

# THERAPEUTIC POTENTIAL OF SODIUM BUTYRATE IN INTESTINAL INFLAMMATION AND COLORECTAL CANCER: A TRANSLATIONAL REVIEW (2018–2025)

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## ABSTRACT

### INTRODUCTION

Sodium butyrate is a salt of butyric acid and one of the main short-chain fatty acids produced by the gut microbiota. Butyric acid influences the proper homeostasis of the gastrointestinal tract. It has a trophic effect by providing energy to colonocytes, stimulating their growth and differentiation. In inflammatory bowel diseases, butyrate concentration decreases. A growing number of studies indicate that butyric acid deficiency may be important in the processes of neoplasia in the large intestine.

### OBJECTIVE

The aim of this review is to analyze present experimental and clinical data (2018-2025) on the biological role of sodium butyrate in keeping normal gastrointestinal homeostasis and, building on this analysis, to evaluate its clinical potential in intestinal diseases.

### METHODS

We reviewed PubMed-indexed experimental and clinical studies and review articles. We focused on molecular pathways, inflammatory markers, epithelial integrity, modulation of the microbiota, and clinical outcomes in IBD and other

gastrointestinal diseases.

## RESULTS

Available data show that sodium butyrate has anti-inflammatory, antioxidant, and anti-ferroptotic effects. In addition, butyric acid supports intestinal barrier integrity and epithelial regeneration. In clinical trials, it can reduce IBD activity and inflammatory markers and improve psychological parameters. Sodium butyrate has documented anticancer potential in CRC in preclinical studies.

## CONCLUSIONS

Sodium butyrate shows anti-inflammatory, antioxidant, barrier-protective, and microbiota-modulating effects, supporting its use as adjunct therapy in inflammatory bowel diseases. It may also have anti-cancer potential in colorectal cancer, but more robust clinical trials are required.

Keywords: Sodium butyrate, Butyrate, Inflammatory bowel disease, Ferroptosis, Colorectal cancer, Histone deacetylase inhibition.

## INTRODUCTION

Inflammatory bowel disease and colorectal cancer are major gastrointestinal problems. Ulcerative colitis and Crohn's disease are among the diseases with increasing incidence in developed countries. The pathogenesis of inflammatory bowel disease is complex. It involves genetic, immunological, and environmental elements, as well as disturbances in the intestinal microbiota [2,3]. An important factor in the development of IBD is the imbalance between the epithelium, intestinal microbiota, and the immune system. Pathological disruption of intestinal barrier integrity leads to increased intestinal epithelial permeability, immune activation, and the persistence of chronic inflammation [6,7].

Disruption of the intestinal microflora leads to a deficiency of butyrate-producing bacteria, which is associated with increased inflammation [1,5]. Butyric acid is a source of energy for colonocytes. It has a trophic and regenerative effect on the intestinal epithelium, strengthening and sealing the intestinal barrier [2]. Sodium butyrate is a compound with anti-inflammatory, immunomodulatory, and antioxidant properties [4,6]. Experimental studies have shown that it can inhibit ferroptosis and modulate the ERK/STAT3 pathway, which regulates the inflammatory response [1,7,8,9]. Experimental models have also shown that regular supplementation with sodium butyrate reduces Fe<sup>2+</sup> concentration, decreases MPO activity, and increases glutathione levels, indicating reduced oxidative stress and inflammation [1,6]. Intestinal dysbiosis in inflammatory bowel diseases reduces butyrate production, thereby increasing inflammation and damaging the intestinal epithelium. In a clinical study, patients with ulcerative colitis who supplemented with sodium butyrate reported reductions in calprotectin, decreased disease activity indices, and improved quality of life [15,16].

Chronic colitis is a risk factor for colorectal cancer, a common malignant tumor [42]. Preclinical studies show that butyrate can inhibit colon cancer cell proliferation and induce apoptosis by inhibiting histone deacetylases (HDACs) and regulating metabolism [19,21,23,37]. The medical literature describes the "butyrate paradox"—the proliferation of healthy colon epithelial cells and the blockage of cancer cell growth [19,20]. Sodium butyrate may also increase cancer cells' sensitivity to 5-fluorouracil [28].

