

Butyrate and Fermentable Fiber as Adjunct Therapy for Covid-19 – Food for Thought

Douglas L. Archer¹ and Dean C. Kramer²

¹Food Science and Human Nutrition Department, Institute of Food and Agricultural Sciences, University of Florida, Gainesville, Florida, USA, 32611-0370

²Gastroenterology, Kramer Medical Clinic, Gainesville, Florida, USA, 32605-4477

Received: October 11, 2022; **Accepted:** October 21, 2022; **Published:** October 27, 2022

Citation: Archer DL, Kramer DC (2022) Butyrate and Fermentable Fiber as Adjunct Therapy for Covid-19 – Food for Thought. *Clar J Infect Dis Ther* 03(02): 232–238.

Abstract

In just this past year the use of butyrate as adjunct therapy for Covid-19 has gained wider recognition and support in the peer-reviewed literature. Presented here is a review of that literature and comments regarding the use of butyrate as a safe and effective adjunct in treating patients with Covid-19 with the aim of preventing the potentially damaging effects of an overactive immune response (cytokine storm).

Keywords: Covid-19, butyrate, sodium butyrate, inflammation, anti-inflammatory, butyrogenic microbiota, cytokine storm

Introduction

In June, 2020 Archer and Kramer[1] published “Opinion: *The Use of Microbial Accessible and Fermentable Carbohydrates and/or Butyrate as Supportive Treatment for Patients With Coronavirus SARS-CoV-2 Infection.*” Since that time, many papers have been published supporting the notion that the short chain fatty acid (SCFA) butyrate may help prevent or mitigate symptomatic Covid-19[1–7]. In most papers, butyrate is not suggested as sole treatment, but as an adjunct to existing therapy. Table 1 presents peer-reviewed publications that have appeared since June, 2020 suggesting a direct or indirect role for butyrate in mitigating symptoms and/or severity of Covid-19. The science strongly points to the need for human clinical trials of butyrate as an adjunct, supportive therapy in Covid-19.

Buyrate Direct and Indirect Mechanisms Of Action

Several papers cite butyrate’s known function as a histone deacetylase (HDAC) inhibitor as a proposed mechanism for its anti-Covid-19 activity[8–10]. For example, HDACs can simultaneously suppress ACE2[8,9], the receptor for SARS-CoV-2, and ABO blood group antigens, as non-O individuals appear to be at higher risk for severe Covid-19 than O group individuals. Another HDAC inhibitor, valproic acid, has been suggested as an alternative therapy for Covid-19, as it reduces ACE2, suppresses IL-6, changed macrophages from a proinflammatory (M1) to an anti-inflammatory (M2) type, and decreases the disseminated intravascular coagulopathy frequently seen as a lung complication, as well as myocardial, renal, and cerebral complications in Covid-19[10].

Table 1: References appearing in the peer-reviewed literature since June 2020 suggesting a direct or indirect role for butyrate in mitigating symptoms and/or severity of Covid-19

