Butyrate: implications for intestinal function

Alda J. Leonel and Jacqueline I. Alvarez-Leite

Purpose of review
Butyrate is physiologically produced by the microbial fermentation of dietary fibers and plays a plurifunctional role in intestinal cells. This review examines the recent findings regarding the role and mechanisms by which butyrate regulates intestinal metabolism and discusses how these findings could improve the treatment of several gastrointestinal disorders.

Recent findings
Butyrate is more than a primary nutrient that provides energy to colonocytes and acts as a cellular mediator in those cells through several mechanisms. One remarkable property of butyrate is its ability to inhibit histone deacetylases, which is associated with the direct effects of butyrate and results in gene regulation, immune modulation, cancer suppression, cell differentiation, intestinal barrier regulation, oxidative stress reduction, diarrhea control, visceral sensitivity and intestinal motility modulation. All of these actions make butyrate an important factor for the maintenance of gut health.

Summary
From studies published over 30 years, there is no doubt of the important role that butyrate plays in maintaining intestinal homeostasis. However, despite these effects, clinical studies are still required to validate the routine use of butyrate in clinical practice and, specifically, in the treatment of intestinal diseases.

Keywords
butyrate, cancer, colon, inflammation, intestine, prebiotic, short-chain fatty acid

INTRODUCTION

Butyrate, a four-carbon short-chain fatty acid (SCFA), is the most interesting bacterial fermentation product in the human colon. Although butyrate can be absorbed within the gastrointestinal tract and into colonic epithelial cells, butyrate is transported mainly by specific carrier-mediated transport systems, including the electroneutral H^+-coupled monocarboxylate co-transporter 1 (i.e., MCT1 and SLC16A1) [1]. Once absorbed, colonocytes rapidly oxidize 95% of the butyrate into ketone bodies for ATP synthesis. Consequently, very little butyrate reaches the portal system [2▪].

The importance of butyrate for colon health is reinforced by the studies that show that colonocytes of patients with colon inflammatory diseases present with an impaired capacity to oxidize butyrate during the acute phase, which suggests that butyrate metabolic defects can be involved in the pathogenesis or severity of these diseases [3,4▪▪]. In addition to its trophic effects, butyrate can also exert other important actions related to cellular homeostasis, such as anti-inflammatory [5▪▪,6–8], antioxidant [9] and anticarcinogenic functions [10,11]. Most of the butyrate effects are related to its action as a histone deacetylase (HDAC) inhibitor [12▪▪]; the inhibitory function of butyrate keeps histones in a more acetylated state, which consequently affects the chromatin organization and leads to the activation of genes involved in cell differentiation, apoptosis and cell cycle arrest in malignant cells as well as the downregulation of inflammatory cytokine expression in intestinal mucosal cells [2▪]. Although butyrate affects several organs and extraintestinal tissues [12▪▪,13▪,14], this review will present the most studied functions and potential clinical uses of this fatty acid in the gastrointestinal tract.

Departamento de Bioquímica e Imunologia, Instituto de Ciências Biológicas, Universidade Federal de Minas Gerais, Belo Horizonte, Minas Gerais, Brazil

Correspondence to Jacqueline I. Alvarez-Leite, MD, PhD, Universidade Federal de Minas Gerais, Caixa Postal 486, Belo Horizonte, CEP 30161-970, Minas Gerais, Brazil. E-mail: alvarez@ufmg.br

Curr Opin Clin Nutr Metab Care 2012, 15:474–479
DOI:10.1097/MCO.0b013e32835665fa

KEY POINTS

- In addition to the trophic effects in the colon mucosa, butyrate can also exert other important actions related to cellular homeostasis, such as anti-inflammatory, antioxidant, anticarcinogenic and intestinal barrier functions.
- Most of the butyrate effects are related to its action as a HDAC inhibitor, which affects chromatin organization and leads to the activation of several genes.
- The paradoxical effect of butyrate in normal and malignant cells occurs because of the fact that almost all of the butyrate is oxidized to produce ATP, while in tumor cells it is inefficiently oxidized and reaches the nucleus, where several genes are regulated via butyrate-mediated HDAC inhibition.
- The mechanism of butyrate's anti-inflammatory action is related to the inhibition of nuclear factor kappa B (NF-κB), which controls the expression of genes that encode for proinflammatory cytokines, inflammation-inducing enzymes, adhesion molecules, growth factors, heat shock proteins and immune receptors.
- Butyrate effects go beyond cancer and inflammatory colon disorders, showing positive results reducing visceral sensitivity, mucositis secondary to chemotherapy and diarrhea following short bowel syndrome or dysbiosis.

