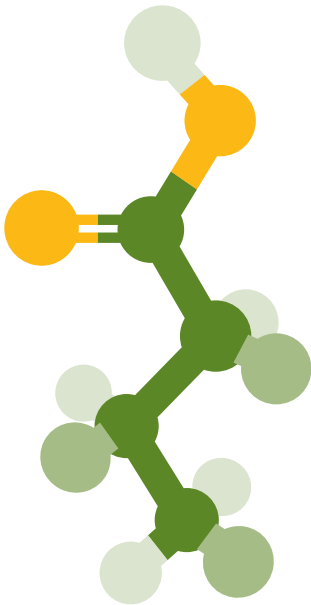




Butyrate's Important Role in Overall Human Health



Butyrate

Introduction: EpiCor fermentate, a dietary ingredient manufactured by Embria Health Sciences, was shown to have prebiotic-like activity in a laboratory model of human digestion.¹ One of the more surprising results was that the EpiCor-induced changes in bacterial populations, including lactobacillus and bifidobacteria, resulted in an equal or greater production of butyrate *in vitro* as compared to the well-known prebiotic fibers inulin and fructo-oligosaccharide (FOS). This led Embria to look more closely at the published benefits of short chain fatty acids (SCFAs), and to the role of butyrate in particular.

Summary: Butyrate is well known for its role as a mediator of colonic inflammatory response. More recent research in humans has shown butyrate's crucial role in gut homeostasis through effects on metabolism, immune response, cancer and more. This paper takes an in-depth look into research on how butyrate supports human health through a variety of mechanisms:

- Acting as the most important SCFA for colonocyte metabolism
- Modulating various proteins that regulate barrier function, a key aspect of pathogen control in the gut
- Reducing inflammation; possibly the inflammation associated with ulcerative colitis, a form of inflammatory bowel disease (IBD)
- Acting through several mechanisms to prevent infection
- Possibly reducing the risk of colorectal cancer



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Short Chain Fatty Acids

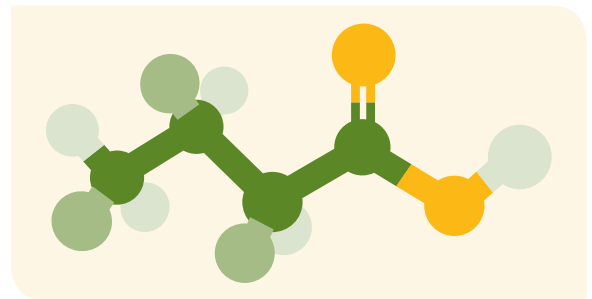
A fatty acid is a carboxylic acid with an aliphatic tail. SCFAs, also known as volatile fatty acids, are a sub-group of fatty acids with chain lengths of six or less carbons. Humans do not produce SCFAs directly – they are the major end products of carbohydrate (dietary fiber) fermentation in the colon by commensal bacteria. The group of SCFAs includes formic acid, acetic acid, propionic acid, isobutyric acid (2-methylpropanoic acid), butyric acid, isovaleric acid (3-methylbutanoic acid) and valeric acid (pentanoic acid). The three major SCFAs are acetate, propionate and butyrate.² While amounts and ratios are dependent on many factors, including diet and resident microflora, in general acetate is most prevalent followed by propionate and butyrate; occurring in an approximate 60:20:20 molar ratio.³ SCFAs function as a major energy source for colonic epithelial cells (colonocytes). Butyrate, although the least abundant of the three major SCFAs, is the most important SCFA for colonocyte metabolism; up to 70-90% of butyrate is metabolized by colonocytes.⁴

In addition to the well-known function of SCFAs as the preferred energy source of colonocytes, SCFAs also play an important role in maintaining normal colon function and prevention of disease. For example, propionate along with the other major SCFAs may help protect against diet-induced obesity.⁵ Although all three major SCFAs are important for gut health, butyrate in particular plays an extensive role in gut homeostasis,⁶ which is the common term describing a healthy interaction between the gut, the resident bacteria and the immune system.

Butyrate Production

As discussed, one of the major SCFAs is butyrate. This simple 4-carbon fatty acid is shown to the right.

Butyrate is produced in the colon by a phylogenetically diverse group of Gram-positive anaerobic bacteria belonging to the Firmicutes phylum. Two of the most important groups are *Faecalibacterium prausnitzii*, belonging to clostridial cluster IV, and *Eubacterium rectale*/Roseburia spp., belonging to clostridial cluster IVa.⁷ The main route for synthesis of butyrate is the catabolism of glucose through the Embden-Meyerhof-Parnas pathway and the subsequent condensation of two molecules of acetyl-CoA.⁸



