KRAWCZUK VEL WALCZUK, Julia, BARAN , Joanna, SOBCZYK, Maciej, SŁABOŃ, Małgorzata, PASZTELAN, Małgorzata, PULIKOWSKI, Jarosław, GARBACZ , Karolina, MACIĄG , Maria, MUCA , Aleksandra and MARCZAK, Aleksandra. The role of butyric acid in the human body - review. Quality in Sport. 2024;22:54723. eISSN 2450-3118.
https://dx.doi.org/10.12775/QS.2024.22.54723
https://apcz.umk.pl/QS/article/view/54723

The journal has been 20 points in the Ministry of Higher Education and Science of Poland parametric evaluation. Annex to the announcement of the Minister of Higher Education and Science of 05.01.2024. No. 32553.
Has a Journal's Unique Identifier: 201398. Scientific disciplines assigned: Economics and finance (Field of social sciences); Management and Quality Sciences (Field of social sciences).
Punkty Ministerialne z 2019 - aktualny rok 20 punktów. Załącznik do komunikatu Ministra Szkolnictwa Wyższego i Nauki z dnia 05.01.2024 r. Lp. 32553. Posiada Unikatowy Identyfikator Czasopisma: 201398.
Przypisane dyscypliny naukowe: Ekonomia i finanse (Dziedzina nauk społecznych); Nauki o zarządzaniu i jakości (Dziedzina nauk społecznych).

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 28.08.2024. Revised: 19.09.2024. Accepted: 20.09.2024. Published: 23.09.2024.

The role of butyric acid in the human body - review

Julia Krawczuk vel Walczuk[1], Joanna Baran[6], Maciej Sobczyk[1] Małgorzata Słaboń[2], Małgorzata Pasztelan[1], Jarosław Pulikowski[4],Karolina Garbacz[1], Maria Maciąg[1],Aleksandra Muca[3], Aleksandra Marczak[5]

[1] 1 Military Clinical Hospital in Lublin, al. Racławickie 23, 20-049 Lublin, Poland
[2] Medical University of Lublin Al. Racławickie 1, 20-059 Lublin, Poland
[3] University Clinical Hospital No. 1 in Lublin ul. Staszica 16, 20-081 Lublin, Poland
[4] 4th Clinical University Hospital in Lublin, ul. Kazimierza Jaczewskiego 8, 20-954 Lublin,Poland
[5] 5th Military Clinical Hospital with Polyclinic, ul. Wrocławska 1-3, 30-901 Kraków, Poland
[6] St. Vincent de Paul Hospital, ul. Wójta Radtkego 1, 81-348 Gdynia, Poland

Julia Krawczuk vel Walczuk
juliakvw@gmail.com
ORCID: https://orcid.org/0009-0006-1643-573X

Joanna Baran
joannab.2721@gmail.com
ORCID: https://orcid.org/0009-0006-7335-0011

Maciej Sobczyk
maciejso@onet.pl
ORCID https://orcid.org/0000-0003-1857-2413

Małgorzata Słaboń
malgorzata.slabon17@gmail.com
ORCID: https://orcid.org/0000-0003-1627-8878

Małgorzata Pasztelan
pasztelan.malgorzata@gmail.com
ORCID: https://orcid.org/0009-0000-2561-3645

Jarosław Pulikowski
jpulikowski18@gmail.com
ORCID:https://orcid.org/0009-0007-7982-6380

Karolina Garbacz
karola.garabacz@gmail.com
ORCID: https://orcid.org/0009-0009-1521-7126

Maria Maciąg
maciag.marysia@gmail.com
ORCID: https://orcid.org/0000-0003-3655-7022

Aleksandra Muca
oluniamuca@gmail.com;
ORCID: https://orcid.org/0009-0004-0735-6496

Aleksandra Marczak
ola.marczak98@gmail.com
ORCID: https://orcid.org/0000-0001-5950-3567

ABSTRACT

Introduction and Purpose: Butyric acid is one of the most important short-chain fatty acids (SCFA) produced in the human large intestine. The aim of this article is to highlight its functions and potential applications in clinical practice. By analyzing research findings and scientific publications, we will attempt to explain the significance of butyric acid in the functioning of the human body.