Despite the growing interest in the role of sodium butyrate in gastrointestinal diseases, the current body of evidence remains fragmented and inconsistent, with most data derived from experimental studies and limited translation into clinical practice. A significant gap in the literature is the lack of comprehensive analyses integrating molecular mechanisms with clinical outcomes in inflammatory bowel diseases and colorectal cancer. The novelty of this review lies in the integrative, translational synthesis of recent experimental and clinical evidence (2018–2025), with particular emphasis on ferroptosis, microbiota modulation, and the potential role of sodium butyrate in combination therapies. This review aims to address the existing knowledge gap by providing a critical and structured synthesis of current data and by identifying future research directions with potential clinical relevance.

## AIM AND RESEARCH OBJECTIVES

This review intends to evaluate scientific data and analyze studies from 2018–2025 on the effects of sodium butyrate regarding maintaining gastrointestinal homeostasis and treating ulcerative conditions. The study examined how sodium butyrate impacts inflammation, oxidative stress, and regulated cell death—specifically ferroptosis—in inflammatory bowel diseases [1,8,9,10]. It also assessed the importance of modulating signaling pathways, such as ERK/STAT3, for epithelial regeneration and immune response control [1,10].

Another task was to examine the effect of sodium butyrate, specifically on the integrity of the intestinal barrier, the proliferation and differentiation of colonocytes, and the function of intercellular junctions. These intercellular junctions play an important function toward maintaining gastrointestinal homeostasis [7,12,13].

The relationship between butyrate supplementation and changes in gut microbiota in animal models and humans during inflammatory bowel disease was evaluated. Available clinical data on the efficacy and safety of sodium butyrate as adjunctive therapy for IBD were also analyzed [1,5,15,16].

The analysis also covered the potential anticancer activity of sodium butyrate in colorectal cancer, with particular emphasis on epigenetic mechanisms such as histone deacetylase inhibition and regulation of the cell cycle and apoptosis [19-25,37]. Furthermore, the potential of sodium butyrate in combination therapy with 5-fluorouracil was also evaluated [28,29].

## MATERIAL AND METHODS

This study was a structured narrative review based on a transparent literature search and selection. A comprehensive literature search was conducted in the PubMed/MEDLINE database on January 15, 2026. Literature was searched in PubMed from 2018 to 2025. The search strategy combined "Sodium Butyrate" with terms such as Colorectal cancer (CRC), Ulcerative colitis (UC), and Crohn's disease (CD). Only English-language publications with full-text access were included. The initial search identified 132 records.

After removal of duplicates (n = 9), 123 records remained for title and abstract screening.

Following title and abstract screening, 45 articles were excluded because they:

- did not directly investigate sodium butyrate,
- focused on other short-chain fatty acids without specific analysis of sodium butyrate,
- were not related to intestinal diseases.

Thus, 78 articles were selected for full-text assessment.

After full-text evaluation, 33 studies were excluded due to:

- insufficient methodological description,
- lack of original data (editorials or commentaries),
- absence of relevance to inflammatory bowel disease or colorectal cancer,
- duplication of previously published data.

Finally, 45 publications met all inclusion criteria and were included in the qualitative synthesis.

### INCLUSION CRITERIA

- in vivo experimental studies evaluating the effect of sodium butyrate on inflammation, ferroptosis, and ERK/STAT3 signaling, inhibition of histone deacetylases (HDAC);
- randomized clinical trials evaluating the efficacy of sodium butyrate supplementation in patients with ulcerative colitis and Crohn's disease ;
- review articles and professional opinions on the use of butyrate in intestinal diseases ;
- publications studying the potential anticancer effects of sodium butyrate in colorectal cancer
- articles published in English and Polish

### EXCLUSION CRITERIA

- Conference reports without full publication,
- Studies on other SCFAs without direct reference to sodium butyrate,
- Papers without a clearly defined methodology,
- Articles not directly related to intestinal diseases.
- Scientific publications prior to 2018.

Because the studies were heterogeneous (in dosage, therapy duration, preparation forms, and experimental models), no quantitative analysis or meta-analysis was done. Instead, results were grouped by topic and qualitatively analyzed to provide a synthetic overview of current knowledge.