Butyrate suggested as a direct treatment for Covid-19	<ol style="list-style-type: none"> 1. Archer DL, Kramer DC. 2020 2. Sarkar P, Borah S, Sharma HK. 2020 3. Anderson G, Reiter RJ. 2020 4. Peng Y, Zhao J, Tun HM. 2020 5. Rowaiye AB, Okpalefe OA, Adejoke OO, et al. 2021 6. Jardou M, Lawson R. 2021 7. Nithin KK, Patil P, Bhandary SK, et al. 2021
Butyrate as an HDAC Inhibitor or related HDAC Inhibitors as direct treatments for Covid-19	<ol style="list-style-type: none"> 8. Takahashi Y, Hayakawa A, Sano R, et al. 2021 9. Li J, Richards EM, Handberg EM, et al. 2021 10. Pitt B, Sutton NR, Wang Z, et al. 2021
Butyrate via Fiber Digestion (prebiotics), probiotics, or diet as indirect treatment(s) or mitigation factor(s) of Covid-19	<ol style="list-style-type: none"> 11. Mondal D, Singh A, Praveen S, Krishnan V. 2020 12. Walton GE, Gibson GR, Hunter KA. 2021 13. de Oliveira GLV, Oliveira CNS, Pinzan CF, et al. 2021 14. Friedlanda RP, Haribabub B. 2020 15. Baud D, Dimopoulou Agri V, Gibson GR, et al. 2020 16. Conte L, Toraldo DM. 2020 17. Shinde T, Hansbro PM, Sohal SS, et al. 2020 18. Fernández-Quintela A, Milton-Laskibar I, et al. 2020 19. He L-H, Ren L-F, Li J-F, et al. 2020 20. Minich DM, Hanaway PJ. 2020 21. Chen J, Vitetta L. 2021 22. Losso JN, Losso MN, Toc M. 2021
Butyrate anti-inflammatory effects in various organ systems	<ol style="list-style-type: none"> 23. Bridgeman SC, Northrup W, Melton PE, et al. 2020 24. Cuoto MR, Goncalves P, Magro F, Martel F, et al. 2020 25. Tan LY, Yeo XI, Bae H-G, et al. 2021
Microbiota Changes/Gut Dysbiosis/Leaky Gut (as they affect butyrate) and Covid-19	<ol style="list-style-type: none"> 26. Kim HS. 2021 27. Tang L, Gu S, Gong Y, et al. 2020 28. Khan M, Mathew BJ, Gupta P, et al. 2021 29. Sencio V, Machado MG, Trottein F. 2021 30. Cao J, Wang C, Zhang Y, et al. 2021 31. Kazemian N, Kao D, Pakpour S. 2021

32. Zeppa SD, Agostini D, Piccoli G, et al. 2020
33. F. Cyprian, Sohail MU, Abdelhafez I, et al. 2021
34. Zhou, Y, Shi X, Fu W, et al. 2021
35. Chen J, Hall S, Vitetta L. 2021
36. Chattopadhyay I, Shankar EM. 2021
37. Zuo T, Zhang F, Lui GCY, et al. 2020

Numerous papers have addressed butyrate as a possible therapy for Covid-19 via increased fiber digestion (prebiotics), by supplementing the intestinal microbiota with bacteria in part responsible for butyrate production (probiotics), or dietary interventions with high fiber foods and fermented foods as indirect treatment(s) or mitigation factor(s) of Covid-19[11–22]. Interventions in this grouping all relate to a measurable lack of butyrogenic microbiota in Covid-19 patients.

Therapeutic Effects

Butyrate exerts anti-inflammatory effects in other disease states and organ systems that provide insight into its possible therapeutic effects in Covid-19[23–25]. For example, butyrate generated by gut microbiota exerts a therapeutic effect in persons with metabolic syndrome. The hallmarks of metabolic syndrome, obesity, high blood pressure, pre-diabetes and diabetes, are established susceptibility factors for Covid-19. These and other clinical features of metabolic syndrome are improved by increasing colonic butyrate production by the butyrogenic microbiota, many by way of HDAC inhibition[23]. Inflammatory Bowel Disease (IBD) is a group of intestinal disorders, the best known being Crohn's disease and Ulcerative colitis. Studies suggest that butyrate, using three mechanisms (including the aforementioned HDAC inhibition) to exert anti-inflammatory effects in the colon, may be a prospective therapy for IBD[24].

Evidence strongly suggests that butyrate-producing gut microbiota may prevent/delay the onset of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD)[25]. Butyrogenic gut microbiota are downregulated in both PD and AD, and dietary factors that modify gut microbiome dysbiosis to favor butyrogenic microbiota may prevent and treat cognitive deficits of Alzheimer's disease and Parkinson's

disease[25]. Thus, butyrate's anti-inflammatory properties influence the course of several diseases that are based on inflammation; it would seem reasonable, therefore, to expect that butyrate might also influence inflammation related to Covid-19 infection.

