IJPSR (2021), Volume 12, Issue 1 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 25 August 2020; received in revised form, 09 December 2020; accepted, 24 December 2020; published 01 January 2021

GUT-MICROBIOME MANAGEMENT: AN ISSUE WORTH CONSIDERING IN COVID-19 TREATMENT

Shahnaz Sultana [1], Ashfaque Hossain [2] and Muhammad Manjurul Karim [*3]

Institute of National Analytical Research and Services (INARS) [1], Bangladesh Council of Scientific and Industrial Research (BCSIR), Dr. Qudrat-I-Khuda Road, New Elephant Rd, Dhaka 1205, Bangladesh.
Department of Medical Microbiology and Immunology [2], Ras Al Khaimah Medical and Health Sciences University, Ras Al Khaimah, United Arab Emirates.
Department of Microbiology [3], University of Dhaka, Dhaka 1000, Bangladesh.

Keywords:

COVID-19, Gut-dysbiosis, Co-morbidities, Prebiotics, Probiotics

Correspondence to Author:
Muhammad Manjurul Karim

Professor,
Department of Microbiology,
University of Dhaka, Dhaka 1000,
Bangladesh.

E-mail: manjur@du.ac.bd

ABSTRACT: The human gut is colonized by an inherent group of microorganisms that cohabits with us and plays a critical role in maintaining homeostasis. Evidence is being piled up, showing the roles of gut micro-flora in the severity and consequences of COVID-19. The gut-lung cross talk is thought to mediate this outcome resulting in an alteration of gut-microbiome, a phenomenon known as gut-dysbiosis during the progression of SARS-CoV-2 infection. A destabilization of gut-microbial homeostasis can upset the host immune system causing critical outcomes in COVID-19 patients with preexisting co-morbidities like CVD and diabetes. This review underlies the interaction between gut micro-flora and SARS-CoV-2 infection and the consequent clinical risk factors. While we are still in the hunt for effective medication and vaccine, the administration of prebiotics along with probiotics as a prophylactic treatment for the management of patients with COVID-19 could help reduce the pro-inflammatory state leading to the new insights of novel safeguard.

INTRODUCTION: The COVID-19 pandemic, after spreading to 213 countries and territories around the world and 2 international conveyances, has taken the lives of almost 749,868 people as of August 13, 2020 [1]. Showing the highest mortality rate of <4% in some countries [2], this viral infection has been found to strike some particular patients more seriously than others. Different variables are suspected of playing a combined role that makes the disease outcome highly unpredictable.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(1).1-7

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(1).1-7

Many reports suggest that the composition of the gut-microbiome could partially explain the difference in susceptibility and severity with the other clinical outcomes like cardiovascular diseases (CVD) and type 2 diabetes (T2D). This adds a new dimension to what is currently known about the disease.

SARS-CoV-2 Affects Gut: Apparently, the linkage of acute respiratory disease-causing SARS-CoV-2 and the gut might seem improbable. However, recent studies revealed that Covid-19 caused gastrointestinal (GI) symptoms, such as nausea, vomiting, and diarrhea in 3.34 to 11.40% of the critically ill patients [3, 4]. Moreover, the detection of viral RNA and live viruses in stool samples provides a subtle suggestion about the

capacity of SARS-CoV-2 to infect and replicate in the gut [5]. Another link between the new coronavirus and the gut involves the presence of the viral entry point into host cells, Angiotensin-converting enzyme 2 (ACE-2), in the GI tract, including epithelial cells of oral mucosa [6], which has been assumed to cause intestinal inflammation by infecting intestinal epithelial cells and inducing proinflammatory chemokine and cytokine release [7]. This suggests a presumption of SARS-CoV-2 infection getting involved with the gut-microbiome therein because the shape of the gut-microbiome partly depends on the host's gut physiology, and vice-versa.