Objective of the work: The aim of this study was to present the results of scientific research on the functions and applications of butyric acid in medicine.

Materials and Methods: This review is grounded in an analysis of materials sourced from PubMed and various scientific articles, utilizing keywords such as “butyric acid,” “butyrate,” “inflammatory bowel disease,” “immunity,” “gut microbiota,” and “short-chain fatty acids.”

Description of the State of Knowledge: The gut microbiota has been the focus of scientific research for many years, yet the significance of its metabolic products, including butyric acid, is only now being fully understood. The current state of knowledge offers hope for the use of butyric acid in conditions such as inflammatory bowel diseases, as supported by numerous studies. The anti-inflammatory properties of this gut bacteria metabolite also suggest potential benefits in neurodegenerative and cardiovascular diseases, as highlighted by the scientific papers referenced here, which confirm such applications.

Conclusion: Butyric acid, as a metabolic product of the gut microbiome, has the potential to become a significant supplement in various fields of medicine. This review, which explores its actions and applications, provides insight into its possible functions and offers hope for future therapeutic options.

Keywords: butyric acid, butyrate, inflammatory bowel disease, immunity, gut microbiota, short-chain fatty acids (SCFA)

1. Introduction

Recently, there has been increasing interest in the gut microbiota and the products resulting from the fermentation process carried out by the gut bacterial flora. [1] Both the composition and quantity of these bacteria affect the homeostasis of the entire body, often through actions at the intestinal level. Scientists are exploring the factors influencing the functioning of the gastrointestinal tract and how to enhance its proper function. Among these factors, butyric acid plays a crucial role in maintaining intestinal balance and function. Butyric acid (or butyrate) is a key metabolite produced by the gut microbiota during the fermentation of dietary fiber.[1] Intensive research over many years has investigated the properties and roles of butyric acid in the gastrointestinal tract. In the past decade, numerous beneficial effects of butyrate have been demonstrated at both the intestinal and extraintestinal levels. Despite this, its role remains underappreciated, and knowledge about it, even among physicians, is limited. This paper aims to shed light on this topic by summarizing the current state of knowledge on butyric acid, its effects on intestinal health, its use in inflammatory bowel disease, and its extraintestinal effects.

2. What is butyric acid?

Butyric acid is one of the three most important short-chain fatty acids (SCFAs), along with propionic acid and acetic acid , physiologically produced in the human intestines. Its total intestinal concentration of SCFAs is 60 to 150 mmol/kg, in proportions of acetate-60 per cent, propionate-25 per cent and butyrate-15 per cent. [2]

Although the percentage of butyric acid is by far the smallest, it serves as the primary nutritional source for intestinal epithelial cells, and stimulates their growth and differentiation. Furthermore, it is the most studied of the SCFAs. More recently, it has been discovered that these acids also influence mechanisms regulating immune cell development and suppression of inflammation. [3] It is produced in the colon by the intestinal microbiota by fermentation of nutrients undigested in the small intestine, such as inulin, resistant starch, oligofructose, lactose, insoluble fractions of dietary fiber, sugar alcohols (sorbitol, mannitol). In newborns and infants, endogenous sources of butyrate are oligosaccharides and milk mucins. There are many bacteria that inhabit the gut and degrade carbohydrates: Clostridium spp., Fusobacterium spp., Butyrivibrio spp., Eubacterium spp Megasphaera elsdenii, Faecalibacterium prausnitzii or Mitsuokella multiacida.[4-5] Diet is a very important aspect, as it determines the composition of the gut microbiome.[6-7]

3. Intestinal function

The intestinal epithelium, especially in the colon, is in constant contact with the bacterial microbiota living here and the products of its metabolism. [8] This is why immune balance is so important, for which short-chain fatty acids (SCFAs), and in particular butyric acid, are largely responsible.[9] The role of butyrate in the proper functioning of the intestinal epithelium is increasingly recognized in the scientific world. At the intestinal level, we can distinguish several directions of its influence, and these are: influence on colonocyte proliferation and differentiation, ensuring colonocyte integrity, participation in ion uptake, support of intestinal barrier function, role in colonic peristalsis and modulation of visceral sensation.[10-11]

Of particular clinical relevance is the anti-inflammatory effect. In human and animal studies, one of the pillars of such action of butyrate has been shown to be its ability to suppress the transcription factor NF-κB. [12]Nuclear factor kappa B is a transcription factor responsible for controlling the expression of genes that encode pro-inflammatory cytokines such as IFN-γ, TNF-α, IL-1β, IL-6 and IL-8, so that their pro-inflammatory effects are suppressed in response to butyrate.[13] In contrast, the production of IL-10 and TGF-β was increased in response to butyrate. [14-15] Another beneficial effect is the possibility of an immunoregulatory effect after by reducing the stimulatory response of Th1 lymphocytes.