## RESULTS

### 1. EFFECT OF SODIUM BUTYRATE ON INFLAMMATORY ACTIVITY IN EXPERIMENTAL IBD MODELS

In the analyzed preclinical studies, including the sodium dextran sulfate (DSS)-induced colitis model, sodium butyrate supplementation significantly reduced disease activity. Specifically, a decrease in the DAI index, reduced weight loss, and reduced colon shortening were noted, along with improved histopathological appearance of the intestinal mucosa. Furthermore, this was accompanied by decreased expression of proinflammatory cytokines and markers of oxidative stress [1,6-13].

### 2. INHIBITION OF FERROPTOSIS AND MODULATION OF SIGNALING CASCADES

Sodium butyrate inhibits ferroptosis, an iron-dependent form of cell death. In animals, this inhibition led to lower Fe<sup>2+</sup> concentration and MPO activity, and higher GSH levels, which protected cells from damage [1,9]. ERK/STAT3 pathway modulation was also observed, showing its role in epithelial regeneration and in regulating the inflammatory response [1,9].

### 3. INTESTINAL BARRIER INTEGRITY AND EPITHELIAL REGENERATION

Scientific articles emphasize that sodium butyrate is the primary energy source for colonocytes and plays a key function toward maintaining intestinal barrier integrity. As a result, improvements in intercellular junction function and reduced epithelial permeability have been demonstrated, which leads to reduced bacterial translocation and secondary immune activation [7,12].

### 4. CHANGES IN THE INTESTINAL MICROBIOTA

Clinical and experimental studies indicate that sodium butyrate supplementation promotes the normalization of the gut microbiota composition [1,5]. In animal model studies, a restoration of the balance between pro- and anti-inflammatory bacteria was observed, which correlated with reduced inflammatory activity [1].

The table below summarizes the principal molecular mechanisms and reported preclinical and clinical effects of sodium butyrate in inflammatory bowel disease and colorectal cancer, based on available experimental and clinical evidence.

Table 1. Mechanisms of action and reported preclinical and clinical effects of sodium butyrate in inflammatory bowel disease and colorectal cancer

Disease entity	Mechanism of action	Effects	References
Ulcerative colitis	Inhibition of ferroptosis; modulation of ERK/STAT3 signaling; reduction of oxidative stress; activation of Nrf2/GPX4-related pathways; improvement of intestinal barrier integrity; modulation of gut microbiota	Decreased disease activity index, reduced pro-inflammatory cytokine expression, lower oxidative stress markers, improved histopathological findings, improved epithelial barrier function; in clinical studies, reduced inflammatory activity and improved selected clinical parameters	[1,6,7,9-12,15,16]
Crohn's disease	Regulation of intestinal barrier function; modulation of gut microbiota; reduction of inflammatory activity	Limited clinical data; potential improvement in epithelial integrity and selected inflammatory parameters in inflammatory bowel disease populations including Crohn's disease	[5,17,18]

Colorectal cancer (CRC)	Histone deacetylase inhibition; induction of apoptosis; cell cycle arrest; metabolic rewiring; modulation of CD44/SLC7A11 and NCOA4/FTH1 pathways; induction of ferroptosis	Reduced colorectal cancer cell proliferation, increased apoptosis and differentiation, inhibition of migration, enhanced ferroptotic cell death	[19–27,31–34,37]
Combination therapy (CRC)	Synergistic interaction with 5-fluorouracil (5-FU)	Increased antitumor efficacy and improved sensitivity to chemotherapy in preclinical models	[28,29]

## 5. RESULTS OF CLINICAL TRIALS IN IBD

Randomized clinical trials in ulcerative colitis have shown a reduction in disease activity during sodium butyrate supplementation, as assessed by clinical and laboratory indicators when using microencapsulated sodium butyrate as adjunctive therapy [15,16]. Improvements in inflammatory markers and quality-of-life parameters were observed, with a good safety profile for the therapy.

Table 2 summarizes key clinical studies evaluating sodium butyrate in inflammatory bowel diseases, including study design, patient populations, dosing regimens, treatment duration, and reported clinical outcomes.