Gut-Lung Axis: The gut-microbiome containing bacteria, fungi (yeast), viruses, and protozoa, is the community of microorganisms living inside the GI tract, mostly in the large bowel. Human gut-microbiota consists of around 10 [14] resident microorganisms, which contribute to maintaining a balanced ecosystem as well as the immune system [8]. Several studies have demonstrated that lung infections are related to the alteration of gut-microbiota composition [9], supporting the eminent 'gut-lung axis' theory. This describes a cross-talk relationship between gut micro-flora and the lungs where the endotoxins and microbial metabolites of gut micro-flora can affect the lung through blood, and once inflammation occurs in the lung, it can alter the gut micro-flora conversely [10]. One study on sub-lethally infected mice with influenza virus measured the production of short-chain fatty acids (SCFAs), one of the major metabolites in the gut that regulates the composition of the gut microbiota and the associated functionality like metabolic activity [11]. They found that the SCFAs concentration, including acetate (the predominant SCFA), propionate, and butyrate was lower relative to non-infected mice. This report explains how influenza infection alters the metabolic output of the gut-microbiota and affects gut and blood concentration of SCFAs, a significant group of dietary derived metabolites endowed with a modulatory role on immune functions [12], host-microbe signaling, energy utilization, and control of colonic pH [12]. Such conditions, where the balance of gut-microbiome gets disrupted, a condition referred to as dysbiosis, results in various metabolic disorders manifested as diabetes and obesity [13], and enhanced susceptibility to secondary enteric infections [14]. Interestingly, severe COVID-19 disease is associated with the same consequences [15].

SARS-CoV-2 and Gut-Microbiome: Reports claim that gut-dysbiosis due to lung injury could further enfeeble lung immunity [16]. As gut bacteria are significantly involved in regulating the immune cells through pro- and anti-inflammatory responses, changes in the gut-microbial composition because of lung infection may affect the susceptibility and severity of various diseases [16]. An experiment on mice, devoid of their intestinal microbiota, noted their disability for pathogen clearance in the lung [17]. A similar report by Enaud *et al*., revealed that germ-free mice lacking gut-microbiota were more prone to death from lung infections [18]. This indicates the causal relation of the gut microbiome and the risk of developing COVID-19 and *vice-versa* due to the gut-lung axis. Supporting to this possibility, a recent report claims that Covid-19 patients harbor altered gut flora devoid of health-beneficial species and supporting the growth of opportunistic pathogens compared to healthy controls [8].

Gut-microbial Composition in COVID-19 Patients and its Clinical Outcome: A growing body of data suggests that exaggerated immune response and the massive release of pro-inflammatory cytokines (such as-IL-1, IL-2, IL-7, G-CSF, IP-10, MCP-1, MIP-1A, and TNFα) termed as 'cytokine storm' is featured in COVID-19 severe cases [19]. Such inflammation creates possible consequences that increases the gut permeability, and therefore affect the commensal gut-flora [20]. Interestingly, these conditions are evident in elderly patients with chronic co-morbidities like cardio-vascular, metabolic and renal diseases suggesting a significant association of gut-dysbiosis with severe viral infection and poor outcome [21]. Covid-19 patients, similar to other co-morbidities had poor gut-microbiota diversity and levels of butyrate-producers, but supports the growth of opportunistic pathogens, known to cause bacteremia to populate the gut in comparison to healthy controls [22]. David *et al*., revealed *Alistipes onderdonkii* and *Faecali-bacterium prausnitzii* as the two prominent bacteria that are correlated with mild Covid-19 prognosis [23]. While *Alistipes* spp participated in the tryptophan-serotonin metabolism essential for gut homeostasis,

F. prausnitzii, one of the largest butyrate producers in the gut, provided an important anti-inflammatory resource [22]. This study also pinpointed 14 gut bacteria responsible for efficient viral clearance and 4 *Bacteroidetes* species known to lower ACE2 expression in the mice gut, which may have a potential protective role in combating SARS-CoV-2 infection by hampering host entry through ACE2. Another striking finding was noted that, in COVID 19 patients, dysbiosis in the form of decreased microbial diversity and decreased Bacteroidetes to Firmicutes ratio has been observed [24]. This gut-microbiome pattern can be considered as biomarkers to distinguish between the COVID-19 group and healthy controls.

