (43). By inspecting funnel plots and performing a linear regression test of funnel plot asymmetry, we determined whether studies had any bias related to the sample size effect. (Hedges's test). Two-tailed statistical tests were used, and a P value of 0.05 was considered statistically significant.

3. Results

3.1. Association between gastrointestinal microbiata and COVID-19

Effect size and 95% confidence interval were evaluated in this study. The standard error margin of 9 publications investigating randomized effects was found to be 0.934486 (Table 2). The heterogeneity within randomized trials is statistically significant (p < 0.05), and upon meticulous inspection of the funnel plot, no discernible evidence of publication bias was observed (Fig. 2). According to the meta-analysis tree graph, the weights of the studies are significantly to the right of the 2 vertical lines. The confidence interval of each study has significant weights. The weights of the studies are significantly to the right of the 2 vertical lines indicated by meta-analysis tree graph. As shown in Fig. 2 and Table 3, the articles identified for meta-analysis were not found to be heterogeneous (p<0.05). These results show the net value of the effect weight for the study (Fig. 3.).
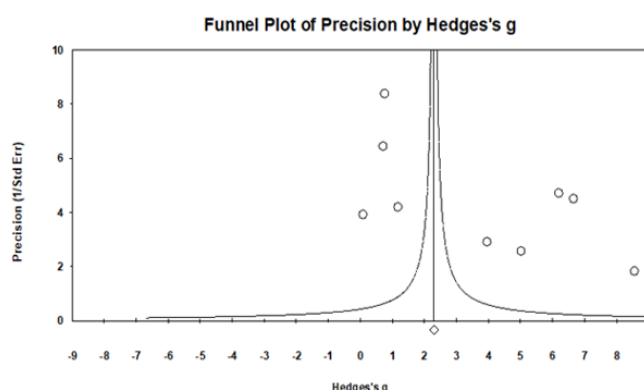
Fig.2. Publication bias on funnel plot inspection

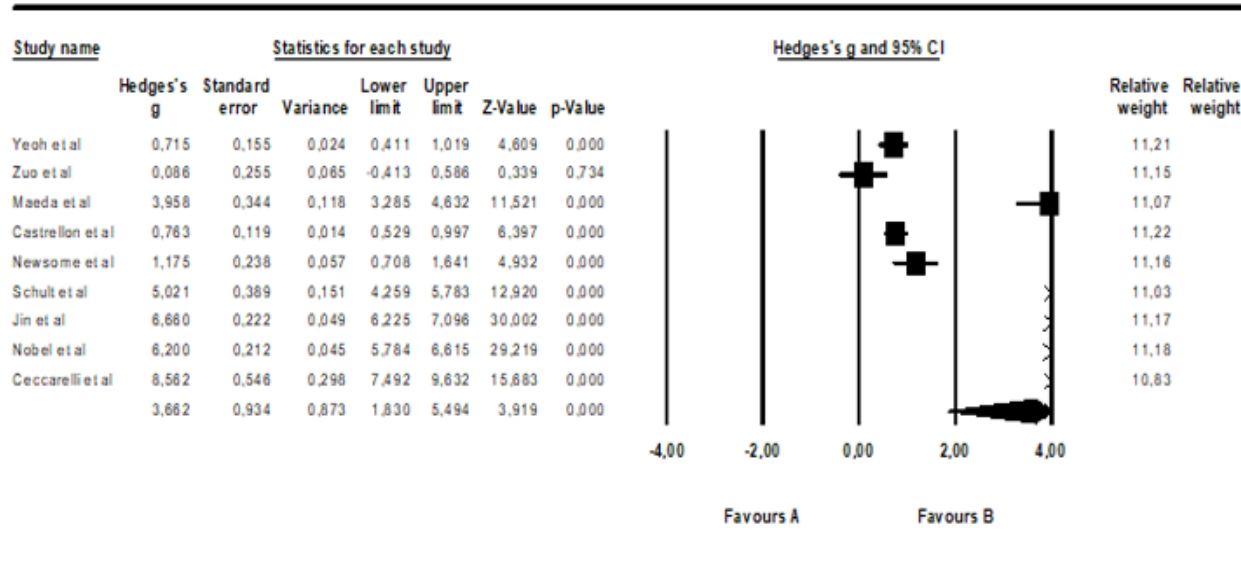**Table 2.** Effect size of gastrointestinal system microbiata association between immun system response and brain axis

Study Model	Number Studies	Point estimate	Standard error	Variance	Lower limit	Upper limit
Fixed effects	9	2.302287	6.97E-02	4.86E-03	2.16565	2.438923
Random effects	9	3.661963	0.934486	0.873264	1.830404	5.493522

Table 3. Heterogeneity of study results

Study Model	Test of null (2-Tail)		Heterogeneity			
	Z value	P value	Q-value	df (Q)	P-value	I-squared
Fixed effects	33.02492	0.000	1295.44022	8	0.000	99.38244931
Random effects						
Study Model	3.918692	0.000				

