

Journal of Gastroenterology and Hepatology Research

Online Submissions: <http://www.ghrnet.org/index./joghr/>
doi: 10.17554/j.issn.2224-3992.2021.10.1031

Journal of GHR 2021 December 21; **10(6)**: 3604-3607
ISSN 2224-3992 (print) ISSN 2224-6509 (online)

EDITORIAL

Exploratory Approaches on Butyrate as an Alternative Savior for COVID-19 Severity

Akira Yagi¹, PhD; Byung P. Yu², PhD

1 Special advisor of Japan Aloe Science Association; Editor-in-Chief of Journal of GHR; Professor Emeritus of Fukuyama University, Hiroshima, Japan;

2 Professor Emeritus of University of Texas, Health Center, Department of Physiology, San Antonio, the United State.

Conflict-of-interest statement: The authors declare that there is no conflict of interest regarding the publication of this paper.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Correspondence to: Akira Yagi, 2-10-1 Hanagaura-ku, Kasuyamachi, Kasuya-gun, Fukuoka-ken, Japan 811-2310.

Email: 0131akirayagi@gmail.com

Telephone: +81-92-938-2717

Received: November 1, 2021

Revised: November 26, 2021

Accepted: November 28, 2021

Published online: December 21, 2021

ABSTRACT

The global corona virus disease (COVID-19) pandemic has caused the unforeseen crisis to the modern society. In this brief review, we discussed the putative role of butyrate derived from intestinal fermentation in attenuating the COVID-19 severity, and suggested the use of multifarious butyrate by targeting cytokine storm and gut microbiota dysbiosis for the suppression of hyper-inflammatory immune response of COVID-19 infection.

Key words: Fermented butyrate; Aloe vera gel; Prevention to COVID-19 infection

© 2021 The Authors. Published by ACT Publishing Group Ltd. All rights reserved.

Yagi A, Yu BP. Exploratory Approaches on Butyrate as an Alternative Savior for COVID-19 Severity. *Journal of Gastroenterology and Hepatology Research* 2021; **10(6)**: 3604-3607 Available from: URL: <http://www.ghrnet.org/index.php/joghr/article/view/3240>

INTRODUCTION

The current pandemic corona virus disease (COVID-19) is caused by the rapaciously infections SARS-Cov-2 virus, globally killing nearly 5 million people^[1]. Although the global medical, pharmaceutical and research community has been racing against time for breakthroughs, presently, no effective individual drugs or treatments are available for Covid-19. Traditionally, herbal medicinal approaches are relatively safe, efficacious ways with fewer side effects compared to allopathic medications^[2]. It is worth noting that aloe vera gel has an antiviral role against several types of viruses^[3]. Our previous study reported the role of the gut microbiota during respiratory viral infections and suggested that the restoration of gut microbiota eubiosis by *Aloe vera* intake and the prebiotic aloe vera gel juice may well be beneficial against the pathogenesis of COVID-19^[4,5].

Our prediction was based on the fact that COVID-19 is primarily due to the excessive immuno- responses causing the hyper-inflammatory states, for which fermentation-derived butyrate could act as a prophylactic savior against the severity of COVID-19.

CYTOKINE STORM IN COVID-19 PATIENTS

Many COVID-19 complications may be caused by a condition known as cytokine release syndrome or a cytokine storm, as it causes the body to produce uncontrollable amounts of cytokines, resulting in the hyper-inflammatory state. The COVID-19 infection caused clusters of severe respiratory syndrome with high mortality. Preliminary clinical trials using blocking/neutralizing antibodies against IL-6/IL-6R showed the improvement that is necessary to lower the mortality rate of COVID-19 patients^[6]. One interesting of observation on cytokine storm is its early rise of pleiotropic anti-inflammatory IL-10 levels. This concurrent rise in IL-10 and other pro-inflammatory cytokines implies either IL-10 is insufficient to attenuate pro-inflammatory conditions, or possibly its altered role. Huang et al reported the epidemiological, clinical, laboratory, and radiological characteristic and treatment and clinical outcomes of COVID-19 patients. The authors showed that compared with non COVID-19 patients, ICU patients had higher plasma levels of IL-2,

IL-7, IL-10, GSCF, IP10, MCP1, and TNF α ^[7].