Heart failure has also been associated with specific gut-microbial species such as increased *Escherichia coli*, *Klebsiella pneumoniae*, *and Streptococcus viridans* [25], similar to COVID-19. Likewise, a decrease in genera, including *Bacteroides, Bifidobacterium, Roseburia, Faecalibacterium, Akkermansia, Ruminococcus,* and *Fusobacteriumin* patients gut have been reported in a positive association with T2D [26]. Since patients with co-morbidities progress to serious adverse clinical outcomes in COVID-19, it is therefore tempting to speculate that the gut-dysbiosis in Covid-19 might resemble its related clinical manifestation like CVD and diabetes **Table 1**.

TABLE 1: THE PROFILE OF GUT-MICROBIOME IN COVID-19, CVD AND DIABETES MELLITUS PATIENTS

Conditions	Gut-Microbiome Composition	Reference
COVID-19	*Erysipelotrichaceae bacterium* ↑, *Streptococcus* ↑, *Rothia* ↑, *Veillonella* ↑, *Actinomyces viscosus* ↑, Bacterial diversity↓, *Ruminococcus obeum* ↓, *Fusicatenibacter* ↓, *Anaerostipes* ↓, *Agathobacter* ↓, *Eubacterium hallii* group ↓	27
	Clostridium hathewayi ↑, *Bacteroides nordii* ↑, *Coprobacillus* ↑, *Clostridium ramosum* ↑, the F/B ratios↑, *Alistipes onderdonkii* ↓, *Faecalibacterium prausnitzii* ↓, *Bacteroides dorei*↓, *Bacteroides thetaiotaomicron*↓, *Bacteroides massiliensis* ↓, *Bacteroides ovatus*↓, *Lachnospiraceae bacterium* ↓, *Eubacterium rectal* ↓, *Dorea formicigenerans* ↓	28
CVD	*Prevotella* ↑, the F/B ratios ↑, *Erwinia* ↑, *Corynebacteriaceae* ↑, *Enterobacteriaceae* ↑, *Lactobacillales* ↑, *Campylobacter* ↑, *Candida* ↑, *Shigella* ↑, *Salmonella* ↑, *Yersinia enterocolitica* ↑, Bacterial diversity↓, *Anaerostipes* ↓, *Lactobacillus murinus* ↓, *Bacteroides* ↓	29
	Clostridium ↑, *Atopobium* ↑, *Bifidobacterium* ↑, *Streptococcus* ↑, *Escherichia* ↑, *Faecalibacterium* ↓, *Ruminococcus* ↓, *Prevotella* ↓	30
Diabetes	*Akkermansia muciniphila* ↑, *Bacteroidescaccae* ↑, *Clostridium hathewayi* ↑, *Clostridium ramosum* ↑, *Desulfovibrio* sp ↑, *Eggerthella lenta* ↑	31
	Ruminococcus ↑, *Fusobacterium* ↑, *Blautia* ↑, *Bifidobacterium* ↓, *Bacteroides* ↓, *Faecalibacterium* ↓, *Roseburia*↓	26
Healthy people	*Romboutsia, Faecalibacterium, Fusicatenibacter, Eubacterium hallii*	27
	Eubacterium rectale, Roseburia intestinalis	31
	Bacteroidetes, Firmicutes, *Actinobacteria, Proteobacteria,Verrucomicrobia*	29
	↑bacterial count goes up ↓ bacterial count goes down	

How does the Gut-Microbiome affect the Severity of COVID-19? Gut bacteria like Bacteroidetes and Firmicutes yielding SCFAs can lower serum lipid levels by blocking cholesterol synthesis and/or redirect them to the liver [32]; therefore, they have been suggested as a protective element in Coronary artery disease (CAD) like CVD development. Patients with certain CAD cases [33] and hypertension [34] have been reported to have reduced SCFAs-producing bacteria. T2D is associated with elevated levels of pro-inflammatory cytokines, chemokines, inflammatory proteins and lipopolysaccharides (LPS) responsible for metabolic endotoxemia and low-grade inflammation.