Meta Analysis

Study name	Hedges's g	Standard error	Variance	Lower limit	Upper limit	Z-Value	p-Value	Hedges's g and 95% CI	Relative weight	Relative weight
Yeoh et al	0,715	0,155	0,024	0,411	1,019	4,609	0,000		11,21	
Zuo et al	0,086	0,255	0,065	-0,413	0,586	0,339	0,734		11,15	
Maeda et al	3,958	0,344	0,118	3,285	4,632	11,521	0,000		11,07	
Castrellon et al	0,763	0,119	0,014	0,529	0,997	6,397	0,000		11,22	
Newsome et al	1,175	0,238	0,057	0,708	1,641	4,932	0,000		11,16	
Schult et al	5,021	0,389	0,151	4,259	5,783	12,920	0,000		11,03	
Jin et al	6,660	0,222	0,049	6,225	7,096	30,002	0,000		11,17	
Nobel et al	6,200	0,212	0,045	5,784	6,615	29,219	0,000		11,18	
Ceccarelli et al	8,562	0,546	0,298	7,492	9,632	15,683	0,000		10,83	
	3,662	0,934	0,873	1,830	5,494	3,919	0,000			

Favours A   Favours B

Meta Analysis

Fig. 3. Meta-analysis tree graph: the weights of the studies are significantly to the right of the 2 vertical lines

4. Discussion

If the microorganisms in the intestinal flora provide sufficient serous structure protection, the neural communication with the brain is healthier. If we evaluate the immune system, any change in the flora may cause a decrease in the defence response to COVID-19 disease (61). This interaction is in constant communication with the brain-gut neural axis (44). Studies report that recovery is accelerated if the intestinal microbiota is good in patients with COVID-19 disease and liver damage (62,63). According to this meta-analysis study data, it is understood that if the intestinal microbiota is healthy enough, the recovery processes of the patients are accelerated (64).

Perturbations in the gut microbiome have been widely acknowledged in association with COVID-19 (65). The proposed interventions involve arresting viral proliferation within the gastrointestinal tract, mitigating inflammation of epithelial cells in the intestinal milieu, ameliorating the dysbiosis of gut bacteria induced by COVID-19, and reinstating the impaired transport and metabolism of tryptophan in individuals affected by the virus (66). Restore the mucus layer in the gastrointestinal tract and tight junction integrity to assure a return to normal intestinal permeability (67). After detoxifying the gut, it is necessary to create a microbiome that will support T memory cell function, which is essential not only for warding off neuropathy but also for protecting against the effects of future infections. There is now ample evidence that ongoing viral infection contributes to prolonged COVID-19. In this meta-analysis, almost all of these mechanisms of the defence system were examined. Spike protein circulating in the blood of people in plasma, even in the cells of people with COVID-19, up to 12 months after they were first infected. And these researchers said there must be a reservoir of chronic viral infection (68). This is present and this creates and then persists, possibly driving long-term COVID-19 and immune response of people especially neuropathic.

An impairment of T effector memory cells of the type that would be seen with chronic antigenic stimulation. So, steps to prevent viral proliferation in the gut, there are drugs that might be used. Researchers mostly are using natural products and flavonoids figure very strongly into that pharmaceutical repertoire, especially those concerning containing quercetin (69). Thus, have effects of protease inhibition and that also destroy bacteriophages. There is very strong evidence that the Coronavirus, not only infects human cells but can infect bacteria and act as a bacteriophage (70). Researchers now exploring the role of antibiotics along with these antiviral herbs, in particular amoxicillin, which in his studies proved to be the most effective. Dietary factors that could impact the activity of bacteriophages, polyphenols, especially the bioflavonoids. So, since we don't know what stevia does in this setting, a study would use caution with stevia in patients who've had COVID-19. Now there also is a probiotic that has antiviral activity.

4.1. The next step: reducing epithelial cell inflammation

Inflammation increases the synthesis of nitric oxide, which results in an increase in the nitrate concentration of the inflamed tissue (71). High nitrate environment, which is what's created, enhances the growth of many bacterial pathogens (72). But it inhibits the growth of many healthy anti-inflammatory natural bacteria. This is a vicious cycle. The high nitrate environment invites the growth of pathogenic bacteria, which then generate more inflammation and maintain this nitrate