ANTIDIARRHEAL FUNCTION

As a result of its absorption, butyrate promotes the absorption of sodium, potassium and water, which is responsible for its antidiarrheal properties. Butyrate or butyrate-producing prebiotics and probiotics can restore water absorption in patients who are affected by infectious diarrhea as well as congenital chloride diarrhea with a reduction in stool volume and a more rapid recovery following oral rehydration therapy [13▪,15]. Moreover, in patients with short bowel syndrome that progresses with a significant loss of water and sodium, butyrate administration improved diarrhea management by reducing the requirement for intravenous electrolyte replacement [16].

Diarrhea is also a well recognized complication in critically ill patients. Dysbiosis, which is one of the primary causes of diarrhea, is caused by an antibiotic disturbance of the microbiota that suppresses fermentation and reduces butyrate production [17▪▪]. In patients receiving fiber-supplemented enteral, fiber supplementation increased the amount of fecal butyrate and specific butyrate-producing bacteria [18,19▪], with the resolution of diarrhea in 75% of the patients [19▪].

BUTYRATE AND COLON CANCER

Although some studies have not confirmed the beneficial effects of butyrate on colon cancer prevention [20,21▪▪,22], several studies reported the beneficial effects of butyrate on the control of cancer colon [10,11,23–27]. The main action of butyrate in cancer colon cells is the induction of cellular apoptosis and cell cycle arrest as a consequence of cell proliferation inhibition [6,11]. Several of the anticancer mechanisms directly result from either butyrate action or its HDAC inhibitor activity [12▪▪]. There is vast literature concerning the cancer-protecting mechanisms of butyrate, including the upregulation of p21, WAF1 downregulation of apoptotic regulator Neuropilin-1 (NRP-1), the upregulation of BAK and downregulation of Bcl-xL and cyclin D1, the upregulation of death receptor pathway inhibition of DNA methylation and the modulation of canonical Wnt signaling, a pathway constitutively activated in the majority of colorectal cancers [13▪,23,24,27–29]. Moreover, butyrate transcriptionally upregulates detoxifying enzymes that protect cells from genotoxic carcinogens [11].

This effect is the opposite of that observed in the colonocytes from a normal inflamed colon, in which butyrate increases cell metabolism and proliferation. This paradoxical effect can be explained by the metabolic characteristics of these cells. In a normal colonocyte, almost all of the butyrate is used to produce ATP by the synthetic pathways, which results in cell proliferation. However, in tumor cells with a predominantly anaerobic metabolism, butyrate is inefficiently oxidized and reaches the nucleus, where several genes are regulated via butyrate-mediated HDAC inhibition [30,31▪▪].

BUTYRATE AND INFLAMMATION

Butyrate may exert anti-inflammatory activity by several mechanisms. Among these mechanisms are the reduction of proinflammatory IFN-γ, TNF-α, IL-1β, IL-6, IL-8, induction of IL-10 and TGF-β expression and signaling, the induction of nitric oxide synthase (iNOS) and metalloproteinases and the reduction of lymphocyte proliferation and activation [2▪,6,8,23,29,32,33▪].

The most studied mechanism of butyrate anti-inflammatory action is the inhibition of nuclear factor kappa B (NF-κB) [7,8,32], which controls the expression of genes that encode for pro-inflammatory cytokines, inflammation-inducing enzymes, adhesion molecules, growth factors, heat shock proteins and immune receptors [8]. Butyrate activity, which modulates NF-κB in different cell types, including cancer cell lines, cells from colon lamina propria, macrophages, neutrophils and

monocytes [8,34], is associated with its potential to inhibit HDACs [7].

Cell adhesion is also influenced by butyrate because butyrate reduces the expression of adhesion molecules, such as ICAM-1, V-CAM and E-selectin, in human umbilical endothelial cells [34–37]. Additionally, the inhibition of proinflammatory mediators released by mast cells and neutrophils was also observed following butyrate treatment [8,36,37].

INFLAMMATORY BOWEL DISEASE

Several studies have reported the association of impaired butyrate metabolism with mucosal damage and inflammation in patients with acute inflammatory bowel disease (IBD), mainly ulcerative colitis [4▪▪,5▪▪,38,39,40▪▪,41]. Defective colonic epithelial oxidation of butyrate in ulcerative colitis has been implicated in its pathogenesis. The mitochondrial enzyme acetoacetyl CoA thiolase, which is responsible for butyrate oxidation as well as 3-hydroxy-3-methylglutaryl CoA synthase 2 (mHMGCS2), an enzyme that regulates butyrate ketogenesis is reduced in the colons of ulcerative colitis patients [42▪▪].