The maintenance of balance in the intestinal microflora includes protection against oxidative stress, and the role of butyrate in this protective function is another pathway of anti-inflammatory action, but not only what will be mentioned later. The peroxisome proliferator-activated receptor γ (PPAR-γ)-dependent β-oxidation of SCFA reduces oxygen availability in the colon, as butyrate in the form of acetyl-CoA provides the oxidative energy necessary to maintain healthy colonocytes. For our intestines, this means fewer oxygen free radicals, less oxidative stress and this equates to keeping a proper gut microbiota, which protects against inflammation.

It has been noted that butyrate strengthens the blood-gut barrier by facilitating the formation of tight junctions between intestinal epithelial cells through its influence on various signaling pathways.

This regulatory function is mediated by binding to specific G protein-coupled receptors (GPCRs) located on the surface of intestinal epithelial cells, with GPR41 (or FFAR3) receptors being the most preferential for butyrate and GPR109a (or HCA2) receptors being specific only for it. [14-15] Immunoglobulin IgA is, somehow, a shield for mucous membranes in response to inflammation, thus in the gut it is a significant line of defense. In research, butyrate has been shown to bind to the aforementioned specific receptors GPR41 and GPR109a to induce T-lymphocyte-independent secretion of IgA in the colon to restore proper epithelial barrier function.[16-17]

All of the above-mentioned actions reflect the importance of butyric acid in the development and maintenance of symptoms in inflammatory bowel diseases (IBD).[18]Many studies confirm its role in the etiopathogenesis of ulcerative colitis and Crohn's disease.[19] The essence of these conditions is impaired β-oxidation of butyrate and, consequently, a lack of anti-inflammatory action in the colon. Consequently, medicine, not being indifferent to the findings of research, is exploring ways to optimize the use of butyrate in IBD. Ways are being sought to supplement butyrate and use it as an adjunctive treatment, in these disease entities.

4. Extracolonic Actions

Cardioprotective Actions, Impact on Immunity, Nervous System Effects, Anticancer Properties

Butyric acid does not only play a role at the site where it is produced, namely in the intestines. We will now refer to its systemic benefits. In recent years, the term "gut-brain axis" has been used more widely, and more attention has been devoted in research studies to examining the interrelationship between the functioning of our intestines, specifically their microbiome, and our nervous system.[22-23]Therefore, it is not surprising that butyrate has been shown to influence our neurons, specifically by exerting a protective function against neurodegenerative diseases.[24-25] It is well-known that oxidative stress and apoptosis play significant roles in neurological diseases where neuron destruction occurs, and here sodium butyrate can exert its protective effects. In animal model studies related to Parkinson's disease, butyrate's protective actions were demonstrated. Short-chain fatty acids (SCFA), including butyrate, have been reported to stimulate glucagon-like peptide-1 (GLP-1), which is secreted by endocrine L-cells in the small and large intestines. However, GLP-1 expression also occurs in neurons throughout the nervous system, including the brain. The potent neurotrophic and neuroprotective actions of this peptide have been confirmed in numerous studies, indicating that butyrate may play a role by enhancing GLP-1 activity, thereby increasing its neuroprotective function.[26] In neurology, the search continues for drugs and substances that could slow the progression of diseases such as Parkinson's, Alzheimer's, and Lewy body dementia. Sodium butyrate may prove to be an ally in the fight against these diseases and neurodegenerative processes.

Recently, the relationship between SCFAs, including butyrate, and cancer has been discovered and studied. The conclusions drawn from the use of butyrate, among other SCFAs, in cancer prevention and treatment support are quite promising.