cycle. There are several natural products that researchers use for this purpose, quercetin. Mastic gum from the Mediterranean food pistachio lenticonus. Curcumin from turmeric, omega-3 fats, Magnolia bark, which is used a lot in Chinese medicine, and bovine serum immunoglobulins have all been shown in controlled studies to reverse intestinal inflammation (73). Because some of these also have antiviral effects, they do double duty. Quercetin has garnered particular attention in scientific inquiry due to its examined antiviral properties and its capacity to mitigate inflammation within the gastrointestinal tract. And there's several studies to that effect now. Improving the gut microbiome. People who did not show these features had a much better outcome and recovered fully from COVID-19. A pivotal bacterial species known as Faecalibacterium prausnitzii holds keystone significance, primarily as a significant producer of the short-chain fatty acid butyrate. This compound, renowned for its pronounced anti-inflammatory effects, exerts its influence within the gastrointestinal tract and, consequently, throughout the entire physiological system. There are higher levels of certain other bacteria that are associated with inflammation, in particular a species called ruminococcus gnavus. Another important gastrointestinal system protective agent is butyrate. When we look at the physiology of butyrate, it becomes clear that. This is not just a coincidence, so next step is to try and restore the depleted bacteria and restrain the inflammatory bacteria once again in a general way. Bioflavonoids play a major role in doing that. Flavonoids, as curators of the gut microbiome, and they encourage the growth of and activity of certain species and inhibit certain other species. And at the same time, we need these flavonoid dependent bacteria because they make the flavonoids more available to human body. Butyrate is what is called a post biotic. It is produced by bacteria in the gut. It's not produced by human cells. About 80% of the energy that maintains the integrity of the lining of the large intestine comes from butyrate. The mitochondria in the large intestine depend on butyrate for their activity (74). Outside the gastrointestinal tract that rate has some important effects. It has main effects in the brain. This is a volatile short chain fatty acid. It passes very readily through membranes which produced in the gastrointestinal tract, goes into the body, which circulates in the blood goes readily into the brain. One of the systemic effects of butyrate is an inhibitor of an enzyme called histone deacetylase. Histone deacetylase inhibits certain genes and it has been shown that in the brain the presence of butyrate activates some quiescent genes, in particular a gene that's involved in producing a protein called brain derived neurotrophic factor (BDNF), which is really important for recovery of neurons from damage and injury it also (75). Activates various complexes on cells called G protein coupled receptors. Some of them are only activated by butyrate, and they have important effects in regulating immune responses and inflammation. So the steps to be taken toward reversing gut bacterial dysbiosis among people with long COVID-19 from a dietary perspective, the science would suggest a high fiber polyphenol rich diet. That increases butyrate secretion production. It increases the growth of Faecalibacterium prausnitzii. The research criteria and adherence to a Mediterranean type diet was also shown to elevate faecal levels of faecal bacterium presidency. Bacteria called Enterococcus fetalis that's associated with worse outcomes in people hospitalized with COVID-19. Resveratrol serves as a significant stimulant to produce gamma interferon, contributing to the cytokine storm observed in acute COVID-19.

A study report focused on adults with allergies investigated the efficacy of Bacillus coagulans, a soil-derived organism. In particular strain GB 130, which was studied in elderly people and found to decrease inflammatory markers like C reactive protein (76). This is a study that just came out on Ruminococcus Navis, and higher levels of Ruminococcus gnavus was associated with an increased risk of long COVID-19 and converts tryptophane and essential amino acid to tryptamine. On a mean that has that promotes migraine headaches and migraine phenomena and migraine type phenomena play an important role in the physiology of neuropathic (77).

Recent studies have shown that disrupted intestinal microorganism balance, such as bacteria, fungi, and viruses, can lead to fatty liver and cirrhosis. The structure of the intestinal microbiota may vary depending on age, gender, race, hormonal status, and nutrition. The microbiota is responsible for the digestion of carbohydrates, balancing bile acids, maintaining the integrity of the intestinal barrier against harmful microbes, supporting the immune system, and vitamin synthesis. Therefore, the most basic way to keep the liver healthy depends on the balance of the intestinal microflora. Disrupted microbiota balance in the intestine leads to inflammatory bowel diseases, colon cancer, cardiovascular diseases, and obesity. Fatty liver, liver inflammation, liver cirrhosis, and cancer are among these diseases. Studies have reported that the rate of beneficial bacteria in the stool of patients with cirrhosis of the liver is low, and the rate of harmful bacteria is high (78).

The mechanisms by which the disrupted intestinal microbiota caused by COVID-19 affects the liver can be listed as follows:

The intestine and liver are organs that are closely related to each other. Blood returning to the heart from the intestines first passes through the liver. The liver is frequently exposed to bacterial waste in the intestine. For this reason, a healthy intestine is essential for a healthy liver. When intestinal permeability is impaired as a result of the change in the microbiota, the antigens in the endotoxin structure of the bacteria come to the liver before the blood circulation. Thus, toxins initiate damage to the liver (79).

Bile acids ensure the maintenance of bacterial balance.

Food and waste materials absorbed from the intestines are also processed in the liver. The liver secretes bile acids in the bile it produces into the intestines. Bile acids, which are responsible for the absorption of fats in the intestines, are changed by the microbiota. Bile acids also protect against excessive bacterial growth in the intestines and increased intestinal permeability. Bile acids and bacteria constantly balance each other. Disruption of this balance leads to diseases in the liver (80).

Another reason for the negative effect of disrupted microbiota on the liver is the deterioration in choline metabolism. Choline is required to remove Very Low-Density Lipoprotein, a type of cholesterol, from the liver. Choline metabolism occurs in the intestine and is affected by the disruption of the microbiota. In this case, triglycerides that cannot be removed from the liver may lead to fatty liver (81,82,83,84).

Due to the close relationship between the liver and intestine, disruption of the intestinal microbiota also disrupts liver functions, and because of insulin resistance, fatty tissue, and inflammation develop in the liver. In such cases, it has been reported that by regulating the patient's diet and giving 2-3 months of treatments containing prebiotics and probiotics, the intestinal flora and intestinal permeability are improved, and there is an improvement in liver enzymes and fatness (85,86,87). Experiments investigating the relationship between microbiota and liver diseases have started in the last 10 years and are continuing.