Decreased mucosal sulfide detoxification related to impaired butyrate oxidation [43] as well as reduced absorption caused by MCT1 transporter downregulation [4▪▪,38] have been described in ulcerative colitis patients. In those patients, a concomitant glucose transporter GLUT1 induction suggests that inflammation could induce a metabolic switch from butyrate to glucose oxidation [38].

Although butyrate or prebiotic intakes clearly show a positive effect in experimental studies of IBD, mainly ulcerative colitis, [3,33▪,44], clinical studies show conflicting results [45▪▪]. Biopsies from IBD patients show an improvement in inflammation symptoms following butyrate irrigation. However, high concentrations of butyrate are required in IBD patients to inhibit the release of the proinflammatory cytokines. Moreover, rectal butyrate enemas have only minor effects on inflammatory and oxidative stress parameters in ulcerative colitis patients in remission that present with low-grade oxidative stress and inflammation [3]. Ulcerative colitis treatment results concerning the association of butyrate and conventional drugs, such as mesalazine, have presented conflicting results, and until now, there is no formal indication for such an association [46].

EFFECTS ON THE SMALL INTESTINE

The effects of butyrate in the gastrointestinal tract extend beyond the colon by influencing the integrity and immune defenses of the small intestine. Experimental studies indicate that oral butyrate administration improves the structural and functional indexes of adaptation in short bowel syndrome [16]. Moreover, butyrate potentiates the effect of anticancer drug therapy, such as ARA-C, vincristine, celecoxib, cisplatin and etoposide [31▪▪,47,48,49▪▪,50]. All of these data indicate that butyrate is an important agent to maintain or accelerate small bowel repair and regeneration.

The mechanistic action of butyrate on intestinal cells is not completely understood but can include anti-inflammatory and antioxidant actions, which are similar to those observed in the colon. Moreover, unlike colon fermentation, the oral administration of butyrate exposes the stomach and small intestinal mucosa to this fatty acid before it reaches the colon, thereby promoting higher concentrations in the liver [14]. In the liver, butyrate can be metabolized into glutamate, glutamine and acetoacetate, which are important fuels for enterocytes. Butyrate also increases pancreatic secretion and jejunal brush-border enzymatic activity [51], which increases nutrient availability that is necessary for enterocyte regeneration and stimulates GLP-2 that enhances bowel digestive and absorptive capacity [52].

ANTIOXIDANT EFFECT

Butyrate may also reduce oxidative stress induced by colon inflammation that is related to the disruption of the intestinal barrier and cancer induction. Butyrate can control oxidative stress by several mechanisms [2▪,8,13▪,45▪▪]. A study conducted in the colon biopsies of healthy volunteers after a rectal butyrate infusion showed a higher concentration of the antioxidant glutathione (GSH) and a decreased uric acid production compared to the placebo treatment [9]. Physiological concentrations of butyrate reduced H_2O_2-induced DNA damage, increased the expression of catalase and reduced the expression of cyclooxygenase-2 in human colonocytes [53].

EFFECTS ON INTESTINAL BARRIER

Butyrate plays an important role in the maintenance of the barrier function [10,32]. The mucus layer is a major factor in the protection of the intestinal epithelium and mainly consists of mucin glycoproteins (primarily MUC2 in the colon), trefoil factor 3 (TFF3) and secretory IgA. Experimental studies show that butyrate stimulates MUC2 synthesis [10,32] and also increases the expression of tff3, the gene responsible for synthesis of trefoils factors, peptides which are also constituents of mucus [54]. However, a clinical study found no differences in the colonic

MUC2 and TFF3 expression levels after butyrate irrigation [3].

The effect of butyrate on the intestinal barrier has been demonstrated in the Caco-2 cell monolayer model and occurs, at least in part, by facilitating the assembly of tight junctions. Specifically, butyrate accelerates the relocation of ZO-1 and occludin to the tight junctions during calcium switch-induced tight junction assembly, which enhances the barrier function. This dynamic process is mediated by AMPK activation [55].

Butyrate also reduces bacterial translocation in animal models of inflammatory disease [39] associated with the decreased expression of steA, which is a virulence effector associated with *Salmonella enterica* translocation [56].