HYPER-INFLAMMATORY CYTOKINE STORM AND MICROBIOTA DYSBIOSIS OF COVID-19 PATIENTS

Alteration in gut microbiota of patients with COVID-19 during time of hospitalization and fecal shedding of virus was investigated by Zuo *et al.*^[8]. Fecal microbiota alterations were associated with fecal levels of SARS-CoV-2 and COVID-19 severity. There was an inverse correlation between abundance of *Faecalibacterium prausnitzii* and disease severity. Over the course of hospitalization, *Bacteroides*, which downregulate expression of angiotensin-converting enzyme 2 in murine gut, correlated inversely with SARS-CoV-2 load in fecal samples from patients. Furthermore the authors investigated temporal transcriptional activity of SARS-CoV-2 and its association with longitudinal fecal microbiome alteration in patients with COVID-19. Fecal samples with a signature of high SARS-CoV-2 infectivity harbored a higher abundance of opportunistic pathogens and an enhanced capacity for biosynthesis of nucleotide, amino acid and carbohydrate metabolism (glycolysis), whereas fecal samples with a signature of low-to-none SARS-CoV-2 infectivity had a higher abundance of short chain fatty acid producing bacteria^[9]. He *et al.*, reported that the intestinal symbiotic bacterium *F. prausnitzii* has emerged as “the sentinel of gut”, with multifunction of anti-inflammation, gut barrier enhancement, and butyrate production. A lower abundance of *F. prausnitzii* has been shown in inflammatory bowel disease and virus infection such as COVID-19. Therefore *F. prausnitzii* may have potential ability to reduce microbial translocation and inflammation, preventing occurrences of gastrointestinal comorbidities especially in COVID-19 patients^[10]. In our previous case report paper, we presented the usefulness of aloe vera gel butyrate fermented with endophytic microbiota, in which the successive ingestion of aloe vera juice provided high concentration of the butyrogenic microbiome *Faecalibacterium* species in fecal^[11].

BUTYRATE AS ADJUVANT THERAPY FOR PATIENTS WITH SARS-COV-2 INFECTION

Butyrate has been considered as a natural alternative to dexamethasone by many researchers. Its potential anti-inflammatory actions are well documented. In addition, it harnesses anti-oxidative powers, reduces leaky gut, and boosts fiber-derived butyrate production in the gut. Its role as a histone deacetylase inhibitor should also be highlighted. It could be administered as supportive therapy to prevent immune system activation and disease progression. Jardou and Lawson suggested that butyrate can be considered as pro-resolving mediator in immune response modulation^[12].

Archer and Kramer described butyrate represents as well characteristic beneficial short chain fatty acid that functions as a key modulator of the immune system both in the intestinal tract as well as in the lungs. They further documented that butyrate is capable of maintaining the structural integrity and balanced permeability of gut mucosal lining^[13]. The authors also proposed use of butyrate by enema would accomplish two things: Direct application of butyrate to the site of the intestinal tract terminal ileum and right colon that contains one of the highest concentrations of SARS-Cov-2 receptors (angiotensin-converting enzyme-2: ACE2), and Increase butyrate absorption for systemic distribution since the colon is the primary site for both fermentation production and absorption of butyrate.

Putative mechanism of anti-inflammatory butyrate and its derivatives in suppressing the ACE-2

Short chain fatty acid in gut metabolites, butyrate modulates the immune system and may play a substantial therapeutic role in the corona virus diseases. The viral disease has its mechanism in the host cells that embrace the binding of the spike protein with the angiotensin converting enzyme-2 (ACE2) receptors of the hosts via damaging the alveolar epithelial type 2 cells, leading to inflammations, and butyrate and its derivatives play a significant role in suppressing these factors, thereby act as a potential therapeutic target. Sarkar *et al.*^[14] discussed butyrate and its derivatives have a major role in suppressing the ACE2 expression. The role of butyrate in angiotensin II (Ang-II)-induced hypertension and the exploration of the underlying mechanism were investigated using the uninephrectomized rats by Wang *et al.*^[15]. Butyrate exerted an antihypertensive action, likely by suppressing the (pro) renin receptor-mediated intrarenal renin-angiotensin system.

The microbiota-derived short chain fatty acids, butyrate and propionate have been described as FOXP3 (Fox proteins; a family of transcription factors induced in Treg cells) inducers and are known to have anti-inflammatory properties. De Souza Vieira *et al.*^[16] demonstrated that butyrate is more effective than propionate in promoting FOXP3 expression and IL-9 repression, and indicated that the anti-inflammatory effects of butyrate may rely on suppressing Th9-mediated immune responses.

Regulation of COVID-19-relevant genes by butyrate in gut epithelial organoid from normotensive rats

Hypertension, one of the most common comorbidities with unfavorable outcomes, shares many common pathophysiological features with COVID-19 including inflammation, endothelial dysfunction, gut microbial dysbiosis, decreased butyrate-producing bacteria, increased gut leakiness, and altered renin-angiotensin system. Li *et al.*, demonstrated that butyrate downregulates gene essential for SARS-CoV-2 infection but also upregulates Toll-like receptor and other antiviral pathways. Therefore these findings imply that increased risk of COVID-19 in hypertension is partly due to cumulative depletion of butyrate producing bacteria in the gut. The treatment with butyrate would regulate ACE2 and its partners influencing antiviral genes. This could be critical in the control of gut viral infection and rebalancing of the gut-lung axis^[17].