Based on the study findings, this interaction in the gut microbiota shows us that there is an area we need to investigate against COVID-19 disease (88,89). Studies conducted for many years explain that the signalling pathways in the intestinal system are related to the brain. On the other hand, we can keep the most basic organs of our body, such as the liver, alive to the extent that we make the digestive system healthy. Therefore, the healthier we keep the digestive system, the better we can keep the liver health. As a result of the study, it was understood that our digestive system is the most important auxiliary element of our brain. Future studies should reveal the basic pathways of this communication.

Conflict of interest
The authors declare no conflicts of interest.

Authors' contributions
Concept: K.Ö., Ş.D., Design: K.Ö., Ş.D., Data Collection or Processing: K.Ö., Analysis or Interpretation: K.Ö., Ş.D., Literature Search: K.Ö., Ş.D., Writing: K.Ö., Ş.D.

References

1. Matijašić M., Meštrović T., Paljetak HČ, Perić M, Barešić A. & Verbanac D. (2020). Gut Microbiota beyond Bacteria-Mycobiome, Virome, Archaeome, and Eukaryotic Parasites in IBD. International journal of molecular sciences, 11;21(8):2668. https://doi.org/ 10.3390/ijms21082668

2. Vemuri R., Shankar E.M., Chieppa M., Eri R. & Kavanagh K. (2020). Beyond Just Bacteria: Functional Biomes in the Gut Ecosystem Including Virome, Mycobiome, Archaeome and Helminths. Microorganisms, 8(4):483. https://doi.org/ 10.3390/microorganisms8040483

3. Davis C.D. (2016). The Gut Microbiome and Its Role in Obesity. Nutrition today, 51(4):167-174. https://doi.org/ 10.1097/NT.0000000000000167

4. Tomasello G., Mazzola M., Jurjus A., Cappello F., Carini F. & Damiani P. (2017). The fingerprint of the human gastrointestinal tract microbiota: a hypothesis of molecular mapping. Journal of Biological Regulators and Homeostatic Agents, 31(1):245-249. https://doi.org/ 28337900

5. Dill-McFarland K.A., Tang Z.Z., Kemis J.H., Kerby R.L., Chen G. & Palloni A. (2019). Close social relationships correlate with human gut microbiota composition. Scientific reports, 24;9(1):703. https://doi.org/ 10.1038/s41598-018-37298-9

6. Rees T., Bosch T. & Douglas A.E. (2018). How the microbiome challenges our concept of self. PLoS Biology, 9;16(2):e2005358. https://doi.org/ 10.1371/journal.pbio.2005358

7. Conlon M.A. & Bird A.R. (2014). The impact of diet and lifestyle on gut microbiota and human health. Nutrients, 24;7(1):17-44. https://doi.org/ 10.3390/nu7010017

8. Krajmalnik-Brown R., Ilhan Z.E., Kang D.W. & DiBaise J.K. (2012). Effects of gut microbes on nutrient absorption and energy regulation. Nutrition in Clinical Practice, 27(2):201-14. https://doi.org/ 10.1177/0884533611436116

9. Morowitz M.J., Carlisle E.M. & Alverdy J.C. (2011). Contributions of intestinal bacteria to nutrition and metabolism in the critically ill. Surgical oncology clinics of North America, 91(4):771-85, https://doi.org/ 10.1016/j.suc.2011.05.001

10. Clapp M., Aurora N., Herrera L., Bhatia M., Wilen E. & Wakefield S. (2017). Gut microbiota's effect on mental health: The gut-brain axis. International journal of clinical practice. 15;7(4):987. https://doi.org/ 10.4081/cp.2017.987

11. Butler M.I., Mörkl S., Sandhu K.V., Cryan J.F. & Dinan T.G. (2019). The Gut Microbiome and Mental Health: What Should We Tell Our Patients?: Le microbiote Intestinal et la Santé Mentale : que Devrions-Nous dire à nos Patients? The Canadian Journal of Psychiatry, 64(11):747-760. https://doi.org/ 10.1177/0706743719874168

12. Taylor V.H. (2019). The microbiome and mental health: Hope or hype? Journal of Psychiatry and Neuroscience, 1;44(4):219-222. https://doi.org/ 10.1503/jpn.190110

13. Dantzer R. (2018). Neuroimmune Interactions: From the Brain to the Immune System and Vice Versa. Physiological reviews, 1;98(1):477-504. https://doi.org/ 10.1152/physrev.00039.2016

14. Rivest S. (2009). Regulation of innate immune responses in the brain. Nature reviews immunology, 9(6):429-39. https://doi.org/ 10.1038/nri2565

15. Hanke M.L. & Kielian T. (2011). Toll-like receptors in health and disease in the brain: mechanisms and therapeutic potential. Clinical science, 121(9):367-87. https://doi.org/ 10.1042/CS20110164

16. Nobel Y.R., Phipps M. & Verna E.C. (2021). COVID-19 and Effect on Liver Transplant. Current treatment options in gastroenterology,19(3):483-499. https://doi.org/ 10.1007/s11938-