Variables in the Effects of Butyrate

Microbiota changes, gut dysbiosis, and increased intestinal permeability are all conditions that can affect butyrate production and utilization, and as such can affect the disease process progression of Covid-19[26–37]. Many clinical studies have demonstrated a loss of butyrogenic microbiota correlating with increasing severity of Covid-19 symptoms[26,27]. References to dysbiosis in nearly all reported studies of the microbiota profile of those infected with Covid-19 translate to a loss of butyrate producers[28,29,32–34]. Kim[26] suggests that fecal viral load in persons with increased intestinal permeability may gain access to readily infected enterocytes, and result in higher plasma virus loads and viral migration throughout the body. Besides facilitated viral entry through a permeable gut lining, toxins and substances such as LPS and other luminal contents may trigger or exacerbate inflammation and disrupt normal immune control mechanisms such as Tregs.

It has been suggested that therapeutic approaches such as fecal microbial transplant, use of dietary fiber (prebiotics) and next-generation butyrate-producing probiotics be explored further once safety concerns and regulatory hurdles are overcome[26]. Fermentable fiber appears to maximize immune defenses in those who are exposed to SARS-Cov-19 and may, likewise, boost immune defenses in those who are infected.

However, the usefulness of microbial accessible and fermentable carbohydrates may be diminished once dysbiosis is established in Covid-19 patients. The microbiota most frequently reported diminished in Covid-19 infection are butyrate-producers. If butyrate producers are missing or diminished during Covid-related dysbiosis, fermentable fiber may provide little or no benefit as an adjunct in treatment, however, the use of exogenous sources of butyrate may prove beneficial.

Therapeutic Applications of Butyrate

The treatment of inflammatory illness by oral administration of butyrate has been addressed in recent patent applications[38,39]. Human studies have been cited, and while not peer-reviewed, results were promising against inflammation in osteoarthritis, gout, multiple sclerosis, and Parkinson's disease.

Elevated IL-6 is an accepted marker for cytokine release in serious Covid-19 infections[40]. Since butyrate has been shown to significantly decrease serum IL-6 in other conditions, like idiopathic subfertility[38], the oral administration of butyrate might be clinically relevant in Covid-19 as well.

Systemic levels of butyrate in blood are 1000-fold less than levels found in the colon[41]. Blood levels of butyrate vary significantly among individuals, likely due to variations in diet, body type, metabolism, and other factors. Although blood levels of butyrate are exceedingly low, overwhelming evidence attests to its importance in the periphery in many organ systems[42,43]. It is unclear presently how or whether oral administration of butyrate can affect the blood concentrations significantly, although evidence would strongly support that it does[38,48,45].

The enteric administration of butyrate has been shown to be safe for human and animals and carries the FDA GRAS designation (Generally Recognized as Safe—GRAS) in human foods[46].

Status of New Formulations

Currently, there are several butyrate formulations available in the United States as dietary supplements, and/or drugs[47–50]. Others are under development[51]. There

are additional calls for controlled studies to explore the use of butyrate in other diseases[52], including Parkinson's disease[54], Alzheimer's disease[55], and Autism spectrum disorder[56]. There are additional studies on direct antimicrobial and immunomodulatory effects of butyrate[57], and more specific recommendations for orally administered butyrate in Covid-19[58].

Based on microbiome studies showing extreme losses of butyrogenic microbiota in Covid-19, fecal microbiota transplant has been recommended[59] and carried out in a small clinical trial with positive results forming the basis for a larger clinical trial[60]. Previous observations regarding the ability of butyrate to support CD8+ cytotoxic T lymphocytes in their anti-cancer role[61] have become relevant to Covid-19 immunity, as CD8+ memory cells specific for Coronavirus epitopes encountered in the past may have led to milder illness in individuals possessing them[62].

Conclusion

Since proposing butyrate as an adjunct therapy for Covid-19 in June, 2020,[1] support for such use in the peer-reviewed literature has accelerated. Unfortunately, despite the introduction of effective vaccines, SARS-CoV-2 continues to evolve within a largely unvaccinated population worldwide. Covid-19 remains at pandemic levels for most countries, and thus effective, readily available, and affordable treatments are of vital importance. Considering all the diseases that butyrate is thought to prevent or mitigate, it would seem reasonable that greater efforts be directed at developing and testing forms of butyrate and its use as an adjunct for treating COVID-19. Jardou and Lawson[63] hypothesize that butyrate can be administered to persons with Covid-19 to prevent immune system activation and disease progression. They propose a testing scheme to be administered in early stages of Covid-19 to determine if SCFA treatment is warranted based on plasma levels of acetate, propionate, and butyrate, pro-inflammatory cytokines in blood, and/or M1/M2 macrophages[64] ratio. They have further provided a proposed human clinical trial scheme for administration of butyrate[63]. These trials need to be conducted now.