EFFECTS ON THE ENTERIC NERVOUS SYSTEM

The effects of butyrate on the enteric nervous system (ENS) were studied in the colons of rats given an intracecal perfusion of SCFAs and in primary ENS cultures [57]. These results suggest that butyrate increased the proportion of acetyltransferase-immunoreactive myenteric neurons and colonic motility and contractile response induced by electrical stimulation by the cholinergic pathways. Induction of a cholinergic phenotype by butyrate involved monocarboxylate co-transporter-2, which was specifically detected in enteric neurons. This effect of butyrate on acetyltransferase expression is involved in the Src-kinase signaling pathway and the acetylation of histone H3 lysine 9, which suggests that butyrate could play an important role in controlling neuromediator gene expression in the enteric nervous system and, consequently, on intestinal motility.

A study in which volunteers underwent daily self-administered butyrate rectal enemas reported that this treatment resulted in a dose-dependent reduction in pain, urges and discomfort after a rectal barostat, which suggests that butyrate decreases visceral sensitivity in healthy humans [58]. This reduction in visceral perception could be caused by directly modulating 5-hydroxytryptamine (5-HT or serotonin) release and activating transient receptor potential vanilloid 1 (TRPV1) receptors in the colonic mucosa, which in turn may indirectly lead to the release of 5-HT in the gut to alter the perception of pain and alternatively attenuate visceral perception via HDAC inhibition [59▪▪].

A recent animal study demonstrated that chronic feeding with a diet that contained 4% enzyme-treated rice fiber enhanced the expression of stress-induced visceral analgesia, thereby reducing the number of animals that displayed stress-induced colonic microscopic alterations by 2.2-fold [60▪▪].

ALTERNATIVE STRATEGIES FOR BUTYRATE DELIVERY IN THE GASTROINTESTINAL TRACT

Many of the effects of butyrate have been defined in cell culture systems or indirectly by the ingestion of probiotics and prebiotics that produce butyrate. Despite its positive effects, the clinical use of butyrate is still limited by its short half-life, its fast metabolism and excretion and the side-effects observed with its oral use, such as headache, nausea and anorexia. Rectal enemas and irrigation are the most common methods, but they impose low acceptability and require several daily applications [61–63]. Alternatives for increasing the amount of butyrate that reaches the colon environment are being studied. Coated tablets and microparticles and nanoparticles that contain butyrate or butyrate-producing prebiotics and probiotics have been tested in IBDs and have shown promising results [11,49▪▪,64,65].

Tributyrin is an oily (liquid) triglyceride that contains three butyrate moieties esterified with glycerol. Tributyrin can be delivered orally and releases butyrate when metabolized by intestinal enzymes. Tributyrin is a component of a variety of foodstuffs that contain dairy products, especially butter. One gram of tributyrin produces 10 mmol of butyrate [66▪]. Because butyrate is proven to be effective when used for the treatment and prevention of intestinal diseases, the oral supplementation of tributyrin in the dietary routine of susceptible patients is a promising alternative [49▪▪,63,66▪]. In animal models, oral administration of tributyrin (1.0 g/kg) resulted in substantial concentrations of butyrate in the portal vein (i.e., 2.4 mM at 1 h and 0.7 mM at 2.5 h) [66▪]. In a clinical study, 20 patients with advanced solid tumors were treated with tributyrin at doses that ranged from 150 to 200 mg/kg three times daily. The results did not show dose-limiting toxicity, and a median butyrate concentration of 52 μM was obtained [67]; this value is at the lower end of the range of effects (50–100 μM) related to butyrate on differentiation and apoptosis. Although more studies are needed, these results demonstrate that oral administration of tributyrin is well tolerated and has similar effects compared with butyrate administration.

CONCLUSION

From these recent studies and several others published during the past 30 years, there is no doubt

concerning the important role that butyrate plays on intestinal homeostasis. However, despite these effects, clinical studies are still required to confirm the routine use of butyrate in clinical practice and, specifically, in the treatment of intestinal diseases.

Acknowledgements

The authors are grateful to the following sources of support: Pro-reitoria de Pesquisa of Universidade Federal de Minas Gerais (PRPq), CNPq (National Counsel of Technological and Scientific Development) and CAPES (Coordination of Personal Improvement of Higher Education).

Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (pp. 517 518).

1. Goncalves P, Araujo JR, Martel F. Characterization of butyrate uptake by nontransformed intestinal epithelial cell lines. J Membr Biol 2011; 240:35 46.
2. ■ Macfarlane GT, Macfarlane S. Fermentation in the human large intestine: its physiologic consequences and the potential contribution of prebiotics. J Clin Gastroenterol 2011; 45 (Suppl.):S120 S127.