021-00355-w

17. Choudhary N.S., Dhampalwar S., Saraf N. & Soin A.S. (2021). Outcomes of COVID-19 in Patients with Cirrhosis or Liver Transplantation. Journal of Clinical and Experimental Hepatology, 11(6):713-719. https://doi.org/ 10.1016/j.jceh.2021.05.003

18. Schult D., Reitmeier S., Koyumdzhieva P., Lahmer T., Middelhoff M. & Erber J. (2022). Gut bacterial dysbiosis and instability is associated with the onset of complications and mortality in COVID-19. Gut Microbes, 14(1):2031840. https://doi.org/ 10.1080/19490976.2022.2031840

19. Cheemerla S. & Balakrishnan M. (2021). Global Epidemiology of Chronic Liver Disease. Clin Liver Dis (Hoboken), 4;17(5):365-370. https://doi.org/ 10.1002/cld.1061

20. Mallet V., Beeker N., Bouam S., Sogni P. & Pol S. (2021). Demosthenes research group. Prognosis of French COVID-19 patients with chronic liver disease: A national retrospective cohort study for 2020. Journal of hepatology, 75(4):848-855. https://doi.org/ 10.1016/j.jhep.2021.04.052

21. Chadalavada P., Padbidri V., Garg R., Alomari M., Babar A., Kewan T. Et al. (2020). Transaminases are Potential Biomarkers of Disease Severity in COVID-19 Patients: A Single-Center Experience. Cureus, 18;12(11):e11555. https://doi.org/ 10.7759/cureus.11555

22. Kaneko S., Kurosaki M., Nagata K., Taki R., Ueda K. & Hanada S. (2020). Liver injury with COVID-19 based on gastrointestinal symptoms and pneumonia severity. PLoS One, 4;15(11):e0241663. https://doi.org/ 10.1371/journal.pone.0241663

23. Pott-Junior H., Bittencourt N.Q.P., Chacha S.F.G., Luporini R.L., Cominetti M.R. & Anibal F.F. (2021). Elevations in Liver Transaminases in COVID-19: (How) Are They Related? Frontiers of medicine, 15;8:705247. https://doi.org/ 10.3389/fmed.2021.705247

24. Schnabl B. & Brenner D.A. Interactions between the intestinal microbiome and liver diseases. Gastroenterology, 146(6):1513-24. https://doi.org/ 10.1053/j.gastro.2014.01.020

25. Belkaid Y. & Hand T.W. (2014). Role of the microbiota in immunity and inflammation. Cell, 27;157(1):121-41. https://doi.org/ 10.1016/j.cell.2014.03.011

26. Newsome R.C., Gauthier J., Hernandez M.C., Abraham G.E., Robinson T.O., Williams H.B. Et al. (2021). The gut microbiome of COVID-19 recovered patients returns to uninfected status in a minority-dominated United States cohort. Gut Microbes, 13(1):1-15. https://doi.org/10.1080/19490976.2021.1926840

27. Carabotti M., Scirocco A., Maselli M.A. & Severi C. (2015). The gut-brain axis: interactions between enteric microbiota, central and enteric nervous systems. Annals of gastroenterology, 28(2):203-209. https://doi.org/ 25830558

28. Martin C.R., Osadchiy V., Kalani A. & Mayer E.A. (2018). The Brain-Gut-Microbiome Axis. Cellular and Molecular Gastroenterology and Hepatology, 12;6(2):133-148. https://doi.org/ 10.1016/j.jcmgh.2018.04.003

29. Fung T.C., Olson C.A. & Hsiao E.Y. (2017). Interactions between the microbiota, immune and nervous systems in health and disease. Nature neuroscience, 20(2):145-155. https://doi.org/ 10.1038/nn.4476

30. Wang Y. & Kasper L.H. (2014). The role of microbiome in central nervous system disorders. Brain, Behavior, and Immunity, 38:1-12. https://doi.org/ 10.1016/j.bbi.2013.12.015

31. Maeda Y., Motooka D., Kawasaki T., Oki H., Noda Y. & Adachi

Y. (2022). Longitudinal alterations of the gut mycobiota and microbiota on COVID-19 severity. BMC infectious diseases, 24;22(1):572. https://doi.org/ 10.1186/s12879-022-07358-7

32. Galland L. (2014). The gut microbiome and the brain. Journal of medicinal food. 17(12):1261-72. https://doi.org/ 10.1089/jmf.2014.7000

33. Madison A. & Kiecolt-Glaser J.K. (2019). Stress, depression, diet, and the gut microbiota: human-bacteria interactions at the core of psychoneuroimmunology and nutrition. Current Opinion in Behavioral Sciences, 28:105-110. https://doi.org/ 10.1016/j.cobeha.2019.01.011

34. Napolitano M. & Covasa M. (2020). Microbiota Transplant in the Treatment of Obesity and Diabetes: Current and Future Perspectives. Frontiers in microbiology, 12;11:590370. https://doi.org/ 10.3389/fmicb.2020.590370