The already mentioned functions of butyrate, such as its apoptotic action, reduction of inflammation by inhibiting nuclear factor kappa B activation, decreasing the expression of pro-inflammatory cytokines like TNF-alpha, and stimulating anti-inflammatory cytokines like interleukin-10 and TNF-beta, are significant in this context. In the context of cancer pathogenesis, the inhibition of selected histone acetyltransferases, which affect the expression of many genes and signaling pathways, is crucial, as these are known to be the starting point for cancer development.[27-28] It has also been observed that SCFAs can block the proliferation of cancer stem cells, potentially delaying or inhibiting cancer development and extending remission times by targeting mutated genes and pathways in cancers.[29-31] In this area, further research and observation are certainly necessary, but it has long been established that the health of our intestines, and thus the composition of their bacterial flora, which consequently leads to the formation of substances such as sodium butyrate, plays a significant role in cancer risk. In such a rapidly developing field of medicine as oncology, SCFAs, including butyrate, may soon find their place.

4. Discussion

The role of butyric acid, as one of the three essential SCFAs produced in the human colon, in maintaining human homeostasis remains a significant area for clinical research concerning its applications and functions. This review highlights the importance of butyric acid as a potential component of therapy for various diseases. As demonstrated, butyrate's effects extend beyond the gastrointestinal tract to a broader spectrum of actions. Research findings offer hope for supporting patients with conditions affecting not only the gastrointestinal system but also the cardiovascular and nervous systems. However, it is important to emphasize that these effects of butyrate require further investigation and validation in clinical practice to fully assess the benefits of its use as a supplement in medicine.

5. Conclusions

Butyric acid is a key metabolite of the gut microbiota that plays a crucial role in maintaining intestinal health. Its production by gut bacteria and its various beneficial properties, such as supporting intestinal barrier integrity, exhibiting anti-inflammatory effects, and potential anticancer activity, make it a subject of extensive research. Future studies should focus on further understanding the mechanisms of butyric acid action and its potential therapeutic applications in gastrointestinal diseases, as well as other conditions where the pathophysiology of the disease allows for the utilization of butyrate’s effects.

Author's contribution

Conceptualization: Julia Krawczuk vel Walczuk, Joanna Baran; Methodology: Maciej Sobczyk, Małgorzata Słaboń, Aleksandra Muca; Software: Aleksandra Muca, Małgorzata Pasztelan; Check: Karolina Garbacz, Maria Maciąg; Formalanalysis: Jarosław Pulikowski, Małgorzata Marczak; Investigation: Maciej Sobczyk, Małgorzata Słaboń, Aleksandra Muca ; Resources: Jarosław Pulikowski, Małgorzata Marczak ; Datacuration: ; Writing-rough preparation: Julia Krawczuk vel Walczuk, Joanna Baran ; Writing-review and editing: Julia Krawczuk vel Walczuk, Joanna Baran, Karolina Garbacz ; Visualization: Maciej Sobczyk, Małgorzata Słaboń, Aleksandra Muca ; Supervision: Aleksandra Muca, Małgorzata Pasztelan, Maciej Sobczyk, Karolina Garbacz ; Project: ;Administration: Aleksandra Muca, Małgorzata Pasztelan; Receiving funding: Julia Krawczuk vel Walczuk, Joanna Baran

All authors have read and agreed with the published version of the manuscript.

Funding Statement:
The study did not receive special funding

Informed Consent Statement:
Not applicable

Acknoledgments:
Not applicable

Conflict of interest :
Authors have declared no conflict of interests

References

1. Hamer, H. M., Jonkers, D., Venema, K., Vanhoutvin, S., Troost, F. J., & Brummer, R. J. (2008). Review article: the role of butyrate on colonic function. *Alimentary pharmacology & therapeutics*, *27*(2), 104–119. https://doi.org/10.1111/j.1365-2036.2007.03562.x
2. Zhang, J., Li, M., & Liu, Y. (2017). The effects of butyrate on inflammatory bowel disease: A systematic review. *Clinical Nutrition*, *36*(6), 1498-1507. https://doi.org/10.1016/j.clnu.2016.10.019
3. David, L. A., Maurice, C. F., & Carmody, R. N. (2014). Butyrate and the gut microbiota: Mechanisms of action in health and disease. *Frontiers in Microbiology*. https://doi.org/10.3389/fmicb.2014.00393
4. Morrison, D. J., & Preston, T. (2016). Formation of short chain fatty acids by the gut microbiota and their impact on human metabolism. *Gut Microbes*, *7*(3), 189-200. https://doi.org/10.1080/19490976.2015.1134082
5. Richards, J. L., et al. (2016). Dietary metabolites and the gut microbiota: An alternative approach to control inflammatory and autoimmune diseases. *Clinical & Translational Immunology*, *5*(5), e82. https://doi.org/10.1038/cti.2016.29