Several reports claim that *Roseburia intestinalis, Bacteroides fragilis, Akkermansia muciniphila, Lactobacillus plantarum* and *L. casei*-induced IL-10 production [35, 36] may improve glucose metabolism, as overexpression of this cytokine is reported to protect muscle from aging-related insulin resistance [37]. *R. intestinalis* in the gut might also increase an anti-inflammatory cytokine production like IL-22 [38], known to restore insulin sensitivity and alleviate diabetes [39].

Various gut bacteria have been found to decrease pro-inflammatory cytokines like IL-1β, Monocyte Chemoattractant Protein-1, Intercellular adhesion molecule-1, IL-8, CD36, C-reactive protein [40], TNF-α [41], IFN-γ [38] and increase anti-inflammatory molecules like NF-kB [42]; that may contribute to metabolism as well as reduce the formation of plaques and blood clots in the arteries [26].

Hypothetically, gut-dysbiosis due to the lung infection with SARS-CoV-2 may also affect a patient's dietary and cardiovascular system, a possible reason that explains the clinical outcome of critical patients with co-morbidities **Fig. 1**.

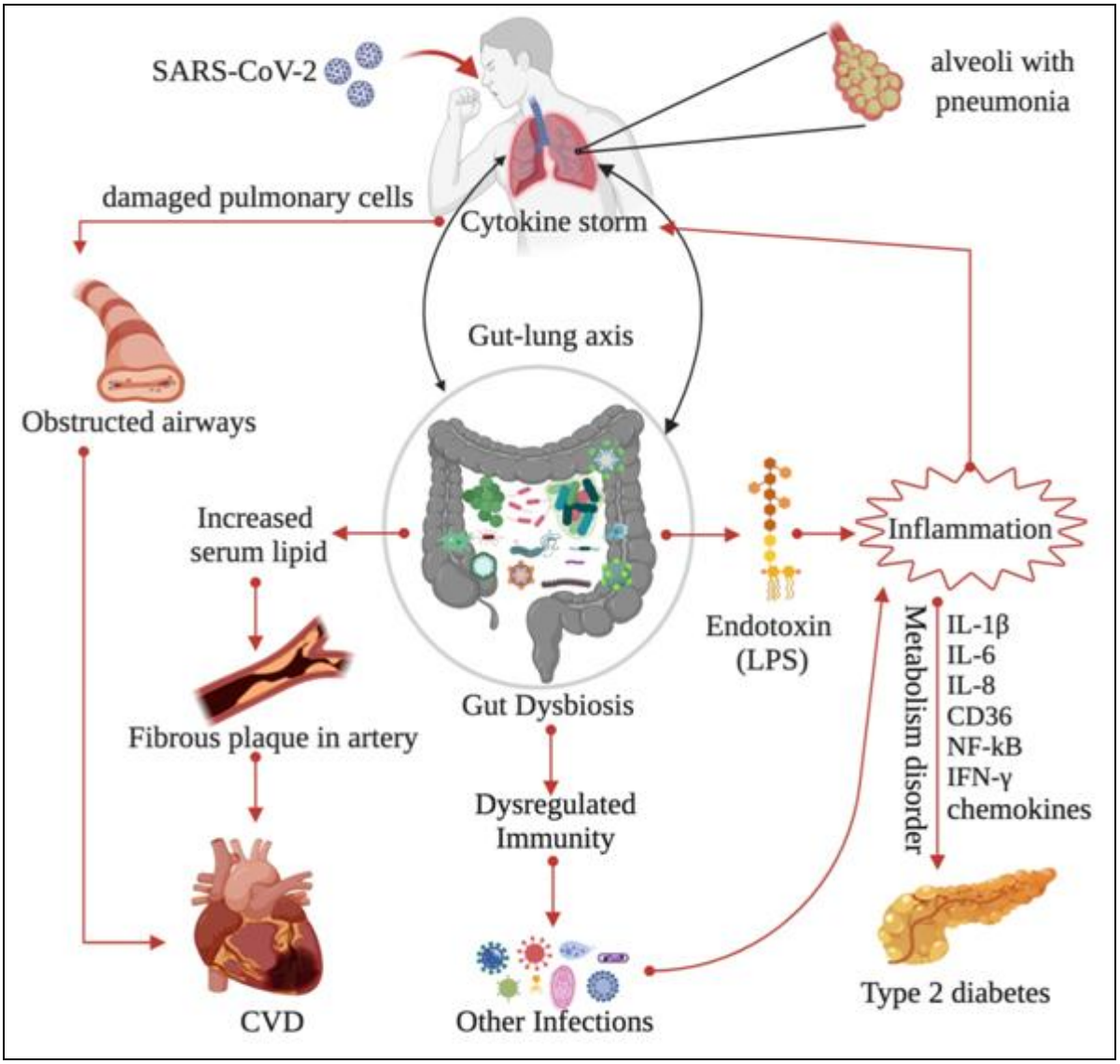

FIG. 1: SARS-COV-2 INFECTION CAUSES 'GUT-DYSBIOSIS' THROUGH GUT-LUNG AXIS AND AFFECTS THE GUT FLORA. CONSEQUENTLY, BENEFICIAL FLORA IS REDUCED WITH THE INCREMENT OF OPPORTUNISTIC PATHOGENS. THEY PRODUCE LIPOPOLYSACCHARIDE (LPS) LEADING TO THE MASSIVE PRODUCTION OF PRO- AND ANTI- INFLAMMATORY MOLECULES. THIS SPURRING INFLAMMATION PROMOTES METABOLIC DISORDERS, TYPE 2 DIABETES, FOR EXAMPLE. ON THE OTHER HAND, SUCH INFLAMMATION MIGHT INDIRECTLY DAMAGE THE PULMONARY CELLS AND CAUSE FURTHER LUNG INFECTION. AGAIN, ALTERED GUT-MICROBIOME INCREASES THE SERUM LIPID CONCENTRATION IN BLOOD, RESULTING IN THE FORMATION OF FIBROUS PLAQUE IN