35. Chinna Meyyappan A., Forth E., Wallace C.J.K. & Milev R. (2020). Effect of fecal microbiota transplant on symptoms of psychiatric disorders: a systematic review. BMC Psychiatry, 15;20(1):299. https://doi.org/ 10.1186/s12888-020-02654-5

36. Sharon G., Sampson T.R., Geschwind D.H. & Mazmanian S.K. (2016). The Central Nervous System and the Gut Microbiome. Cell, 3;167(4):915-932. https://doi.org/ 10.1016/j.cell.2016.10.027

37. Wiertsema S.P., van Bergenhenegouwen J., Garssen J. & Knippels L.M.J. (2021). The Interplay between the Gut Microbiome and the Immune System in the Context of Infectious Diseases throughout Life and the Role of Nutrition in Optimizing Treatment Strategies. Nutrients, 13(3):886. https://doi.org/ 10.3390/nu13030886

38. Kho Z.Y. & Lal SK. (2018). The Human Gut Microbiome - A Potential Controller of Wellness and Disease. Frontiers in microbiology, 14;9:1835. https://doi.org/ 10.3389/fmicb.2018.01835

39. Martin A.M., Sun E.W., Rogers G.B. & Keating D.J. (2019). The Influence of the Gut Microbiome on Host Metabolism Through the Regulation of Gut Hormone Release. Frontiers in Physiology, 16;10:428. https://doi.org/ 10.3389/fphys.2019.00428

40. Gilbert J.A., Blaser MJ, Caporaso JG, Jansson JK, Lynch SV & Knight R. (2018). Current understanding of the human microbiome. Nature medicine, 10;24(4):392-400. https://doi.org/ 10.1038/nm.4517

41. Conlon M.A. & Bird A.R. (2014). The impact of diet and lifestyle on gut microbiota and human health. Nutrients, 24;7(1):17-44. https://doi.org/ 10.3390/nu7010017

42. Kelly S.A., Nzakizwanayo J., Rodgers A.M., Zhao L., Weiser R. & Tekko I.A. (2021). Antibiotic Therapy and the Gut Microbiome: Investigating the Effect of Delivery Route on Gut Pathogens. ACS infectious diseases, 14;7(5):1283-1296. https://doi.org/ 10.1021/acsinfecdis.1c00081

43. Ramirez J., Guarner F., Bustos Fernandez L., Maruy A., Sdepanian V.L. & Cohen H. (2020). Antibiotics as Major Disruptors of Gut Microbiota. Frontiers in cellular and infection microbiology, 24;10:572912. https://doi.org/ 10.3389/fcimb.2020.572912

44. Ceccarelli G., Borrazzo C., Pinacchio C., Santinelli L., Innocenti G.P., Cavallari E.N. et al. (2021). Oral Bacteriotherapy in Patients With COVID-19: A Retrospective Cohort Study. Frontiers in Nutrition, 11;7:613928. https://doi.org/ 10.3389/fnut.2020.613928

45. Looft T. & Allen H.K. (2012). Collateral effects of antibiotics on mammalian gut microbiomes. Gut Microbes, 3(5):463-7. https://doi.org/ 10.4161/gmic.21288

46. Khlevner J., Park Y. & Margolis K.G. (2018). Brain-Gut Axis: Clinical Implications. Gastrointestinal endoscopy clinics of North America, 47(4):727-739. https://doi.org/ 10.1016/j.gtc.2018.07.002

47. Sasselli V., Pachnis V. & Burns A.J. (2012). The enteric nervous system. (2014). Dev Biol, 366(1): 64-73. https://doi.org/ 10.1016/j.ydbio.2012.01.012

48. Furness J.B., Callaghan B.P., Rivera L.R. & Cho H.J. (2014). The enteric nervous system and gastrointestinal innervation: integrated local and central control. Advances in Experimental Medicine and Biology, 817:39-71. https://doi.org/ 10.1007/978-1-4939-0897-4_3

49. Li J.H., Duan R., Li L., Wood J.D., Wang X.Y. & Shu Y. [Unique characteristics of "the second brain" - The enteric nervous system]. Sheng Li Xue Bao, 2020 Jun 25;72(3):382-390. https://doi.org/ 10.3389/fnagi.2021.698988

50. Arneth B.M. (2018). Gut-brain axis biochemical signalling from the gastrointestinal tract to the central nervous system: gut dysbiosis and altered brain function. Postgraduate medical journal, 94(1114):446-452. https://doi.org/ 10.1136/postgradmedj-2017-135424

51. D'Agata A.L., Wu J., Welandawe MKV, Dutra SVO, Kane B & Groer MW. (2019). Effects of early life NICU stress on the developing gut microbiome. Developmental psychobiology. 61(5):650-660. https://doi.org/ 10.1002/dev.21826

52. Shen H.H. News Feature: Microbes on the mind. (2015). The Proceedings of the National Academy of Sciences, 28;112(30):9143-5. https://doi.org/ 10.1073/pnas.1509590112

53. Gutiérrez-Castrellón P., Gandara-Martí T., Abreu A.T., Nieto-Rufino C.D., López-Orduña E. & Jiménez-Escobar I. (2022). Probiotic improves symptomatic and viral clearance in COVID19 outpatients: a randomized, quadruple-blinded, placebo-controlled trial. Gut Microbes, 14(1):2018899. https://doi.org/ 10.1080/19490976.2021.2018899.