This study analyzes the importance of prebiotics and SCFAs on intestinal physiology.

3. Hamer HM, Jonkers DM, Vanhoutvin SA, et al. Effect of butyrate enemas on in ammation and antioxidant status in the colonic mucosa of patients with ulcerative colitis in remission. Clin Nutr 2010; 29:738 744.
4. ■■ De Preter V, Geboes KP, Bulteel V, et al. Kinetics of butyrate metabolism in the normal colon and in ulcerative colitis: the effects of substrate concentration and carnitine on the beta-oxidation pathway. Aliment Pharmacol Ther 2011; 34:526 532.

The authors investigated whether higher butyrate concentrations could normalize the oxidation rate in ulcerative colitis, concluding that the butyrate metabolism is signi cantly impaired in active ulcerative colitis and that the addition of compounds interfering with the β-oxidation pathway had no effect on the butyrate metabolism in ulcerative colitis.

5. ■■ Kovarik JJ, Tillinger W, Hofer J, et al. Impaired anti-in ammatory ef cacy of n-butyrate in patients with IBD. Eur J Clin Invest 2011; 41:291 298.

This study shows that there is an impaired sensitivity to the inhibitory action of butyrate in IBD and that it may constitute a determinant in the pathogenesis of these in ammatory diseases.

6. Bailon E, Cueto-Sola M, Utrilla P, et al. Butyrate in vitro immune-modulatory effects might be mediated through a proliferation-related induction of apoptosis. Immunobiology 2010; 215:863 873.
7. Lakhdari O, Tap J, Beguet-Crespel F, et al. Identi cation of NF-kappaB modulation capabilities within human intestinal commensal bacteria. J Biomed Biotechnol 2011; 41:282356; doi: 10.1155/2011/282356.
8. Vinolo MA, Rodrigues HG, Hatanaka E, et al. Suppressive effect of short-chain fatty acids on production of proin ammatory mediators by neutrophils. J Nutr Biochem 2011; 22:849 855.
9. Hamer HM, Jonkers DM, Bast A, et al. Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. Clin Nutr 2009; 28:88 93.
10. Bai Z, Zhang Z, Ye Y, Wang S. Sodium butyrate induces differentiation of gastric cancer cells to intestinal cells via the PTEN/phosphoinositide 3-kinase pathway. Cell Biol Int 2010; 34:1141 1145.
11. Clarke JM, Young GP, Topping DL, et al. Butyrate delivered by butyrylated starch increases distal colonic epithelial apoptosis in carcinogen-treated rats. Carcinogenesis 2012; 33:197 202.
12. ■■ Canani RB, Di Costanzo M, Leone L. The epigenetic effects of butyrate: potential therapeutic implications for clinical practice. Clin Epigenet 2012; 4:4; doi: 10.1186/1868-7083-4-4.

This review is focused on the recent data regarding the epigenetic effects of butyrate (as HDAC inhibitor) with potential clinical implications in human medicine.

13. ■ Canani RB, Costanzo MD, Leone L, et al. Potential bene cial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol 2011; 17:1519 1528.

This review discusses the anti-in ammatory, antioxidant and anticancer effects of butyrate in intestinal and extraintestinal tissues.

14. Guilloteau P, Martin L, Eeckhaut V, et al. From the gut to the peripheral tissues: the multiple effects of butyrate. Nutr Res Rev 2010; 23:366 384.
15. Canani RB, Terrin G, Cirillo P, et al. Butyrate as an effective treatment of congenital chloride diarrhea. Gastroenterology 2004; 127:630 634.
16. Tappenden KA. Emerging therapies for intestinal failure. Arch Surg 2010; 145:528 532.
17. ■■ Whelan K, Schneider SM. Mechanisms, prevention, and management of diarrhea in enteral nutrition. Curr Opin Gastroenterol 2011; 27:152 159.

This review focuses on the mechanisms of diarrhea during enteral nutrition and discusses emerging evidences for its prevention and management, especially by the use of prebiotics and probiotics and their subproduct, butyrate.

18. Majid HA, Emery PW, Whelan K. Faecal microbiota and short-chain fatty acids in patients receiving enteral nutrition with standard or fructo-oligosaccharides and bre-enriched formulas. J Hum Nutr Diet 2011; 24:260 268.
19. ■ O'Keefe SJ, Ou J, Delany JP, et al. Effect of ber supplementation on the microbiota in critically ill patients. World J Gastrointest Pathophysiol 2011; 2:138 145.

