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Sodium butyrate in Irritable Bowel Syndrome

Aleksandra Kołodziej, Wiktoria Zamirska, Nadia Hornig, Aleksandra Cieplak, Zuzanna Czyżewicz

Aleksandra Kołodziej
Municipal Hospital No.4 in Gliwice ul. Zygmunta Starego 20, 44-100 Gliwice, Poland
ORCID:0009-0007-7322-3116
olakolodziej18@gmail.com
WiktoriaZamirska
Katowice Oncology Centre, ul.Raciborska 26, 40-074 Katowice, Poland
ORCID:0009-0006-6520-1876
zamirskawiktoria@gmail.com
Nadia Hornig
Independent Public Health Care Facility of the Ministry of Internal Affairs and Administrationin Katowice named after Sergeant Grzegorz Załoga, ul.WitaStwosza39-41 40-042 Katowice, Poland
ORCID:0009-0001-3247-4660
nadia.hornig5@gmail.com

Aleksandra Cieplak University Clinical Center named after Prof. K. Gibiński, ul. Medyków 14, 40-514 Katowice, Poland

ORCID:0009-0008-2700-5211

ola.cieplak@gmail.com

Zuzanna Czyżewicz Medical University of Silesia, ul.Poniatowskiego 15, 40-055 Katowice, Poland

ORCID:0009-0005-8809-2708

zuzannace@gmail.com

Abstract:

Introduction and Purpose: Irritable bowel syndrome (IBS) is a widespread functional gastrointestinal disorder characterized by chronic abdominal pain, bloating, and altered bowel habits, significantly affecting patients' quality of life. Despite the unclear pathophysiology, factors such as gut microbiota dysbiosis, increased intestinal permeability, and low-grade inflammation have been implicated. Recent studies suggest that gut microbiota-derived metabolites, particularly short-chain fatty acids (SCFAs), play a vital role in intestinal homeostasis. Sodium butyrate, an SCFA, shows promise as a therapeutic agent in IBS management due to its capacity to enhance gut barrier integrity and exert anti-inflammatory effects. This review aims to evaluate the evidence regarding sodium butyrate's role in IBS treatment, focusing on its mechanisms of action and clinical outcomes.

Material and Methods: An extensive literature review was performed using databases such as PubMed and Google Scholar. Articles published in peer-reviewed scientific journals were selected based on relevant keywords aligned with the 'Medical Subject Headings' (MeSH).

Description of the State of Knowledge: Sodium butyrate's impact on intestinal health is well-documented, with studies demonstrating its ability to strengthen the gut barrier, reduce inflammation, and modulate microbial composition. Preclinical and clinical studies show variable improvements in IBS symptoms like pain and bloating, although inconsistencies in methodology and patient selection challenge the comparability of outcomes.

Conclusions: While sodium butyrate exhibits potential benefits for IBS management, clinical application is hindered by variability in study designs, dosage regimens, and the lack of large-scale randomized controlled trials. Future research should prioritize the optimization of supplementation protocols and explore specific patient subgroups that may derive the greatest benefit. Addressing these research gaps could position sodium butyrate as an effective adjunct therapy in the management of IBS, contributing to improved gut health and symptom relief.

Keywords: "sodium butyrate", "irritable bowel syndrome", "IBS"

Introduction:

Irritable Bowel Syndrome (IBS) is a chronic, functional gastrointestinal disorder characterized by recurrent abdominal pain, discomfort, and alterations in bowel movements, such as constipation, diarrhea, or a mixed pattern. IBS is one of the most commonly diagnosed gastrointestinal disorders worldwide, affecting approximately 10-15% of the adult population, with a higher prevalence in women than in men. Although IBS does not lead to structural changes in the digestive tract, its symptoms can significantly impact the quality of life of patients, causing pain, bloating, changes in bowel habits, and a sensation of fullness in the abdomen.