54. Bathina S. & Das U.N. (2015). Brain-derived neurotrophic factor and its clinical implications. Archives of medical sciences, 10;11(6):1164-78. https://doi.org/ 10.5114/aoms.2015.56342

55. Binder D.K. & Scharfman H.E. (2004). Brain-derived neurotrophic factor. Growth Factors, 22(3):123-31. https://doi.org/ 10.1080/08977190410001723308

56. Rodriguez D.M., Benninghoff A.D., Aardema N.D.J., Phatak S. & Hintze K.J. (2019). Basal Diet Determined Long-Term Composition of the Gut Microbiome and Mouse Phenotype to a Greater Extent than Fecal Microbiome Transfer from Lean or Obese Human Donors. Nutrients, 17;11(7):1630. https://doi.org/ 10.3390/nu11071630

57. Luo Y., Zeng B., Zeng L., Du X., Li B. & Huo R. (2018). Gut microbiota regulates mouse behaviors through glucocorticoid receptor pathway genes in the hippocampus. Translational psychiatry, 7;8(1):187. https://doi.org/ 10.1038/s41398-018-0240-5

58. Argou-Cardozo I. & Zeidán-Chuliá (2018). F. Clostridium Bacteria and Autism Spectrum Conditions: A Systematic Review and Hypothetical Contribution of Environmental Glyphosate Levels. Medical Sciences, 4;6(2):29. https://doi.org/10.3390/medsci6020029

59. Wasilewska J. & Klukowski M. (2015). Gastrointestinal symptoms and autism spectrum disorder: links and risks- a possible new overlap syndrome. Pediatric Health, Medicine and Therapeutics, 6:153-166. https://doi.org/ 10.2147/PHMT.S85717

60. Dunn A.B., Jordan S., Baker B.J. & Carlson N.S. (2017). The Maternal Infant Microbiome: Considerations for Labor and Birth.

MCN The American Journal of Maternal Child Nursing, 42(6):318-325. https://doi.org/ 10.1097/NMC.0000000000000373

61. Suganya K. & Koo B.S. (2020). Gut-Brain Axis: Role of Gut Microbiota on Neurological Disorders and How Probiotics/Prebiotics Beneficially Modulate Microbial and Immune Pathways to Improve Brain Functions. International journal of molecular sciences, 21(20):7551. https://doi.org/ 10.3390/ijms21207551

62. Chowdhury M.A., Hossain N., Kashem M.A., Shahid M.A. & Alam A. (2020). Immune response in COVID-19: A review. Journal of infection prevention, 13(11):1619-1629. https://doi.org/ 10.1016/j.jiph.2020.07.001

63. Farsi Y., Tahvildari A., Arbabi M., Vazife F., Sechi L.A. & Shahidi Bonjar A.H. (2022). Diagnostic, Prognostic, and Therapeutic Roles of Gut Microbiota in COVID-19: A Comprehensive Systematic Review. Frontiers in cellular and infection microbiology, 4;12:804644. https://doi.org/ 10.3389/fcimb.2022.804644

64. Gagliardi A., Totino V., Cacciotti F., Iebba V., Neroni B. & Bonfiglio G. (2018). Rebuilding the Gut Microbiota Ecosystem. International journal of environmental health research, 7;15(8):1679. https://doi.org/ 10.3390/ijerph15081679

65. Sun Z., Song Z.G., Liu C., Tan S., Lin S., Zhu J. Et al. (2022). Gut microbiome alterations and gut barrier dysfunction are associated with host immune homeostasis in COVID-19 patients. BMC Medicine, 20;20(1):24. https://doi.org/ 10.1186/s12916-021-02212-0

66. Somsouk M., Estes J.D., Deleage C., Dunham R.M., Albright R. & Inadomi J.M. (2015). Gut epithelial barrier and systemic inflammation during chronic HIV infection. AIDS, 29(1):43-51. https://doi.org/ 10.1097/QAD.0000000000000511

67. Gold J.E., Okyay R.A., Licht W.E. & Hurley D.J. (2021). Investigation of Long COVID Prevalence and Its Relationship to Epstein-Barr Virus Reactivation. Pathogens, 17;10(6):763. https://doi.org/ 10.3390/pathogens10060763

68. Carvalho T., Krammer F. & Iwasaki A. (2021). The first 12 months of COVID-19: a timeline of immunological insights. Nature reviews Immunology, 21(4):245-256. https://doi.org/ 10.1038/s41577-021-00522-1

69. D'Andrea G. (2015). Quercetin: A flavonol with multifaceted therapeutic applications? Fitoterapia, 106:256-71. https://doi.org/ 10.1016/j.fitote.2015.09.018

70. Górski A., Międzybrodzki R., Żaczek M. & Borysowski J. (2020). Phages in the fight against COVID-19? Future Microbiol, 15:1095-1100. https://doi.org/ 10.2217/fmb-2020-0082