References

1. Archer DL and Kramer DC (2020) The Use of Microbial Accessible and Fermentable Carbohydrates and/or Butyrate as Supportive Treatment for Patients With Coronavirus SARS-CoV-2 Infection. *Front. Med.* 7: 292. [View]
2. Sarkar P, Borah S and Sharma HK (2020) CAN MICROBIAL SCFA, BUTYRATE BE THE ALTERNATE SAVIOR AGAINST COVID-19? Current Trends in Pharmaceutical Research 2020 Vol 7 Issue 1 © Dibru Garh University www.dibru.ac.in/ctpr ISSN: 2319-4820 (Print) 2582-4783 (Online)
3. Anderson G and Reiter RJ (2020) Melatonin: Roles in influenza, Covid-19, and other viral infections. *Rev Med Virol.* 30: e2109. [View]
4. Peng Y, Zhao J and Tun HM (2020). The New Foe and Old Friends: Are We Ready for Microbiota-based Therapeutics in Treating COVID-19 Patients? *Gastroenterology* 160: 2192–2193. [View]
5. Rowaiye AB, Okpalefe OA, Adejoke OO, Ogidigo JO, Oladipo OH, et al. (2021) Attenuating the Effects of Novel COVID-19 (SARS-CoV-2) Infection-Induced Cytokine Storm and the Implications. *Journal of Inflammation Research* 14: 1487–1510. [View]
6. Jardou M and Lawson R (2021) COVID-19 and intestinal dysbiosis: the proposed mechanism of short-chain fatty acids for preventing cytokine storm and multi-organ failure. *Preprint from Authorea Preprints*, 08 Jan 2021. [View]
7. Nithin KK, Patil P, Bhandary SK, Haridas V, Kumari S, et al. (2021) Is butyrate a natural alternative to dexamethasone in the management of Covid-19? *F1000Research*. 10: 273. [View]
8. Takahashi Y, Hayakawa A, Sano R, Fukuda H, Harada M, et al. (2021) Histone deacetylase inhibitors suppress *ACE2* and *ABO* simultaneously, suggesting a preventive potential against COVID-19. *Sci Rep* 11: 3379. [View]
9. Li J, Richards EM, Handberg EM, Pepine CJ and Raizada MK (2021) Butyrate Regulates COVID-19–Relevant Genes in Gut Epithelial Organoids From Normotensive Rats. *Hypertension* 77: e13–e16. [View]
10. Pitt B, Sutton NR, Wang Z, Goonewardena SN and Holinstat M (2021) Potential repurposing of HDAC inhibitor valproic acid for patients with Covid-19. *European J Pharmacology* 898: 173988. [View]
11. Mondal D, Singh A, Praveen S and Krishnan V (2020) Resistant Starch Could This Immunity Booster Play a Positive Role in COVID-19 Management? *Science Reporter* 57: 30–31. [View]
12. Walton GE, Gibson GR and Hunter KA (2021) Mechanisms linking the human gut microbiome to prophylactic and treatment strategies for COVID-19. *British Journal of Nutrition* 126: 219–227. doi:10.1017/S0007114520003980 [View]
13. de Oliveira GLV, Oliveira CNS, Pinzan CF, de Salis LVV and Cardoso CRB (2021) Microbiota Modulation of the Gut-Lung Axis in COVID-19. *Front. Immunol.* 12: 635471. [View]
14. Friedlanda RP and Haribabub B (2020) Commentary: The role for the metagenome in the pathogenesis of COVID-19. *EBioMedicine* 61. [View]
15. Baud D, Dimopoulou Agri V, Gibson GR, Reid G and Giannoni E (2020) Using Probiotics to Flatten the Curve of Coronavirus Disease COVID-2019 Pandemic. *Front. Public Health* 8:186. [View]
16. Conte L and Toraldo DM (2020). Targeting the gut-lung microbiota axis by means of a high-fibre diet and probiotics may have anti-inflammatory effects in COVID-19 infection. *Ther Adv Respir Dis.* 14: 1753466620937170. [View]
17. Shinde T, Hansbro PM, Sohal SS, Dingle P, Eri R and Stanley R (2020) Microbiota Modulating Nutritional Approaches to Countering the Effects of Viral Respiratory Infections Including SARS-CoV-2 through Promoting Metabolic and Immune Fitness with Probiotics and Plant Bioactives. *Microorganisms*. 8(6): 921. [View]
18. Fernández-Quintela A, Milton-Laskibar I, Trepiana J, Gómez-Zorita S, Kajarabille N, et al. (2020) Key Aspects in Nutritional Management of COVID-19 Patients. *J. Clin. Med.* 9: 2589. [View]
19. He L-H, Ren L-F, Li J-F, Wu Y-N, Li X and Zhang L (2020) Intestinal Flora as a Potential Strategy to Fight SARS-CoV-2 Infection. *Front. Microbiol.* 11: 1388. [View]
20. Minich DM and Hanaway PJ (2020) The Functional Medicine Approach to COVID-19: Nutrition and Lifestyle Practices for Strengthening Host Defense. *Integr Med (Encinitas)*. 19 (Suppl 1): 54–62. [View]
21. Chen J and Vitetta L (2021) Modulation of Gut Microbiota for the Prevention and Treatment of COVID-19. *J. Clin. Med.* 10: 2903. [View]
22. Losso JN, Losso MN, Toc M, Inungu JN and Finley JW (2021) The Young Age and Plant-Based Diet Hypothesis for Low SARS-CoV-2 Infection and COVID-19 Pandemic in Sub-Saharan Africa. *Plant Foods Hum Nutr.* 24: 1–11. [View]