Although the pathophysiology of IBS is not fully understood, several theories regarding its causes have been proposed. These include alterations in the gut microbiome, dysfunction of the gut-brain axis, intestinal motility disturbances, and visceral hypersensitivity. These changes may lead to disturbances in gut content flow and induce inflammatory states within the gastrointestinal tract, which may be associated with the exacerbation of clinical symptoms. Despite a wide range of available pharmacological treatments, including antidiarrheal, laxative, analgesic, and antidepressant drugs, IBS treatment remains challenging and often does not provide complete relief. (1)

In the context of recent research, increasing attention is being paid to the role of bioactive substances, such as sodium butyrate, which may represent a promising therapeutic alternative for IBS treatment, particularly regarding its potential impact on the gut microbiome and inflammatory processes in the intestines. Studies on sodium butyrate suggest that it may positively influence gut health by improving barrier function and reducing inflammation, which could lead to symptom relief in IBS.

Symptoms and Classification of IBS

Irritable Bowel Syndrome (IBS) is a heterogeneous disorder characterized by a range of symptoms that affect the gastrointestinal system. The hallmark symptoms of IBS include recurrent abdominal pain, bloating, and changes in bowel habits, such as diarrhea, constipation, or alternating episodes of both. The severity and frequency of these symptoms can vary significantly among individuals, and they are often triggered or exacerbated by stress, dietary factors, or other environmental influences.

The clinical presentation of IBS is typically divided into three main subtypes based on the predominant bowel pattern:

1. IBS with Diarrhea (IBS-D): Characterized primarily by frequent loose or watery stools, along with abdominal cramping and discomfort. Diarrhea tends to be more prominent in this subtype, often accompanied by urgency and a sense of incomplete evacuation.
2. IBS with Constipation (IBS-C): In this subtype, constipation is the predominant symptom, with individuals experiencing infrequent and difficult-to-pass stools,

bloating, and abdominal discomfort. This form of IBS is often associated with a sensation of incomplete evacuation and excessive straining during bowel movements.

3. Mixed IBS (IBS-M): A combination of both diarrhea and constipation, with patients experiencing alternating episodes of each. This subtype presents a challenge in management due to the fluctuating nature of symptoms.

Additionally, some patients may experience IBS-Unclassified (IBS-U), a form of IBS where symptoms do not fit neatly into any of the above categories, making diagnosis and treatment more complex.

The classification of IBS into these subtypes is essential for guiding treatment decisions and understanding the pathophysiology underlying the condition. While the symptoms can be distressing, IBS is generally considered a functional disorder, as it does not result in observable structural abnormalities in the gastrointestinal tract. However, the impact on quality of life is significant, and effective symptom management remains a key challenge in clinical practice. (2)

Current Guidelines and Therapeutic Approach in the Treatment of IBS

The treatment of Irritable Bowel Syndrome (IBS) is complex and depends on the subtype of the disease, the severity of symptoms, and the individual needs of the patient. Due to the multifactorial pathophysiology of IBS, therapeutic strategies include both pharmacological and non-pharmacological approaches. Current guidelines emphasize the importance of individualized treatment, focusing primarily on symptom control and improving the quality of life of patients.

1. Dietary Approach: Diet plays a key role in the management of IBS. Guidelines suggest the use of a low FODMAP diet (Fermentable Oligo-, Di-, Mono-saccharides and Polyols), which involves eliminating foods that cause excessive fermentation in the gut. This diet has shown effectiveness in reducing symptoms, particularly in patients with diarrhea-predominant IBS (IBS-D) or mixed IBS (IBS-M).(3) Additionally, for patients with IBS-C, increasing fiber intake is recommended; however, it is important to avoid excessive consumption of insoluble fiber, which can exacerbate symptoms.(4)
2. Pharmacological Treatment: Depending on the predominant symptoms, pharmacological treatment may include:
    a. Antidiarrheal medications (e.g., loperamide) for IBS-D, which help control diarrhea and improve stool frequency.
    b. Laxatives (e.g., polyethylene glycol) for IBS-C, which facilitate bowel movements by increasing stool volume and improving gut hydration.
    c. Prokinetic agents (e.g., prucalopride) may be used to enhance gut motility, especially in patients with chronic constipation.
    d. Antispasmodic and analgesic medications (e.g., hyoscine, mebeverine) are used to treat abdominal pain and cramps, which are common symptoms in IBS.
    e. Antidepressants (e.g., tricyclic antidepressants or selective serotonin reuptake inhibitors) are used in patients with predominant pain or comorbid depression,

as they can help alleviate pain and improve gut function by modulating the nervous system.