This study shows that critically ill patients receiving elemental diet and broad-spectrum antibiotics present suppression of the colonic microbiota and butyrate production. Diet supplementation with butyrate-producing ber has the potential to improve microbiota mass and function, thereby reducing the risks of diarrhea because of dysbiosis.

20. Turk HF, Kolar SS, Fan YY, et al. Linoleic acid and butyrate synergize to increase Bcl-2 levels in colonocytes. Int J Cancer 2011; 128:63 71.
21. ■■ Serpa J, Caiado F, Carvalho T, et al. Butyrate-rich colonic microenvironment is a relevant selection factor for metabolically adapted tumor cells. J Biol Chem 2011; 285:39211 39223.

This study highlights the possible adverse effect of butyrate in tumor cells. The results show that aggressive tumor cells that retain the capacity of metabolizing butyrate are positively selected when cultivated in presence of butyrate. These selected cells are able to colonize the animals locally and at distant organs.

22. Silva FG, Penido LC, Valente FX, et al. Sodium butyrate does not decrease the evolution of precancerous lesions in rats. Acta Cir Bras 2010; 25:507 512.
23. Daroqui MC, Augenlicht LH. Transcriptional attenuation in colon carcinoma cells in response to butyrate. Cancer Prev Res (Phila) 2010; 3:1292 1302.
24. Yu DC, Waby JS, Chirakkal H, et al. Butyrate suppresses expression of neuropilin I in colorectal cell lines through inhibition of Sp1 transactivation. Mol Cancer 2010; 9:276; doi: 10.1186/1476-4598-9-276.
25. Scharlau D, Borowicki A, Habermann N, et al. Mechanisms of primary cancer prevention by butyrate and other products formed during gut ora-mediated fermentation of dietary bre. Mutat Res 2009; 682:39 53.
26. Dos Santos MP, Schwartsmann G, Roesler R, et al. Sodium butyrate enhances the cytotoxic effect of antineoplastic drugs in human lymphoblastic T-cells. Leuk Res 2009; 33:218 221.
27. Bordonaro M, Tewari S, Cicco CE, et al. A switch from canonical to non-canonical Wnt signaling mediates drug resistance in colon cancer cells. PLoS One 2011; 6:e27308; doi: 10.1371/journal.pone.0027308.
28. Hofmanova J, Ciganek M, Slavik J, et al. Lipid alterations in human colon epithelial cells induced to differentiation and/or apoptosis by butyrate and polyunsaturated fatty acids. J Nutr Biochem 2012; 23:430 436.
29. Cao Y, Gao X, Zhang W, et al. Dietary ber enhances TGF-beta signaling and growth inhibition in the gut. Am J Physiol Gastrointest Liver Physiol 2011; 301:G156 G164.
30. Zhou Q, Dalgard CL, Wynder C, Doughty ML. Histone deacetylase inhibitors SAHA and sodium butyrate block G1-to-S cell cycle progression in neurosphere formation by adult subventricular cells. BMC Neurosci 2011; 12:50; doi: 10.1186/1471-2202-12-50.
31. ■■ Koprinarova M, Botev P, Russev G. Histone deacetylase inhibitor sodium butyrate enhances cellular radiosensitivity by inhibiting both DNA nonhomologous end joining and homologous recombination. DNA Repair (Amst) 2011; 10:970 977.

This study shows, using HeLa cells, that butyrate could be used as a radiosensitizer, reducing the radiation doses and, consequently, the adverse effects of the treatment.

32. Hudcovic T, Kolinska J, Klepetar J, et al. Protective effect of Clostridium tyrobutyricum in acute dextran sodium sulphate-induced colitis: differential regulation of tumour necrosis factor-alpha and interleukin-18 in BALB/c and severe combined immunode ciency mice. Clin Exp Immunol 2012; 167:356 365.
33. ■ Vieira EL, Leonel AJ, Sad AP, et al. Oral administration of sodium butyrate attenuates in ammation and mucosal lesion in experimental acute ulcerative colitis. J Nutr Biochem 2011.

This study shows that the oral administration of butyrate improves mucosa lesion and attenuates the in ammatory pro le of intestinal mucosa, local draining lymph nodes and Peyer's patches in DSS-induced colitis, detailing the immune pathways that could be controlled by butyrate administration.

34. Maa MC, Chang MY, Hsieh MY, et al. Butyrate reduced lipopolysaccharide-mediated macrophage migration by suppression of Src enhancement and focal adhesion kinase activity. J Nutr Biochem 2010; 21:1186 1192.