*Table 2. Clinical studies evaluating sodium butyrate in inflammatory bowel diseases*

Authors (years)	Study design	Number of patients	Disease	Form and dosage of sodium butyrate	Duration	Main clinical outcomes
Firoozi et al. (2024)	Double-blind randomized placebo-controlled trial	36	Active ulcerative colitis	Oral sodium butyrate, 600 mg/kg with the main meal	12 weeks	Reduction in Mayo score, ESR, and neutrophil-to-lymphocyte ratio; improvement in sleep quality, quality of life, anxiety, and depression scores.
Pietrzak et al. (2022)	Randomized placebo-controlled multicenter trial	72	Pediatric inflammatory bowel disease (Crohn’s disease and ulcerative colitis)	Oral sodium butyrate, 150 mg twice daily (300 mg/day)	12 weeks	No significant difference versus placebo in remission rate, disease activity, or fecal calprotectin concentration; good safety profile.
Goldiş et al. (2025)	Randomized placebo-controlled trial	88	Pediatric inflammatory bowel disease	Microencapsulated sodium butyrate, 150 mg once daily	12 weeks	Higher remission rate, lower C-reactive

			(Crohn's disease and ulcerative colitis)			protein concentration, lower fecal calprotectin concentration, and lower disease activity scores compared with placebo; no significant adverse effects reported.
Vernero et al. (2020)	Prospective observational study	42	Ulcerative colitis in remission	Microencapsulated sodium butyrate, 500 mg twice daily (1000 mg/day)	12 months	Improved maintenance of remission, better quality of life, reduced abdominal pain, and favorable biochemical trends during follow-up.
Facchin et al. (2020)	Double-blind placebo-controlled pilot study	49	Inflammatory bowel disease	Microencapsulated oral sodium butyrate, 3 capsules/day (1800 mg/day)	60 days	Modulation of gut microbiota composition; the study mainly demonstrated microbiota-related effects, with limited direct clinical endpoint data.

## 6. ANTICANCER POTENTIAL IN COLORECTAL CANCER

In experimental studies, sodium butyrate has shown anticancer activity by inhibiting histone deacetylases (HDACs), inducing apoptosis, and regulating the cell cycle in colorectal cancer cells [19–25,37]. The “butyrate paradox” has also been described, resulting from metabolic variations between normal and cancer cells. This paradox indicates that in cancer cells, butyrate accumulates in the cell nucleus and has an enhanced epigenetic effect [19,20]. In addition, it has been shown that sodium butyrate regulates pathways involved in cell survival [24,31].

## 7. COMBINATION OF SODIUM BUTYRATE THERAPY WITH 5-FLUOROURACIL.

Scientific studies have shown that sodium butyrate increased the effectiveness of 5-fluorouracil by modulating mitochondrial signaling and remodeling the gut microbiota [28].

## DISCUSSION

An analysis of 45 publications from 2018 to 2025 indicates that sodium butyrate is associated with modulation of inflammatory, epigenetic, and metabolic processes in the large intestine. However, the majority of these data originate from experimental models, and their direct clinical relevance remains limited. The available evidence supports biological activity of sodium butyrate, but does not allow definitive conclusions regarding its therapeutic efficacy in patients.

One of the mechanisms most often discussed in recent studies is the inhibition of ferroptosis, an iron dependent form of

regulated cell death [1,9]. In DSS induced colitis models, sodium butyrate has been associated with reduced oxidative stress markers, modulation of iron related pathways, and improvement of histopathological findings [1,6–13]. These observations suggest that sodium butyrate may contribute to the attenuation of inflammatory tissue damage at the cellular level. Modulation of signaling pathways such as ERK and STAT3 has also been reported [1,7,12]. However, interpretation of these findings should remain cautious, since these pathways are involved in both epithelial repair and inflammatory regulation. At present, the available evidence does not allow a clear conclusion as to whether these effects translate into a consistent long term therapeutic benefit.

With regard to intestinal barrier integrity, experimental data consistently indicate that sodium butyrate serves as an energy source for colonocytes and is associated with regulation of tight junction protein expression [7,12]. These effects have been demonstrated primarily in preclinical models and are supported by limited clinical observations. In the analyzed clinical studies in ulcerative colitis, sodium butyrate supplementation was associated with reductions in selected inflammatory markers, including calprotectin, and with improvements in clinical activity indices in some trials [15,16]. At the same time, other studies did not demonstrate significant differences compared to control groups, and the overall evidence remains inconsistent. The included clinical studies differ in design, patient populations, dosing regimens, and outcome measures, which substantially limits comparability and does not allow firm conclusions regarding clinical efficacy.