3. Behavioral and Psychological Therapies: Since psychological stress and emotional factors play a significant role in the onset and exacerbation of IBS symptoms, behavioral therapies such as cognitive-behavioral therapy (CBT) can be effective in symptom reduction. These therapies help patients manage stress, anxiety, and other emotional factors that can worsen IBS symptoms. Additionally, relaxation techniques, such as meditation, can also provide relief from stress associated with the condition.
4. Probiotics and Prebiotics: Recent studies highlight the role of probiotics and prebiotics in the management of IBS, especially in relation to gut microbiota imbalances. Probiotics, such as strains of *Lactobacillus* and *Bifidobacterium*, can improve gut microbiota balance and alleviate symptoms of IBS, particularly bloating, abdominal pain, and irregular bowel movements. Prebiotics, such as fructooligosaccharides, support the growth of beneficial gut bacteria and can improve gut motility.
5. New Therapeutic Approaches: In recent years, new therapeutic strategies have been developed, such as the use of sodium butyrate and other short-chain fatty acids (SCFAs), which show potential in treating inflammatory conditions and dysfunctions of the gut barrier, common features of IBS pathophysiology. Research on these substances is promising, particularly in terms of modulating the gut microbiome and improving gut function.

In summary, the therapeutic approach to IBS should be tailored to the individual patient's needs, taking into account the type and severity of symptoms, as well as the impact on quality of life. Optimizing treatment requires collaboration between the patient and the healthcare provider, incorporating pharmacological therapy, lifestyle and dietary modifications, and psychological interventions.(5) (6)(7)(8)

Definition of Sodium Butyrate

Sodium butyrate (NaB) is the sodium salt of butyric acid, a short-chain fatty acid (SCFA) produced in the intestines through the fermentation of carbohydrates, particularly fiber, by gut microbiota. It is one of the main SCFAs present in the human gut, where it plays a crucial role in maintaining gastrointestinal health. Sodium butyrate is actively studied in scientific research due to its anti-inflammatory, immunomodulatory properties, and its ability to support gut barrier integrity.

As an active metabolite, sodium butyrate interacts with intestinal epithelial cells, improving their protective and regenerative functions. It also serves as an energy source for enterocytes, supporting their health and function. Furthermore, sodium butyrate has the potential to modulate the gut microbiota, which may be of significant importance in the treatment of disorders such as Irritable Bowel Syndrome (IBS), where dysbiosis and inflammation occur within the intestines.

Sodium butyrate may also influence the immune system's activity in the gut by modulating cytokine release and the activity of inflammatory cells. Due to its properties, sodium butyrate is gaining interest as a potential therapeutic agent for various inflammatory bowel diseases and motility disorders, as seen in IBS.(9)(10) (11)

Integrity of the intestinal mucosa

Sodium butyrate plays a crucial role in maintaining the integrity of the intestinal mucosa, which is vital for gastrointestinal health. It acts through G protein-coupled receptors (GPCRs) found on epithelial cells, which serve as receptors for butyrate. The binding of butyrate to these receptors influences the modulation of various cellular functions in tissues and cells such as B and T lymphocytes, neutrophils, adipose tissue, and colon myeloid cells. One of the key actions of butyrate is its ability to stimulate the proliferation of epithelial cells and enhance the production of the mucous layer, which improves the tightness of the intestinal barrier. A critical component of this barrier is the claudin family of membrane proteins, which are responsible for maintaining tight intercellular connections. Butyrate has been shown to increase the expression of claudin-1, which contributes to the stability of the intestinal barrier.(12) Additionally, butyrate promotes the expression of the MUC2 gene, which is involved in the synthesis of mucins that protect epithelial cells from the harmful effects of toxins.(13) Given these effects, butyrate is considered an essential metabolite that influences the function of the intestinal barrier, making it particularly relevant for patients with conditions like colorectal cancer, where there is often increased disruption and damage to the intestinal barrier. (9) It helps improve the stability of the intestinal barrier, reducing intestinal permeability and preventing the passage of pathogens and toxins into the bloodstream. (14)(15)