ARTERIES. ALTOGETHER, THE OBSTRUCTED AIRWAYS DUE TO LUNG INFECTION AFFECT THE CARDIAC CONDITIONS. HENCE, ANY INDIVIDUAL WITH SARS-CoV-2 WOULD PROBABLY FACE FURTHER COMPLICATIONS IF THEY HAVE OTHER CO-MORBIDITIES LIKE CVD OR T2D DUE TO ALTERED GUT- MICROFLORA. (ORIGINAL IMAGE HAS BEEN CREATED WITH BIORENDER)

Covid-19 Drug and Gut-Microbiome Connection: Although no certain medication has been approved so far to treat COVID-19 patients, physicians around the world keep prescribing some empirical antibiotics as a concern to counter subsequent bacterial infections. Patients undertaking such antibiotics have been reported to show worse gut-dysbiosis and undesirable altered gut-flora [28]. Supporting their premise, a study on mice revealed that susceptibility to influenza virus gets escalated owing to antibiotics-induced gut-dysbiosis [17]. Another report on mice showed that antibiotics therapy in early life changed gut-flora, which could possibly enhance the risk of allergic airways

diseases in mice [43]. Also, antibiotics-mediated gut-microbiome disorder has been reported to affect the effectiveness of vaccines in humans [44]. All these reports advocate for the cautious use of antibiotics during the infection period of COVID-19 to minimize the possible alteration of gut-flora and to secure the efficacy of vaccines in this crisis [23].

How the Gut-Microbiome might Assist when Fighting COVID-19: The effects of SARS-CoV-2 on other co-morbidities and its possible link to altered gut-microbiota make GI tract a potential target for management of the disease. Administration of prebiotics and probiotics have indicated decreased inflammation during an infection [45], increased SCFAs, improvement of the gut environment, regulation of immune functions, and the prevention of pathogenic infections [46].