23. Bridgeman SC, Northrup W, Melton PE, Ellison GC, Newsholme P, et al. (2020) Butyrate generated by gut microbiota and its therapeutic role in metabolic syndrome. *Pharmacological Research* 105:174. [View]
24. Cuoto MR, Goncalves P, Magro F and Martel F (2020). Microbiota-derived butyrate regulates intestinal inflammation: Focus on inflammatory bowel disease. *Pharmacological Research* 159: 104947. [View]
25. Tan L.Y., Yeo, X.Y., Bae, H.-G., Lee, D.P.S., Ho, R.C, et al. (2021) Association of Gut Microbiome Dysbiosis with Neurodegeneration: Can Gut Microbe-Modifying Diet Prevent or Alleviate the Symptoms of Neurodegenerative Diseases? *Life*. 11: 698. [View]
26. Kim HS (2021) Do an altered gut microbiota and an associated leaky gut affect COVID-19 severity? *mBio* 12: e03022-20. [View]
27. Tang L, Gu S, Gong Y, Li B., Lu H, et al. (2020) Clinical Significance of the Correlation between Changes in the Major Intestinal Bacteria Species and COVID-19 Severity. *Engineering* 6: 1178–1184. [View]
28. Khan M, Mathew BJ, Gupta P, Garg G, Khadanga S, et al. (2021) Gut Dysbiosis and IL-21 Response in Patients with Severe COVID-19. *Microorganisms* 9: 1292. [View]
29. Sencio V, Machado MG and Trottein F (2021) The lung–gut axis during viral respiratory infections: the impact of gut dysbiosis on secondary disease outcomes. *Mucosal Immunol* 14: 296–304. [View]
30. Cao J, Wang C, Zhang Y, Lei G, Xu K, et al. (2021) Integrated gut virome and bacteriome dynamics in COVID-19 patients. *Gut Microbes* 13: 1–21. [View]
31. Kazemian N, Kao D and Pakpour S (2021) Fecal Microbiota Transplantation during and Post-COVID-19 Pandemic. *Int. J. Mol. Sci.* 22: 3004. [View]
32. Zeppa SD, Agostini D, Piccoli G, Stocchi V and Sestili P (2020) Gut Microbiota Status in COVID-19: An Unrecognized Player? *Front. Cell. Infect. Microbiol.* 10: 576551. [View]
33. Cyprian F, Sohail MU, Abdelhafez I, Salman S, Attique Z, et al. (2021) Review: SARS-CoV-2 and immune-microbiome interactions: Lessons from respiratory viral infections *International J. Infect. Dis.* 105: 540–550. [View]
34. Zhou Y, Shi X, Fu W, Xiang F, He X, Yang B, Wang X, Ma WL, et al. (2021) Gut Microbiota Dysbiosis Correlates with Abnormal Immune Response in Moderate COVID-19 Patients with Fever. *J. Inflamm. Res.* 14: 2619–2631 [View]
35. Chen J, Hall S and Vitetta L (2021) Altered gut microbial metabolites could mediate the effects of risk factors in Covid-19. *Rev. Med. Virol.* 31(5):1-13. [View]