Influence on gut microbiota

The gut microbiota of patients with irritable bowel syndrome (IBS) exhibits significant alterations in both diversity and richness. Specifically, studies have shown that individuals with IBS often experience a reduction in microbial diversity, characterized by a lower number of different microbial species compared to healthy controls. Additionally, the richness of the gut microbiota, which refers to the total number of microbial species present, tends to be decreased in IBS patients. Several studies have highlighted an imbalance between specific bacterial groups in IBS, with a decrease in beneficial microbes such as *Bifidobacterium*, *Lactobacillus*, and *Faecalibacterium prausnitzii*, and an overgrowth of pathogenic bacteria, including *Escherichia coli* and *Enterococcus*. These changes in microbial composition are thought to contribute to the dysbiosis observed in IBS, with a predominance of certain bacterial groups,

such as Firmicutes and Bacteroidetes, being altered. Furthermore, the imbalance in the gut microbiota may play a role in the pathophysiology of IBS by affecting intestinal permeability, immune function, and gut motility, all of which are implicated in the development and exacerbation of IBS symptoms.(16)(17)(18)(19)(20)

Sodium butyrate influences the gut microbiome by modulating its composition and activity. As a short-chain fatty acid (SCFA), butyrate is a product of fiber fermentation by gut microbiota and plays a crucial role in maintaining microbial balance. Sodium butyrate supports the growth of beneficial bacteria such as *Firmicutes* and *Bacteroidetes*, while inhibiting the growth of pathogenic microorganisms that could lead to intestinal disturbances. This action contributes to improving gut health by reducing inflammation and enhancing intestinal barrier stability, which is particularly important in the treatment of disorders like Irritable Bowel Syndrome (IBS), where dysbiosis often occurs. Furthermore, sodium butyrate influences the production of other SCFAs, which can further support microbial balance, improve gut barrier function, and reduce intestinal permeability. (21)

Anti- inflamatory effects

Sodium butyrate is thought to exert its anti-inflammatory effects through several mechanisms. It acts as an inhibitor of histone deacetylases (HDACs), leading to the upregulation of anti-inflammatory cytokines and the suppression of pro-inflammatory mediators. This process helps maintain the integrity of the intestinal barrier, which is often compromised in inflammatory conditions. Furthermore, sodium butyrate promotes the production of regulatory T cells (Tregs), which play a crucial role in modulating the immune system and preventing excessive inflammatory responses.(22) These mechanisms are particularly important in the context of treating disorders such as Irritable Bowel Syndrome, in which the intestinal barrier is weakened and inflammation occurs.

Analysis of Clinical and Experimental Studies on Sodium Butyrate in IBS Treatment

SCFAs effect on gastrointestinal motility

Short-chain fatty acids (SCFAs), including butyrate, play a significant role in the pathophysiology of irritable bowel syndrome (IBS). SCFAs are primarily produced by the gut microbiota through the fermentation of fiber and other carbohydrates, and their levels in feces reflect the bowel habits of IBS patients. Studies have shown that individuals with IBS exhibit reduced SCFA production, which may contribute to gastrointestinal motility disturbances and symptoms such as constipation or diarrhea.(23) Butyrate, as one of the main SCFAs, has anti-inflammatory properties, supports intestinal barrier regeneration, and influences gut motility, all of which may be crucial in the treatment of IBS. (24)Decreased SCFA production in IBS may result from dysbiosis, and therapies aimed at enhancing SCFA production, such as butyrate supplementation, could improve symptoms, particularly in terms of regulating bowel movements and alleviating intestinal inflammation.(25)(26)