Orally administered probiotics have been reported to reduce cholesterol in the blood by 22–33% due to their bile salt hydrolase activity [47]. Probiotics, as immunomodulatory and anti-inflammatory substances, are useful nutritional supplements that show promising effects in respiratory disorders [48]. Two meta-analyses on humans reported efficacy of probiotics in minimizing the incidence and duration of respiratory virus infections [49, 50]. Another study showed that probiotics like *Lactobacillus rhamnosus*, live *Bacillus subtilis*, and *Enterococcus faecalis* could help critically ill patients on mechanical ventilation by developing less ventilator-associated pneumonia [51].

Besides, investigation on mice model showed that introduction of probiotic bacteria like *Lactobacillus rhamnosus*, *Bifidobacterium lactis*, and *B. breve* can down-regulate allergic response [52]. Providing support to this observation, some scientists reported that probiotics, after metabolizing dietary fiber, increase the levels of SCFAs in the blood, which help against allergic inflammation in the lungs and liver without affecting blood glucose [26]. These studies support the base of using probiotics to calm the 'cytokine storm' and slow down the progression of severity in patients with COVID-19.

However, the management of critically ill patients demands more evidence. A balanced diet providing nutrients to the gut-microbes should therefore be prioritized all-time for boosting long time immunity to the lungs to keep it in sound shape.

CONCLUSION: Evidences suggest that a disturbed microbial community in the gut can establish an inflammatory environment that can be exploited by SARS-CoV-2 to augment the fatality of COVID-19 more likely. Therefore, when clinicians prescribe drugs with little anti-COVID-19 data that can be further antagonistic towards the health conditions, probiotic strains documented for gut- microbiome homeostasis could be a part of the regimen to reduce the likely dysbiosis and consequent clinical fragility. Dietary foods, prebiotics, or probiotics can dramatically influence the gut micro-flora, which can rejuvenate the inherent immunity, restore the intestinal mucosa damage during infection, recover the intestinal eubiotic state and attenuate relevant inflammation, thus driving the patients' health in a favorable direction [53]. More research involving the well-reported probiotics and a gut-favoring diet are needed to shed light on the management of the patients to lessen the risk of COVID-19.

Funding: The author(s) received no financial support for the research, authorship, and/or publication of this article.

ACKNOWLEDGEMENT: MMK conceptualized the idea, SS and MMK drafted the manuscript and worked on literature review, AH critically reviewed the manuscript. Financial support from the Dean, Faculty of Biological Sciences, University of Dhaka, Bangladesh is gratefully appreciated that covered partially the publication charges of the article.

CONFLICTS OF INTEREST: Nil

REFERENCES:

1. Worldometer. COVID-19 CORONAVIRUS PANDEMIC. August 13, 2020. Available from: https://www.worldometers.info/coronavirus/.
2. Worldometer. COVID-19 CORONAVIRUS PANDEMIC. August 11, 2020. Available from: https://www.worldometers.info/coronavirus/.
3. Jin X: Epidemiological, clinical and virological characteristics of 74 cases of coronavirus-infected disease 2019 (COVID-19) with gastrointestinal symptoms. Gut 2020; 69(6): 1002-09.
4. Du M: Multiomics evaluation of gastrointestinal and other clinical characteristics of severe acute respiratory syndrome coronavirus 2 and coronavirus disease 2019. Gastroenterology 2020 DOI: 10.1053/j.gastro.2020.03.045.
5. Gu J, Han B and Wang J: COVID-19: gastrointestinal manifestations and potential fecal–oral transmission. Gastroenterology 2020; 158(6): 1518-19.