PREVENTIVE POTENTIAL AGAINST COVID-19 HISTONE DEACETYLASE INHIBITORS

Since SARS-CoV-2 virus uses angiotensin-converting enzyme 2 (ACE2) as a receptor for cellular entry, increment of ACE2 would lead to an increased risk of SARS-CoV-2 infection. Takahashi *et al.*^[18] reported that an association of the ABO blood type with COVID-19 has been highlighted: there is increasing evidence to suggest that non-O-individuals are at higher risk of severe COVID-19 than O-individuals. These findings imply that simultaneous suppression of ACE2 and ABO would be a promising approach for prevention or treatment of COVID-19. Further the authors have clarified histone deacetylase inhibitors (HDACis) are able to suppress ABO expression. Based this background the authors evaluated the effect of HDACis on cultured epithelial cell lines and found that HDACis suppress both ACE2 and ABO expression simultaneously. Furthermore the amount of ACE2 protein was decreased in using of

panobinostat, one of the clinically used HDACis. Thus the authors concluded that panobinostat could have the potential to serve as a preventive drug against COVID-19.

BUTYRATE MEDIATION BY INHIBITING THE EXPRESSION OF HISTONE DEACETYLASES

The proposed mechanism of butyrate to prevent cytokine storm

The cytokine storm acts as a critical factor in the occurrence of severe-to-death patients with COVID-19. Macrophages maintain gut homeostasis by eliminating invasive pathogens and regulating inflammatory responses. Schulthess *et al*^[19] demonstrated that butyrate imprints potential antimicrobial activity during macrophage differentiation through histone deacetylase 3 inhibitor function. Jardou *et al*^[12] proposed that the inflammatory response during COVID-19 involved an increased M1/M2 macrophage phenotype ratio. The M1 phenotype is likely to be associated to the activation of the NF- κ B pathway and the pro-inflammatory cytokine production (e.g., IL-6, IL-12, TNF α). A relevant alternative is to restore the M1/M2 balance ratio by favoring M2 macrophage differentiation. Butyrate induces differentiation of macrophages with potent antimicrobial function, and butyrate supplementation is expected to help polarize macrophages into more favorable M2 phenotype, which in turn might decrease pro-inflammatory cytokine production.

SUMMARY

We presented data in this review that the anti-inflammatory properties of fermentation derived butyrate can be a potential supported therapy in reducing the severity of COVID-19 to patients. It is worth mentioning that aloe vera's antiviral efficacy could be related its butyrate content. The multifarious actions of butyrate, including its anti-inflammation, immune modulation, gut microbiota provide biochemical and pathophysiological bases for the attenuation of COVID-19. The restoration of imbalanced microbiota by butyrate can be added benefit, since the COVID-19 infections significantly decrease butyrate producing bacteria in host gut. Based on the various beneficial responses, we proposed that butyrate can be a potent supportive candidate for the preventive management of primary and secondary complications related to COVID-19 infection.

REFERENCE

1. Source: Johns Hopkins University, National public health agencies. October 1, 2021
2. Das A and Shaji D. Recognition of Aloe vera compounds as potential inhibitors of SARS-CoV-2 NSP-16: *Molecular docking approaches for drug development (Preprint)*
3. Yagi A, Hasegawa M, Ataka S. Beneficial efficacy of Aloe vera to viral infections: Case reports of Kampo medicine with Aloe vera juice *J. of GHR* 2020; **9(4)**: 3242-3247 [DOI: 10.17554/j.issn.2224-3992.2020.09.930]
4. A Kabbash, A Yagi, BP Yu, S Ataka Exploratory approaches for the use of Aloe for Covid-19 treatment: prevention and mitigation effect *J. of Diabetes Research Reviews & Reports* 2020; **2(4)**: 1-6
5. Yagi A, Abe H. Beneficial efficacy of histone deacetylase inhibitor butyrate and histone crotonylation to human immunodeficiency virus infected subjects *J. of GHR* 2020; **9(1)**: 3054-3059 [DOI: 10.17554/j.issn.2224-3992.2020.09.896]
6. Del Valle, Kim-Schlze S, Hueng HH, Beckmann ND, Nirenberg S, Wang Bo, Lavin Y, Swarty TH, Maddri D, Stock A, Marron TU, Xie H, Patel M, Tuballes K, Oebelen OV, Rahman A, Kavatch P, Aberg JA, Schadt E, Jagannath S, Mazumdar M, Charney AW,