In a study conducted by Zhang et al. (2019), the researchers utilized animal models, including rats, to evaluate the impact of sodium butyrate on gut microbiota and IBS symptoms. The animals underwent sodium butyrate therapy for a specified duration, followed by the assessment of changes in the gut microbiota composition using 16S DNA sequencing analysis, which enabled precise identification of bacteria in fecal samples. Additionally, biochemical and histopathological analyses were performed to evaluate inflammation and gut barrier function. The results showed that sodium butyrate improved the balance of the gut microbiota by increasing the number of beneficial bacteria, such as *Firmicutes*, and decreasing the abundance of pathogenic bacteria, which had a positive effect on intestinal inflammation. Specifically, sodium butyrate led to a reduction in levels of inflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), suggesting its anti-inflammatory effects. Furthermore, therapy resulted in improved intestinal barrier integrity, which was crucial in alleviating IBS symptoms such as abdominal pain, bloating, and irregular bowel movements. These findings highlight the potential of sodium butyrate as an effective therapeutic approach for IBS, particularly in cases associated with gut dysbiosis and chronic inflammation. (14)

In the article "Diarrhea Predominant-Irritable Bowel Syndrome (IBS-D): Effects of Different Nutritional Patterns on Intestinal Dysbiosis and Symptoms", it is emphasized that gut dysbiosis, commonly observed in patients with IBS-D, significantly affects gut motility, leading to disturbances such as diarrhea and frequent bowel movements. Sodium butyrate, one of the main short-chain fatty acids (SCFAs), improves gut motility by regulating the function of smooth muscle cells in the intestines. Studies have shown that sodium butyrate can enhance sodium ion flux in epithelial cells, promoting better absorption of water and electrolytes and improving bowel movement rhythm. Additionally, butyrate exhibits anti-inflammatory properties, which reduce visceral hypersensitivity and improve gut motility function. In the context of IBS-D, sodium butyrate supplementation may help stabilize gut motility, reducing the frequency of diarrhea and improving overall gastrointestinal function.(1)

Dosage and Bioavailability of Sodium Butyrate

The study “Sodium Butyrate Effectiveness in Children and Adolescents with Newly Diagnosed Inflammatory Bowel Diseases—Randomized Placebo-Controlled Multicenter Trial” described utilizing a dosage of 150 mg twice daily (Debutir®) for 12 weeks. This is considered a relatively low dose compared to clinical studies in adults, where daily doses have ranged from 900 mg to 4000 mg.

The article also highlights several important factors related to the bioavailability of sodium butyrate:

- Rapid Absorption in the Small Intestine – Sodium butyrate is predominantly absorbed in the proximal small intestine, which significantly reduces its availability in the colon. Since its primary effects are expected in the large intestine, this early absorption limits its therapeutic potential.
- Strategies to Improve Colonic Delivery – To enhance its bioavailability, different formulation techniques have been explored. Microencapsulation and enteric-coated

formulations help delay the release of butyrate, ensuring it reaches the colon before being fully absorbed.

- Impact of Dosage on Efficacy – Studies suggest that higher doses may be required to achieve meaningful clinical effects, particularly in conditions affecting the distal gut. A dose-dependent response has been observed in some trials, indicating that inadequate dosing may contribute to inconsistent findings regarding butyrate's efficacy.
- Duration of Supplementation – While some studies have evaluated butyrate supplementation over periods of 4 to 8 weeks, longer administration might be necessary to observe significant improvements in gut health and inflammation markers.
- Comparative Effectiveness of Different Butyrate Forms – Butyrate can be administered in various forms, including sodium butyrate, tributyrin (a triglyceride form), or butyrate-producing dietary fibers. These different formulations may exhibit varying degrees of absorption and efficacy, which should be considered in future research.