35. Minelli R, Serpe L, Pettazzoni P, et al. Cholesteryl butyrate solid lipid nanoparticles inhibit the adhesion and migration of colon cancer cells. Br J Pharmacol 2012; 166:587 601.
36. Menzel T, Luhrs H, Zirlik S, et al. Butyrate inhibits leukocyte adhesion to endothelial cells via modulation of VCAM-1. In amm Bowel Dis 2004; 10:122 128.
37. Zapolska-Downar D, Siennicka A, Kaczmarczyk M, et al. Butyrate inhibits cytokine-induced VCAM-1 and ICAM-1 expression in cultured endothelial cells: the role of NF-kappaB and PPARalpha. J Nutr Biochem 2004; 15:220 228.
38. Thibault R, Blachier F, Darcy-Vrillon B, et al. Butyrate utilization by the colonic mucosa in in ammatory bowel diseases: a transport de ciency. In amm Bowel Dis 2010; 16:684 695.
39. Lewis K, Lutgendorff F, Phan V, et al. Enhanced translocation of bacteria across metabolically stressed epithelia is reduced by butyrate. In amm Bowel Dis 2010; 16:1138 1148.
40. ■■ De Preter V, Arijs I, Windey K, et al. Impaired butyrate oxidation in ulcerative colitis is due to decreased butyrate uptake and a defect in the oxidation pathway. In amm Bowel Dis 2012; 18:1127 1136.
Using colonic mucosal biopsies of ulcerative colitis and control patients, the authors show that the de ciency in the colonic butyrate metabolism in ulcerative colitis is initiated at the gene-expression level and is the result of a decreased expression of monocarboxylate transporter 1 encoding gene SLC16A1 and enzymes in the butyrate β-oxidation pathway.
41. Scholz D. The role of nutrition in the etiology of in ammatory bowel disease. Curr Probl Pediatr Adolesc Healthcare 2011; 41:248 253.
42. ■■ Lepage P, Hasler R, Spehlmann ME, et al. Twin study indicates loss of interaction between microbiota and mucosa of patients with ulcerative colitis. Gastroenterology 2011; 141:227 236.
The study shows that transcriptional pro le of the mucosa appears to interact with the colonic microbiota; this interaction appears to be lost in the colon of patients with ulcerative colitis. Bacterial functions, such as butyrate production, might affect mucosal gene expression.
43. De Preter V, Arijs I, Windey K, et al. Decreased mucosal sul de detoxi cation is related to an impaired butyrate oxidation in ulcerative colitis. In amm Bowel Dis 2012.
44. Komiyama Y, Andoh A, Fujiwara D, et al. New prebiotics from rice bran ameliorate in ammation in murine colitis models through the modulation of intestinal homeostasis and the mucosal immune system. Scand J Gastroenterol 2011; 46:40 52.
45. ■■ Russo I, Luciani A, De Cicco P, et al. Butyrate attenuates lipopolysaccharide-induced in ammation in intestinal cells and Crohn's mucosa through modulation of antioxidant defense machinery. PLoS One 2012; 7:e32841; doi: 10.1371/journal.pone.0032841.
This study was conducted in the biopsies of colonic mucosa from normal and Crohn's disease patients challenged with LPS, in presence of butyrate. The results show that butyrate rescues the redox machinery and controls the intracellular ROS balance, reducing LPS-induced in ammation.
46. Cottone M, Renna S, Modesto I, Orlando A. Is 5-ASA still the treatment of choice for ulcerative colitis? Curr Drug Targets 2011; 12:1396 1405.
47. Maruyama T, Yamamoto S, Qiu J, et al. Apoptosis of bladder cancer by sodium butyrate and cisplatin. J Infect Chemother 2012; 18:288 295.
48. Ramos MG, Rabelo FL, Brumatti G, et al. Butyrate increases apoptosis induced by different antineoplastic drugs in monocytic leukemia cells. Chemotherapy 2004; 50:221 228.
49. ■■ Kang SN, Hong SS, Lee MK, Lim SJ. Dual function of tributyrin emulsion: solubilization and enhancement of anticancer effect of celecoxib. Int J Pharm 2012; 428:76 81.
This study analyzes the effect of combined treatment of human colon cancer cells with the selective COX-2 inhibitor celecoxib plus tributyrin emulsion, showing that the combination inhibited the cellular proliferation more effectively than that of each drug alone, suggesting that tributyrin emulsion can be used as a potential celecoxib carrier.