The potential anticancer effect of sodium butyrate is supported primarily by preclinical studies. Reported mechanisms include histone deacetylase inhibition, induction of apoptosis, and regulation of cell cycle processes in colorectal cancer cells [19,20,25]. The so called butyrate paradox reflects differences in cellular metabolism between normal and malignant cells and may account for selective effects observed under experimental conditions [19,20].

Despite the substantial volume of experimental data, these effects have not been translated into consistent clinical evidence. This discrepancy may be explained by several factors. First, most studies are based on in vitro systems or animal models that do not adequately reproduce the complexity of human colorectal cancer, including tumor heterogeneity, microenvironment, and interactions with systemic therapies. Second, the concentrations of sodium butyrate used in experimental settings often exceed those achievable in vivo with standard formulations. Third, variability in drug delivery, including differences between oral and microencapsulated forms, may limit the ability to reach therapeutically relevant concentrations at the tumor site.

In addition, colorectal cancer development is influenced by multiple host and environmental factors, including microbiota composition, immune response, and metabolic status, which are not fully captured in controlled experimental models. As a result, the observed epigenetic and metabolic effects of sodium butyrate cannot be directly extrapolated to clinical outcomes.

At present, clinical data evaluating the anticancer efficacy of sodium butyrate are lacking. Therefore, its role in colorectal cancer prevention or treatment remains unproven, and any potential therapeutic application should be considered hypothetical until confirmed in well-designed clinical studies.

Studies reporting enhanced efficacy of 5 fluorouracil and modulation of microbial factors such as *Fusobacterium nucleatum* indicate possible interactions relevant for combination therapy [28,29]. These findings are of potential interest but are derived mainly from experimental settings and require confirmation in clinical studies.

## LIMITATIONS

This review is limited by the predominance of preclinical data, while clinical evidence remains scarce and insufficient for direct clinical translation. The included clinical studies are heterogeneous in design, endpoints, and outcome measures, which reduces comparability and weakens the reliability of conclusions. Considerable variability in dosage, treatment duration, and formulation of sodium butyrate further limits the identification of optimal therapeutic regimens.

Methodologically, the narrative design lacks standardized quality assessment and does not include quantitative synthesis, which introduces a risk of bias. The inclusion of review articles may lead to duplication of data and overestimation of effects. Publication bias toward positive findings and restriction to selected languages also limit completeness.

These limitations require cautious interpretation. Current evidence remains insufficient to support definitive clinical recommendations and should be considered hypothesis generating.

## CONCLUSIONS

Sodium butyrate is associated with regulation of intestinal homeostasis through anti inflammatory, antioxidant, and barrier related mechanisms demonstrated mainly in experimental models, while clinical relevance remains insufficiently established.

In inflammatory bowel disease, some studies report reductions in disease activity and inflammatory markers, but clinical

evidence is limited and heterogeneous, with inconsistent results.

Experimental data suggest potential anticancer effects in colorectal cancer, but these findings lack clinical confirmation.

Overall, current evidence does not support definitive clinical conclusions and remains insufficient to define its therapeutic role. Further well designed clinical studies are required.

## DISCLOSURE

### AUTHORS' CONTRIBUTIONS

Conceptualization: Błażej Boruszcak, Anna Aleksandra Szwankowska.

Literature search and data curation: Błażej Boruszcak, Karolina Jolanta Pilarska.

Methodology: Marta Kołodziej-Sieradz, Hubert Jarosław Ćwiek, Paulina Klaudia Gryz.

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Writing - review and editing: Kacper Komorowski, Anna Magdalena Terlecka, Anna Baczyńska. All authors have read and agreed with the final version of the manuscript.

### USE OF AI

ChatGPT was used solely to facilitate language editing and improve the clarity and arrangement of the manuscript. The authors independently developed the study concept, conducted the literature analysis, interpreted the data, and prepared the scientific content. All academic judgments and final decisions regarding the manuscript were made exclusively by the authors, ensuring full responsibility regarding its accuracy and scholarly value.

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