6. Xu H: High expression of ACE2 receptor of 2019-nCoV on the epithelial cells of oral mucosa. International Journal of Oral Science 2020; 12(1): 1-5.
7. Effenberger M: Faecal calprotectin indicates intestinal inflammation in COVID-19. Gut 2020 DOI: 10.1136/ gutjnl-2020-321388.
8. Dhar D and Mohanty A: Gut microbiota and Covid-19- possible link and implications. Virus Research, 2020; 198018. DOI: 10.1016/j.virusres.2020.198018.
9. Groves HT: Respiratory viral infection alters the gut microbiota by inducing inappetence. Mbio 2020; 11(1): DOI: 10.1128/mBio.03236-19.
10. Dumas A: The role of the lung microbiota and the gut–lung axis in respiratory infectious diseases. Cellular Microbiology 2018; 20(12): p.e12966.
11. Koh A: From dietary fiber to host physiology: short-chain fatty acids as key bacterial metabolites. Cell 2016; 165(6): 1332-45.
12. Musso G, Gambino R and Cassader M: Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. Annual Review of Medicine 2011; 62: 361-80.
13. Koh A and Bäckhed F: From Association to Causality: the Role of the Gut Microbiota and Its Functional Products on Host Metabolism. Molecular Cell, 2020 DOI: 10.1016/ j.molcel.2020.03.005.
14. Deriu E: Influenza virus affects intestinal microbiota and secondary salmonella infection in the gut through type I interferons. PLoS Pathogens 2016; 12(5): e1005572.
15. Jordan RE, Adab P and Cheng K: Covid-19: risk factors for severe disease and death. 2020, British Medical Journal Publishing Group DOI: 10.1136/bmj.m1198
16. Negi S: Gut microbiota regulates mincle mediated activation of lung dendritic cells to protect against Mycobacterium tuberculosis. Frontiers in Immunology 2019; 10: 1142.
17. Looft T and Allen HK: Collateral effects of antibiotics on mammalian gut microbiomes. Gut Microbes 2012; 3(5): 463-67.
18. Enaud R: The gut-lung axis in health and respiratory diseases: a place for inter-organ and inter-kingdom crosstalks. Frontiers in Cellular and Infection Microbiology 2020. 10: 9.
19. Huang C: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. The Lancet 2020. 395(10223): 497-506.
20. Viana SD, Nunes S and Reis F: ACE2 imbalance as a key player for the poor outcomes in COVID-19 patients with age-related comorbidities–Role of gut microbiota dysbiosis. Ageing Research Reviews 2020; 101123.
21. Franceschi C: Inflammaging and 'Garb-aging'. Trends in Endocrinology & Metabolism 2017; 28(3): 199-212.
22. Gou W: Gut microbiota may underlie the predisposition of healthy individuals to COVID-19. medRxiv 2020. DOI: 10.1101/2020.04.22.20076091.
23. Baud D: Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. Frontiers in Public Health 2020; 8.
24. Li HB: Maternal treatment with captopril persistently alters gut-brain communication and attenuates hypertension of male offspring. Hypertension 2020; 75(5): 1315-24.
25. Tang WW, Kitai T and Hazen SL: Gut microbiota in cardiovascular health and disease. Circulation Research 2017; 120(7): 1183-96.
26. Gurung M: Role of gut microbiota in type 2 diabetes pathophysiology. EBioMedicine 2020; 51: 102590.
27. Gu S: Alterations of the Gut Microbiota in Patients with COVID-19 or H1N1 Influenza. Clinical Infectious Diseases 2020. DOI: 10.1093/cid/ciaa709.
28. Zuo T: Alterations in Gut Microbiota of patients with COVID-19 during time of hospitalization. Gastroenterology, 2020. DOI: 10.1053/j.gastro.2020.05. 048.
29. Xu H: The gut microbiota and its interactions with cardiovascular disease. Microbial Biotechnology 2020; 13(3): 637-56.
30. Sanchez-Rodriguez E: The gut microbiota and its implication in the development of atherosclerosis and related cardiovascular diseases. Nut 2020; 12(3): 605.
31. Qin J: A metagenome-wide association study of gut microbiota in type 2 diabetes. Nature 2012; 490(7418): 55-60.
32. Qin J: A human gut microbial gene catalogue established by metagenomic sequencing. Nat 2010; 464(7285): 59-65.
33. Karlsson FH: Symptomatic atherosclerosis is associated with an altered gut metagenome. Nature Communications 2012; 3(1): 1-8.
34. Mell B: Evidence for a link between gut microbiota and hypertension in the Dahl rat. Physiological Genomics 2015; 47(6): 187-97.
35. Plovier H: A purified membrane protein from *Akkermansia muciniphila* or the pasteurized bacterium improves metabolism in obese and diabetic mice. Nature Medicine 2017; 23(1): 107-13.
36. Shen Z: Insights into *Roseburia intestinalis* which alleviates experimental colitis pathology by inducing anti-inflammatory responses. Journal of Gastroenterology and Hepatology 2018; 33(10): 1751-60.
37. Dagdeviren S: IL-10 prevents aging-associated inflammation and insulin resistance in skeletal muscle. The FASEB Journal 2017; 31(2): 701-10.
38. Zhu C: *Roseburia intestinalis* inhibits interleukin17 excretion and promotes regulatory T cells differentiation in colitis. Molecular Medicine Reports 2018; 17(6): 7567-74.
39. Wang X: Interleukin-22 alleviates metabolic disorders and restores mucosal immunity in diabetes. Nature 2014; 514(7521): 237-41.
40. Liu WC: *Lactobacillus plantarum* reverse diabetes-induced Fmo3 and ICAM expression in mice through enteric dysbiosis-related c-Jun NH2-terminal kinase pathways. PloS One 2018; 13(5): e0196511.
41. Li X: Effects of *Lactobacillus plantarum* CCFM0236 on hyperglycaemia and insulin resistance in high-fat and streptozotocin-induced type 2 diabetic mice. Journal of Applied Microbiology 2016. 121(6): 1727-36.
42. Inan MS: The luminal short-chain fatty acid butyrate modulates NF-κB activity in a human colonic epithelial cell line. Gastroenterology 2000; 118(4): 724-34.
43. Noverr MC: Development of allergic airway disease in mice following antibiotic therapy and fungal microbiota increase: role of host genetics, antigen, and interleukin-13. Infection and Immunity 2005; 73(1): 30-38.
44. Hagan T: Antibiotics-driven gut microbiome perturbation alters immunity to vaccines in humans. Cell 2019; 178(6): 1313-28.
45. Kekkonen RA: Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults. World journal of gastroenterology: WJG 2008; 14(13): 2029.
46. Gareau MG, Sherman PM and Walker WA: Probiotics and the gut microbiota in intestinal health and disease. Nature Reviews Gastroenterology & Hepatology 2010; 7(9): 503.
47. Pereira DI and Gibson GR: Effects of consumption of probiotics and prebiotics on serum lipid levels in humans.