Given these factors, optimizing the formulation and dosage of sodium butyrate remains a critical challenge in maximizing its therapeutic potential for gastrointestinal disorders.(27)

Some studies suggest that the effects of sodium butyrate on intestinal barrier function may be context-dependent and influenced by the inflammatory state. Findings from the study *"Butyrate Does Not Protect Against Inflammation-induced Loss of Epithelial Barrier Function and Cytokine Production in Primary Cell Monolayers From Patients With Ulcerative Colitis"* indicate that butyrate does not prevent inflammation-induced epithelial barrier dysfunction in primary intestinal epithelial cell monolayers derived from patients with ulcerative colitis (UC). In some cases, it may even exacerbate these effects. This suggests that the impact of butyrate may be modulated by the severity of inflammation and the integrity of the intestinal epithelium.

In the context of irritable bowel syndrome (IBS), which is not traditionally classified as an inflammatory disease but may involve epithelial barrier dysfunction, the effects of sodium butyrate could differ. Since IBS is not associated with the same level of mucosal inflammation as UC, butyrate might exert more favorable protective effects in this patient population. However, further research is needed to determine the specific conditions and optimal dosage under which sodium butyrate can support intestinal barrier function without posing a risk of adverse outcomes.(28)

Based on the review presented in the article "Determination of butyric acid dosage based on clinical and experimental studies – a literature review," sodium butyrate generally shows good tolerance, and its use is considered safe within a broad range of doses, provided they are adjusted to the patient's needs. Clinical studies involving various forms of butyrate, such as capsules, powders, or oral solutions, have not reported significant adverse effects, suggesting its relative safety. However, in some cases, patients have reported mild symptoms, such as bloating or abdominal pain, particularly at higher doses. Therefore, it is crucial to monitor patient responses and appropriately adjust the dosage, especially in individuals who may be more sensitive to the components of the supplements.

Moreover, the body's response to sodium butyrate can vary depending on the individual characteristics of the patients, as emphasized by the study results. The response to butyrate

supplementation may be more or less pronounced depending on the patient's health status, particularly the state of the gut microbiome and the integrity of the intestinal barrier. Studies have shown that individuals with more dysbiotic microbiomes may exhibit a stronger response to supplementation with butyrate, potentially leading to more rapid improvements in gut function. Conversely, patients with less severe metabolic disturbances or a well-functioning gut flora may show a less noticeable response to sodium butyrate. Therefore, an individualized approach to dosage, accounting for these differences, is essential for effective and safe treatment.

These findings suggest that further research into the individual responses to sodium butyrate and the determination of optimal doses for various health conditions, including IBS, is necessary to better understand the therapeutic mechanisms and ensure patient safety.(29)

Contribution to improvement in quality of life

A study investigating the effects of microencapsulated sodium butyrate in patients with inflammatory bowel disease (IBD) demonstrated that supplementation with this compound may contribute to an improvement in quality of life, even in the absence of significant changes in disease activity. Notably, patients with ulcerative colitis (UC) reported a subjective improvement in well-being and a reduction in gastrointestinal symptoms following sodium butyrate supplementation. This suggests that its effects may extend beyond direct anti-inflammatory and microbiota-modulating properties to include symptom modulation, which can significantly impact daily functioning.

A similar mechanism may be relevant in the context of irritable bowel syndrome (IBS), where quality of life is often compromised due to persistent symptoms such as abdominal pain, bloating, and irregular bowel habits. If sodium butyrate enhances the well-being of IBD patients, its potential role in IBS management may stem from analogous mechanisms—namely, its influence on gut microbiota composition, epithelial barrier integrity, and local inflammatory responses. Although further research is needed, these findings indicate that sodium butyrate supplementation could be a promising adjunctive strategy for managing patients with functional gastrointestinal disorders.(30)

Disclosure:

Authors’contribution:

Conceptualization: Aleksandra Kołodziej

Methodology: Nadia Hornig

Software: Aleksandra Cieplak

Check: Wiktoria Zamirska

Formal analysis: Zuzanna Czyżewicz

Investigation: Aleksandra Kołodziej

Resources: Wiktoria Zamirska

Data curation: Zuzanna Czyżewicz

Writing-rough preparation: Aleksandra Kołodziej

Writing-review and editing: Nadia Hornig

Supervision: Aleksandra Cieplak

Project administration: Aleksandra Kołodziej

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