- Betancourt AF, Mendu DR, Jhang J, Reich D, Sigel K, Condon-Cardo C, Feldmann M, Parekh S, Merad M, Gnjaicic S. An inflammatory cytokine signature predicts COVID-19 severity and survival *Nature Med.* 2020; **26**: 1636-1643 [DOI: 10.1038/S41591-020-1051-9]
7. Huang C, Wang Y, Li X, Zhao J, Hu Y, Zhang Li, Fan G, Xu J, Gu X, Cheng Z, Yu T, Xia J, Wei Y, Wu W, Xie X, Yin W, Li H, Liu M, Xiao Y, Gao H, Guo Li, Xie J, Wang G, Jiang R, Gao Z, Jin Q, Wang J, Cao B. Clinical features of patients infected with COVID-19 novel coronavirus in Wuhan, China. *The Lancet* 2020; **395**: 497-506. [DOI: 10.1016/S0140-6736(20)30183-5]
8. Zuo T, Zhang F, Lui GC, Yeoh YK, Lui AYL. Alterations in gut microbiota of patients with COVID-19 during time of hospitalization *Gastroenterology* 2020; **159**: 944-955 [DOI: 10.1053/j.gastro.2020.05.048]
9. Zuo T, Liu Q, Zhang F, Lui GCY, Tso EY, Yeoh YK, Chen Z, Boon SS, Chan FKI, Chan PK, Ng SC. Depicting SARS-CoV-2 fecal viral activity in association with gut microbiota composition in patients with COVID-19 *Gut.* 2021; **70(2)**: 276-284 [DOI: 10.1136/gutjnl-2020-322294]; [PMID: 32690600]
10. He X, Zhao S, Li Y. *Faecalibacterium prausnitzii*; A next-generation probiotic in gut disease improvement *Canadian J. of Infectious Diseases and Medical Microbiology* 2021; Article ID 6666114, 10 pages
11. A Yagi, M Hasegawa, S Ataka Prophylactic role of aloe components, butyrate fermented, micRNAs, and hyaluronan on Alzheimer's disease, Parkinson's disease, and osteoarthritis in knee joints: case reports of aloe vera juice ingestion producing intestinal butyrogenic microbiome and bone regeneration *J. of GHR* 2021; **10(1)**: 3398-3406 [DOI: 10.17554/j.issn.2224-3992.2020.10.983]
12. Jardou M, Lawson R. Supportive therapy during COVID-19: The proposed mechanism of short chain fatty acids to prevent cytokine storm and multi-organ failure *Med Hypotheses* 2021; **154**: 110661 [DOI: 10.1017/j.mehy.2021.110661]
13. Archer DL and Kramer DC. The use of microbial accessible and fermentable carbohydrates and/or butyrate as supportive treatment for patients with coronavirus SARS-CoV-2 infection *Frontiers in Medicine* 2020; **7**: 292 [DOI: 10.3389/fmed.2020.00292]
14. Sarkar P, Borah S, Sharma HK. Can microbial SCFA, butyrate, be the alternate savior against COVID-19? *Pharmaceutical Research* 2020; **7(1)**: 11-14.
15. Wang L, Zhu Q, Liu X, Zhang L, Xu C, Liu X, Li H, Yang T. Sodium butyrate suppresses angiotensin II-induced hypertension by inhibition of renal (pro)renin receptor and intrarenal renin-angiotensin system *J. Hypertens.* 2017; **35(9)**: 1899-1908 [DOI: 10.1097/HJH.0000000000001378]
16. De Souza Vieira R, Castoldi A, Basso PJ, Hiyane MI, Camera NOS, Almeida RR. Butyrate attenuates lung inflammation by negatively modulating Th9 cells *Front Immunol.* 2019; **10**: 67 [DOI: 10.3389/fimmu.2019.00967]
17. Li J, Richards EM, Handberg EM, Pepine CJ, Raizada MK. Butyrate regulates COVID-19-relevant genes in gut epithelial organoids from normotensive rats *Hypertension* 2021; **77**: 215-216 [DOI: 10.1161/HYPERTENSIONAHA.120.16647]
18. Takahashi Y, Hayakawa A, Sano R, Fukuda H, Harada M, Kubo R, Okawa T, Kominato Y. Histone deacetylase inhibitors suppress ACE2 and ABO simultaneously, suggesting a preventive potential against COVID-19 *Sci Rep.* 2021; **9(11)**: 3379 [DOI: 10.1038/s41598-021-82970-2]
19. Schulthess J, Pandey S, Capitani M, Rue-Albrecht KC, Arnold I, Franchini F, Chomka A, Ilott NE, Johnston DGW, Pires E, McCullagh J, Sansom SN, Arancibia-Carcamo A, Uhlig HH, Powrie F. The short chain fatty acid butyrate imprints an antimicrobial program in macrophages *Immunity* 2019; **50(2)**: 432-445.e7 [DOI: 10.1016/j.immuni.2018.12.018]