Critical reviews in biochemistry and molecular biology, 2002; 37(4): 259-81.
48. Alexandre Y: Probiotics: a new way to fight bacterial pulmonary infections? Médecine et Maladies Infectieuses 2014; 44(1): 9-17.
49. Hao Q, Dong BR and Wu T: Probiotics for preventing acute upper respiratory tract infections. Cochrane Database of Systematic Reviews 2015; 2.
50. King S: Effectiveness of probiotics on the duration of illness in healthy children and adults who develop common acute respiratory infectious conditions: a systematic review and meta-analysis. British Journal of Nutrition 2014; 112(1): 41-54.
51. Chen N: Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. The Lancet 2020; 395(10223): 507-13.
52. Feleszko W: Probiotic-induced suppression of allergic sensitization and airway inflammation is associated with an increase of T regulatory-dependent mechanisms in a murine model of asthma. Clinical & Experimental Allergy 2007; 37(4): 498-505.
53. Liu Q: Surface components and metabolites of probiotics for regulation of intestinal epithelial barrier. Microbial Cell Factories 2020; 19(1): 23.

How to cite this article:
Sultana S, Hossain A and Karim MM: Gut-microbiome management: an issue worth considering in Covid-19 treatment. Int J Pharm Sci & Res 2021; 12(1): 1-7. doi: 10.13040/IJPSR.0975-8232.12(1).1-7.