50. Palani CD, Beck JF, Sonnemann J. Histone deacetylase inhibitors enhance the anticancer activity of nutlin-3 and induce p53 hyperacetylation and downregulation of MDM2 and MDM4 gene expression. Invest New Drugs 2012; 30:25 36.
51. Guilloteau P, Savary G, Jaguelin-Peyrault Y, et al. Dietary sodium butyrate supplementation increases digestibility and pancreatic secretion in young milk-fed calves. J Dairy Sci 2010; 93:5842 5850.
52. Hornby PJ, Moore BA. The therapeutic potential of targeting the glucagon-like peptide-2 receptor in gastrointestinal disease. Expert Opin Ther Targets 2011; 15:637 646.
53. Sauer J, Richter KK, Pool-Zobel BL. Physiological concentrations of butyrate favorably modulate genes of oxidative and metabolic stress in primary human colon cells. J Nutr Biochem 2007; 18:736 745.
54. Song M, Xia B, Li J. Effects of topical treatment of sodium butyrate and 5-aminosalicylic acid on expression of trefoil factor 3, interleukin 1beta, and nuclear factor kappaB in trinitrobenzene sulphonic acid induced colitis in rats. Postgrad Med J 2006; 82:130 135.
55. Peng L, Li ZR, Green RS, et al. Butyrate enhances the intestinal barrier by facilitating tight junction assembly via activation of AMP-activated protein kinase in Caco-2 cell monolayers. J Nutr 2009; 139:1619 1625.
56. Cardenal-Munoz E, Ramos-Morales F. Analysis of the expression, secretion and translocation of the Salmonella enterica type III secretion system effector SteA. PLoS One 2011; 6:e26930; doi: 10.1371/journal.pone.0026930.
57. Soret R, Chevalier J, De Coppet P, et al. Short-chain fatty acids regulate the enteric neurons and control gastrointestinal motility in rats. Gastroenterology 2010; 138:1772 1782.
58. Vanhoutvin SA, Troost FJ, Kilkens TO, et al. The effects of butyrate enemas on visceral perception in healthy volunteers. Neurogastroenterol Motil 2009; 21:e952 e976.
59. ■■ Kannampalli P, Shaker R, Sengupta JN. Colonic butyrate algesic or analgesic? Neurogastroenterol Motil 2011; 23:975 979.
This review discusses the studies and molecular mechanisms responsible for the effect of butyrate in IBS patients.
60. ■■ Larauche M, Mulak A, Yuan PQ, et al. Stress-induced visceral analgesia assessed noninvasively in rats is enhanced by prebiotic diet. World J Gastroenterol 2012; 18:225 236.
This animal study provides the rst evidence of enhanced psychological stress-related visceral analgesia by chronic intake of a butyrate-producing prebiotic.
61. Dianzani C, Cavalli R, Zara GP, et al. Cholesteryl butyrate solid lipid nanoparticles inhibit adhesion of human neutrophils to endothelial cells. Br J Pharmacol 2006; 148:648 656.
62. Gassull MA. Review article: the intestinal lumen as a therapeutic target in in ammatory bowel disease. Aliment Pharmacol Ther 2006; 24:90 95.
63. Hamer HM, Jonkers D, Venema K, et al. Review article: the role of butyrate on colonic function. Aliment Pharmacol Ther 2008; 27:104 119.
64. Roda A, Simoni P, Magliulo M, et al. A new oral formulation for the release of sodium butyrate in the ileo-cecal region and colon. World J Gastroenterol 2007; 13:1079 1084.
65. Rose DJ, Venema K, Keshavarzian A, Hamaker BR. Starch-entrapped microspheres show a bene cial fermentation pro le and decrease in potentially harmful bacteria during in vitro fermentation in faecal microbiota obtained from patients with in ammatory bowel disease. Br J Nutr 2010; 103:1514 1524.
66. ■ Miyoshi M, Sakaki H, Usami M, et al. Oral administration of tributyrin increases concentration of butyrate in the portal vein and prevents lipopolysaccharide-induced liver injury in rats. Clin Nutr 2011; 30:252 258.
This study shows the effects of tributyrin on livers, showing that the oral administration is able to increase plasma butyrate in the portal vein and attenuate liver injury in endotoxemic rats.
67. Edelman MJ, Bauer K, Khanwani S, et al. Clinical and pharmacologic study of tributyrin: an oral butyrate prodrug. Cancer Chemother Pharmacol 2003; 51:439 444.