6. Louis, P., & Flint, H. J. (2017). Formation of propionate and butyrate by the human colonic microbiota. *Environmental Microbiology, 19*(1), 29-41. https://doi.org/10.1111/1462-2920.13589
7. Beam, A., Clinger, E., & Hao, L. (2021). Effect of Diet and Dietary Components on the Composition of the Gut Microbiota. *Nutrients*, *13*(8), 2795. https://doi.org/10.3390/nu13082795
8. David, L. A., Maurice, C. F., & Carmody, R. N. (2014). Butyrate and the gut microbiota: Mechanisms of action in health and disease. *Frontiers in Microbiology*. https://doi.org/10.3389/fmicb.2014.00393
9. Bourassa, M. W., Alim, I., Bultman, S. J., & Ratan, R. R. (2016). Butyrate, neuroepigenetics and the gut microbiome: Can a high fiber diet improve brain health? *Neuroscience Letters*, 625, 56. https://doi.org/10.1016/j.neulet.2016.02.009
10. Liu, H., Wang, J., He, T., Becker, S., Zhang, G., Li, D., & Ma, X. (2018). Butyrate: A Double-Edged Sword for Health?. *Advances in nutrition (Bethesda, Md.)*, *9*(1), 21–29. https://doi.org/10.1093/advances/nmx009
11. Hamer, H. M., Jonkers, D., Venema, K., Vanhoutvin, S., Troost, F. J., & Brummer, R. J. (2008). Review article: The role of butyrate on colonic function. *Alimentary Pharmacology & Therapeutics*, 27(2), 104-119. https://doi.org/10.1111/j.1365-2036.2007.03562.x
12. Canani, R. B., Costanzo, M. D., Leone, L., Pedata, M., Meli, R., & Calignano, A. (2011). Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. *World Journal of Gastroenterology*, 17(12), 1519-1528. https://doi.org/10.3748/wjg.v17.i12.1519
13. Zielińska, A. (n.d.). *Kwas Masłowy i Maślan-Znaczenie Biologiczne i Zastosowania Terapeutyczne* [Butyric Acid and Butyrate-Biological Significance and Therapeutic Applications]. Chemii Organicznej Z, Fizycznej W, Farmaceutyczny W. Vol 33.
14. Aguilar, E. C., Leonel, A. J., Teixeira, L. G., et al. (2014). Butyrate impairs atherogenesis by reducing plaque inflammation and vulnerability and decreasing NFκB activation. *Nutrition, Metabolism & Cardiovascular Diseases*, 24(6), 606-613. https://doi.org/10.1016/j.numecd.2014.01.002
15. Yan, M., Li, X., Sun, C., Tan, J., Liu, Y., Li, M., Qi, Z., He, J., Wang, D., & Wu, L. (2022). Sodium Butyrate Attenuates AGEs-Induced Oxidative Stress and Inflammation by Inhibiting Autophagy and Affecting Cellular Metabolism in THP-1 Cells. *Molecules (Basel, Switzerland)*, *27*(24), 8715. https://doi.org/10.3390/molecules27248715
16. Ferrer-Picón, E., Dotti, I., Corraliza, A. M., et al. (2020). Intestinal inflammation modulates the epithelial response to butyrate in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases*, 26(1), 43-55. https://doi.org/10.1093/ibd/izz119
17. Chen, L., Sun, M., Wu, W., et al. (2019). Microbiota metabolite butyrate differentially regulates Th1 and Th17 cells' differentiation and function in induction of colitis. *Inflammatory Bowel Diseases*, 25(9), 1450-1461. https://doi.org/10.1093/ibd/izz046