36. Chattopadhyay I and Shankar EM (2021) SARS-CoV-2-Indigenous Microbiota Nexus: Does Gut Microbiota Contribute to Inflammation and Disease Severity in COVID-19? *Front. Cell. Infect. Microbiol.* 11: 590874. [View]
37. Zuo T, Zhang F, Lui GCY, Yeoh YK, Li AYL, et al. (2020) Alterations in gut microbiota of patients with Covid-19 during time of hospitalization. *Gastroenterol.* 159: 944–955. [View]
38. Jan Pieter Willem Vermeiden, Inventor and BirrBeheer B.V (2020) Butyrate salts for use in inflammatory diseases. United States Patent Application Publication US 2020/0038351. [View]
39. Gary Dean Wu, Inventor; University of Pennsylvania, (1996) The use of tributyrin in the treatment of inflammatory bowel disease. Worldwide Patent Application WO1996025380A1 [View]
40. Del Valle DM, Kim-Schulze S, Huang HH, Beckmann ND, Nirenberg S, et al. (2020) An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat. Med.* 26: 1636–1643. [View]
41. Cummings JH, Pomare EW, Branch HW, Naylor CP and Macfarlane GT (1987) Short chain fatty acids in human large intestine, portal, hepatic and venous blood. *Gut*, 28: 1221–1227. [View]
42. Walton GE, Gibson GR and Hunter KA (2021) Mechanisms linking the human gut microbiome to prophylactic and treatment strategies for COVID-19. *Brit. J. Nutr.* 126: 219–227. [View]
43. den Besten G, van Eunen K, Groen AK, Venema K, Reijngoud D-J, et al. (2013) The role of short-chain fatty acids in the interplay between diet, gut microbiota, and host energy metabolism. *J. Lipid Res.* 54, 2325–2340. [View]
44. Guilloteau P, Martin L, Eeckhaut V, Ducatelle R, Zabielski R and Van Immerseel F (2010) From the gut to the peripheral tissues: The multiple effects of butyrate. *Nutrition Research Reviews* 23: 366–384. [View]
45. Kim SW, Hooker JM, Otto N, Win K, Muench L, et al. (2013). Whole-body pharmacokinetics of HDAC inhibitor drugs, butyric acid, valproic acid and 4-phenylbutyric acid measured with carbon-11 labeled analogs by PET. *Nuclear Med. Biol.* 40: 912–918, [View]
46. Bedford A and Gong J (2018) Implications of butyrate and its derivatives for gut health and animal production. *Animal Nutrition* 4: 151e159. [View]
47. Heidor R, Ortega JF, de Conti A, Ong TP and Moreno FS (2012) Anticarcinogenic Actions of Tributyrin, A Butyric Acid Prodrug. *Current Drug Targets* 13: 1720–1729. [View]