Butyrate's anti-inflammatory and anti-carcinogenic properties in the gut

Inflammatory Bowel Disease IBD: The role of the intestinal barrier in gastrointestinal disease is the subject of increased attention and research conducted across many fields. There is considerable evidence that butyrate supports barrier function in the gut.⁹ Support of the paracellular tight junction (TJ) barrier would be beneficial for IBD. TJ barrier lesions are thought to be involved in “leaky gut” and may allow toxins and bacteria to escape from the intestines, resulting in inflammation and disease. Altered TJ structure resulting in deterioration of barrier function is thought to contribute to both types of IBD, ulcerative colitis¹⁰ and Crohn’s disease.¹¹ How butyrate supports barrier function is an area of active research, but it appears butyrate is able to modulate various proteins that regulate barrier function.^{12,13,14} Clinically, it is known that butyrate treatment can reduce inflammation associated with ulcerative colitis.¹⁵

Antimicrobial Activity: In addition to prevention of infection through support of barrier function, butyrate also acts through other mechanisms to prevent infection. For example, antimicrobial peptides (AMP), also known as host defense peptides (HDPs), are a critical part of innate immunity.¹⁶ The two major families of HDPs are defensins¹⁷ and cathelicidins.¹⁸ The only cathelicidin identified in humans is LL-37, a 37 amino acid α -helical peptide with strong antimicrobial activity.¹⁹ Butyrate has been shown to up-regulate LL-37 production in cultured human colon epithelial cells.²⁰ Since LL-37 is active against *Shigella* infections, and since butyrate increases levels of LL-37, the

question arises as to whether or not butyrate could be a treatment for infections like shigellosis. Butyrate treatment for *Shigella* infected rabbits resulted in reduced clinical illness, up-regulation of CAP-18 (the rabbit homologue to LL-37) and reduced inflammation and bacterial load in the feces.²¹ Butyrate has also been shown to enhance disease resistance to *Salmonella enteritidis* in chickens by inducing synthesis of various HDPs.²² In a human clinical trial, butyrate was found to reduce inflammation and improve rectal histopathology relative to placebo.²³

Anti-Carcinogenic Activity: As has been discussed, dietary fiber is fermented into butyrate and other SCFAs in the colon. The fact that butyrate plays a protective role for normal colonocytes but has the opposite effect on neoplastic cells has been referred to as the “butyrate paradox.”²⁴ Since epidemiological evidence suggests a protective role for dietary fiber,²⁵ much research has been done to determine the possible effects of butyrate on colorectal cancer (CRC). Early studies have shown that butyrate can arrest cancer cell proliferation and promote cell differentiation.²⁶ Many *in vitro* studies have shown butyrate induces apoptosis of CRC cells.²⁷ Butyrate is a known histone deacetylase inhibitor (HDACi).²⁸ As early as 1977 it was shown that butyrate caused histone modification in HeLa and Friend erythroleukaemia cells.²⁹ Histone deacetylase inhibitors induce growth arrest, differentiation and/or apoptosis of cancer cells *in vitro* and *in vivo*.³⁰ It is likely that butyrate has other targets in addition to HDAC.

DNA microarray analysis has indicated that butyrate may hyperacetylate other non-histone proteins, alter DNA methylation, inhibit histone phosphorylation and modulate intracellular kinase signaling.³¹ Considering all the evidence, butyrate seems an obvious candidate for cancer prevention and/or treatment. However, butyrate metabolizes rapidly making it difficult to get it to the colon to study its effects on CRC; therefore, alternative methods must be utilized. For example, in a study of bacterial populations in CRC patients, it was found that butyrate producers were significantly lower when compared to control subjects.³² In a separate study it was postulated that decreased butyrate producers and increased opportunistic pathogens constitute a major structural imbalance of gut microbiota in CRC patients.³³ Additionally, analysis of fecal extracts from CRC patients showed significantly lower concentrations of butyrate relative to controls.³⁴

One way to increase butyrate in the colon would be to create a more favorable environment for butyrate producers. This can be accomplished by consuming more dietary fiber. In one study CRC patients and control subjects consumed 10 grams of FOS per day for 3 months. It was concluded from this study that FOS affected the colonic environment and could be a factor in prevention of colorectal neoplasia.³⁵ Considering all the evidence, it has been suggested that human studies should be conducted to study the interactions between fiber, butyrate, gut microbiota, and prevention of CRC.³⁶

Conclusion

It is important to emphasize that SCFAs like butyrate are not produced directly by the human body, nor is butyrate stable or palatable enough to be taken directly. The level of butyrate production in the gut is primarily due to dietary habits, particularly to the consumption of dietary fiber. However, the average American consumes roughly 15 grams of dietary fiber, whereas some sources recommend that women get 25 grams of fiber per day and men up to 38 grams per day.³⁷ Therefore, the need for alternative measures beyond normal dietary intake as a possible source for butyrate production is apparent.

Of all the effects of butyrate discussed in this paper, some are more relevant to the consumption of dietary supplements such as EpiCor than others. Supporting a healthy gut wall and increasing the efficiency of tight junctions is of great importance. Similarly, regular consumption of natural food supplements that increase gut exposure to butyrate should have positive effects on the immune system and help support overall good health. The fact that EpiCor has been shown to significantly increase butyrate production *in vitro* helps explain its impact on the immune system in general, and suggests how it might help strengthen the body's natural defenses.



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