71. Sharma J.N., Al-Omran A. & Parvathy S.S. (2007). Role of nitric oxide in inflammatory diseases. Inflammopharmacology, 15(6):252-9. https://doi.org/ 10.1007/s10787-007-0013-x

72. Vázquez-Torres A. & Bäumler A.J. (2016). Nitrate, nitrite and nitric oxide reductases: from the last universal common ancestor to modern bacterial pathogens. Current Opinion in Microbiology, 29:1-8. https://doi.org/ 10.1016/j.mib.2015.09.002

73. Thota R.N., Acharya S.H. & Garg M.L. (2019). Curcumin and/or omega-3 polyunsaturated fatty acids supplementation reduces insulin resistance and blood lipids in individuals with high risk of type 2 diabetes: a randomised controlled trial. Lipids in Health and Disease, 18(1):31. https://doi.org/ 10.1186/s12944-019-0967-x

74. Davie J.R. (2003). Inhibition of histone deacetylase activity by butyrate. The Journal of Nutrition, 133(7 Suppl):2485S-2493S. https://doi.org/ 10.1093/jn/133.7.2485S

75. Wei Y. & Melas P.A. Wegener G, Mathé A.A., Lavebratt C. (2014). Antidepressant-like effect of sodium butyrate is associated with an increase in TET1 and in 5-hydroxymethylation levels in the Bdnf gene. International Journal of Neuropsychopharmacology, 31;18(2). https://doi.org/ 10.1093/ijnp/pyu032

76. Madempudi R.S., Ahire JJ, Neelamraju J, Tripathi A. & Nanal S. (2019). Randomized clinical trial: the effect of probiotic Bacillus coagulans Unique IS2 vs. placebo on the symptoms management of irritable bowel syndrome in adults. Scientific reports, 21;9(1):12210. https://doi.org/ 10.1038/s41598-019-48554-x

77. Liu Q., Mak J.W.Y., Su Q., Yeoh Y.K., Lui G.C. & Ng S.S.S. (2022). Gut microbiota dynamics in a prospective cohort of patients with post-acute COVID-19 syndrome. Gut, 71(3):544-552. https://doi.org/ 10.1136/gutjnl-2021-325989

78. Hrncir T. (2022). Gut Microbiota Dysbiosis: Triggers, Consequences, Diagnostic and Therapeutic Options. Microorganisms. 10(3):578-643. doi: 10.3390/microorganisms10030578.

79. Tilg H, Adolph TE, Trauner M (2022). Gut-liver axis: Pathophysiological concepts and clinical implications. Microorganism. 34(11):1700-1718. doi: 10.1016/j.cmet.2022.09.017.

80. An C, Chon H, Ku W, Eom S, Seok M, Kim S et al., (2022). Bile Acids: Major Regulator of the Gut Microbiome. Microorganisms. 10(9):1792. doi: 10.3390/microorganisms10091792.

81. Arias N, Arboleya S, Allison J, Kaliszewska A, Higarza SG, Gueimonde M et al., (2020). The Relationship between Choline Bioavailability from Diet, Intestinal Microbiota Composition, and Its Modulation of Human Diseases. Nutrients. 12(8):2340. doi: 10.3390/nu12082340.

82. Latif A, Shehzad A, Niazi S, Zahid A, Ashraf W, Iqbal MW et al., (2023). Probiotics: mechanism of action, health benefits and their application in food industries. Frontiers in Microbiology. 14(1): 21-67. doi: 10.3389/fmicb.2023.1216674.

83. Bax L., Yu L.M., Ikeda N & Moons KGA. (2007). systematic comparison of software dedicated to meta-analysis of causal studies. BMC medical research methodology, 10;7:40. https://doi.org/ 10.1186/1471-2288-7-40

84. Chelakkot C., Ghim J. & Ryu S.H. (2018). Mechanisms regulating intestinal barrier integrity and its pathological implications. Experimental and Molecular Medicine, 16;50(8):1-9. https://doi.org/ 10.1038/s12276-018-0126-x

85. Chowdhury M.A., Hossain N., Kashem M.A., Shahid M.A. & Alam A. (2020). Immune response in COVID-19: A review. Journal of infection prevention, 13(11):1619-1629. https://doi.org/ 10.1016/j.jiph.2020.07.001

86. Dill-McFarland K.A., Tang Z.Z., Kemis J.H., Kerby R.L., Chen G. & Palloni A. (2019). Close social relationships correlate with human gut microbiota composition. Scientific reports, 24;9(1):703. https://doi.org/ 10.1038/s41598-018-37298-9

87. Jin X., Lian J.S., Hu J.H., Gao J., Zheng L. & Zhang Y.M. (2020). Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut, 69(6):1002-1009. https://doi.org/ 10.1136/gutjnl-2020-320926

88. Suárez-Reyes A. & Villegas-Valverde C.A. (2021). Implications of Low-grade Inflammation in SARS-CoV-2 Immunopathology. MEDICC Review, 23(2):42. https://doi.org/ 10.37757/MR2021.V23.N2.4

89. Yeoh Y.K., Zuo T., Lui G.C., Zhang F. & Liu Q. (2021). Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19. Gut, 70(4):698-706. https://doi.org/10.1136/gutjnl-2020-323020