48. Roda A, Simoni P, Magliulo M, Nanni P, Baraldini M, et al. (2007) A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon. *World J Gastroenterol.* 13: 1079–1084. [View]
 49. Banasiewicz T, Krokowicz Ł, Stojcev Z, Kaczmarek BF, Kaczmarek E, et al. (2012) Microencapsulated sodium butyrate reduces the frequency of abdominal pain in patients with irritable bowel syndrome. *Colorectal Disease* 15: 204–209. [View]
 50. de Groot P, Nikolic Y, Imangaliyev S, Bekkering S, Duinkerken G, et al. (2020) Oral butyrate does not affect innate immunity and islet autoimmunity in individuals with longstanding type 1 diabetes: a randomised controlled trial. *Diabetologia* 63: 597–610 [View]
 51. Russo R, Santarcangelo C, Badolati N, Sommella E, De Filippis A, et al. In vivo bioavailability and *in vitro* toxicological evaluation of the new butyric acid releaser N-(1-carbamoyl-2-phenyl-ethyl) butyramide. *Biomed. Pharmacother.* 137: 111385. [View]
 52. Canani BR, Di Costanzo M, Leone L (2012) The epigenetic effects of butyrate: potential therapeutic implications for clinical practice. *Clin Epigenet* 4: 4 [View]
 53. Silva YP, Bernardi A and Frozza RL (2020) The Role of Short-Chain Fatty Acids From Gut Microbiota in Gut-Brain Communication. *Front. Endocrinol.* 11: 25. [View]
 54. Tizabi Y, Getachew B and Aschner M (2021) Novel Pharmacotherapies in Parkinson's Disease. *Neurotox Res* 39: 1381–1390. [View]
 55. Binoshia Fernandoa WMAD, Martins IJ, Morici M, Bharadwaj P, Rainey-Smith S.R, et al. (2020) Sodium Butyrate Reduces Brain Amyloid Levels and Improves Cognitive Memory Performance in an Alzheimer's Disease Transgenic Mouse Model at an Early Disease Stage. *J. Alzheimer's Dis.* 74 : 91–99. [View]
 56. Liu S., Li E, Sun Z, Fu D, Duan G, et al (2019) Altered gut microbiota and short chain fatty acids in Chinese children with autism spectrum disorder. *Scientific Reports* 9: 287 [View]
 57. Du K, Bereswill S and Heimesaat MM (2021) A literature survey on antimicrobial and immune-modulatory effects of butyrate revealing non-antibiotic approaches to tackle bacterial infections *Eur. J. Microbiol. Immunol. (Bp).* 111: 1–9. [View]
 58. Devaux CA, Lagier J-C and Raoult D (2021) New insights Into the physiopathology of COVID-19: SARS-CoV-2-associated gastrointestinal illness. *Front. Med.* 8: 640073. [View]
 59. Liu F, Ye S, Wang J, Zhu X., Liu Y, et al. FMT: a potential therapeutic and rehabilitative intervention for Covid-19. *Journal of Clinical and Nursing Research.* 4: 49–53. [View]
 60. Biliński J, Winter K, Jasiński M, Szczes A, Bilinska N, et al. (2021) Rapid resolution of COVID-19 after faecal microbiota transplantation. *Gut*, Epub ahead of print: 06 July 2021. [View]
 61. He Y, Fu L, Li Y, Wang W, Gong M, et al. (2021) Gut microbial metabolites facilitate anticancer therapy efficacy by modulating cytotoxic CD8+ T cell immunity. *Cell Metabolism.* 33: 988-1000.e7 [View]
 62. Mallajosyula V, Ganjavi C, Chakraborty S, McSween AM, Pavlovitch-Redzyk AJ, et al. (2021). CD8+ T cells specific for conserved coronavirus epitopes correlate with milder disease in COVID-19 patients. *Sci. Immunol.* 6: eabg5669 [View]
 63. Jardou M and Lawson R (2021) Supportive therapy during COVID-19: The proposed mechanism of short-chain fatty acids to prevent cytokine storm and multi-organ failure. *Medical Hypotheses* 154: 110661. [View]
 64. Merad M and Martin JC (2020) Pathological inflammation in patients with COVID-19: a key role for monocytes and macrophages. *Nat Rev Immunol* 20: 355–62. [View]
- *Corresponding author: Professor Douglas L. Archer, Food Science and Human Nutrition Department, Institute of Food and Agricultural Sciences, P.O. Box 110370, University of Florida, Gainesville, Florida, USA 32611-0370
- Telephone: +1 (352 226 5507)
- E-mail: dlarcher@ufl.edu