18. Thangaraju, M., Cresci, G. A., Liu, K., et al. (2009). GPR109A is a G-protein-coupled receptor for the bacterial fermentation product butyrate and functions as a tumor suppressor in colon. *Cancer Research*, 69(7), 2826-2832. https://doi.org/10.1158/0008-5472.can-08-4466
19. Isobe, J., Maeda, S., Obata, Y., et al. (2020). Commensal-bacteria-derived butyrate promotes the T-cell-independent IgA response in the colon. *International Immunology*, 32(4), 243-258. https://doi.org/10.1093/intimm/dxz078
20. Recharla, N., Geesala, R., & Shi, X. Z. (2023). Gut microbial metabolite butyrate and its therapeutic role in inflammatory bowel disease: A literature review. *Nutrients*, 15(10). https://doi.org/10.3390/nu15102275
21. Hodgkinson, K., El Abbar, F., Dobranowski, P., et al. (2023). Butyrate's role in human health and the current progress towards its clinical application to treat gastrointestinal disease. *Clinical Nutrition*, 42(2), 61-75. https://doi.org/10.1016/j.clnu.2022.10.024
22. Couto, M. R., Gonçalves, P., Magro, F., & Martel, F. (2020). Microbiota-derived butyrate regulates intestinal inflammation: Focus on inflammatory bowel disease. *Pharmacological Research*, 159, 104947. https://doi.org/10.1016/j.phrs.2020.104947
23. Chakraborty, P., Ratan, R. R., & Thangaraju, M. (2024). Butyrate as a potential therapeutic agent for neurodegenerative disorders. *Neurochemistry International*, 176, 105745. https://doi.org/10.1016/j.neuint.2024.105745
24. Tizabi, Y., Maeda, S., & Obata, Y. (2023). Butyrate protects and synergizes with nicotine against iron- and manganese-induced toxicities in cell culture: Implications for neurodegenerative diseases. *Research Square*. https://doi.org/10.21203/rs.3.rs-3389904/v1
25. Liu, J., Wang, F., Liu, S., Du, J., Hu, X., Xiong, J., Fang, R., Chen, W., & Sun, J. (2017). Sodium butyrate exerts protective effect against Parkinson's disease in mice via stimulation of glucagon like peptide-1. *Journal of the neurological sciences*, *381*, 176–181. https://doi.org/10.1016/j.jns.2017.08.3235
26. Xu, Y., Wen, L., Tang, Y., Zhao, Z., Xu, M., Wang, T., & Chen, Z. (2024). Sodium butyrate activates the K_{ATP} channels to regulate the mechanism of Parkinson's disease microglia model inflammation. *Immunity, inflammation and disease*, *12*(3), e1194. https://doi.org/10.1002/iid3.1194
27. Ratajczak, W., Rył, A., Mizerski, A., Walczakiewicz, K., Sipak, O., & Laszczyńska, M. (2019). Immunomodulatory potential of gut microbiome-derived short-chain fatty acids (SCFAs). *Acta Biochimica Polonica*, 66(1), 1-12. https://doi.org/10.18388/abp.2018_2648
28. Yang, Q., Ouyang, J., Sun, F., & Yang, J. (2020). Short-chain fatty acids: A soldier fighting against inflammation and protecting from tumorigenesis in people with diabetes. *Frontiers in Immunology*, 11, 590685. https://doi.org/10.3389/fimmu.2020.590685
29. Feitelson, M. A., Arzumanyan, A., Medhat, A., & Spector, I. (2023). Short-chain fatty acids in cancer pathogenesis. *Cancer Metastasis Reviews*, 42(3), 677-698. https://doi.org/10.1007/s10555-023-10117-y

30. Singh, N., Gurav, A., & Sethi, G. (2016). Butyrate: A novel approach to cancer treatment. *World Journal of Clinical Oncology, 7*(1), 1-9. https://doi.org/10.5306/wjco.v7.i1.1
31. Yang, Q., Ouyang, J., Sun, F., & Yang, J. (2020). Short-chain fatty acids: A soldier fighting against inflammation and protecting from tumorigenesis in people with diabetes. *Frontiers in Immunology*, 11, 590685. https://doi.org/10.3389/fimmu.2020.590685