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Protective Effects of Short-Chain Fatty Acids on Gut Mucosa

Nurwiye^{1,2}, A Ellyanti³, N Hilbertina⁴ and Almurdi⁵

¹ Department of Biomedical, Faculty of Medicine, Andalas University, Padang, Indonesia.

² Department of Anatomical Pathology, Faculty of Medicine, Baiturrahmah University, Padang, West Sumatra, Indonesia.

³ Nuclear Medicine Division of the Radiology Department, Faculty of Medicine, Universitas Andalas, Padang, Indonesia.

⁴ Department of Anatomical Pathology, Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia.

⁵ Department of Clinical Pathology, Faculty of Medicine, Andalas University, Padang, West Sumatra, Indonesia.

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CORRESPONDING AUTHOR

*E-mail: aelliyanti@med.unand.ac.id

ABSTRACT

Background: Short-chain fatty acids (SCFAs) are key metabolites produced by microbial fibre fermentation and act as an epigenetic link between diet and gene expression. SCFA production is highly dependent on dietary fiber diversity to support a healthy microbial ecosystem. Through the gut-brain axis, SCFAs influence cognitive function by altering the brain's response to food signals and reducing systemic inflammation. Objective: This study aimed to determine the effects of short-chain fatty acids on the gastrointestinal mucosa and their relationships with diet, fibre, and the gut-brain axis. Methods: This study used a systematic review guided by PRISMA 2020 (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). The literature was searched across three databases: PubMed, EBSCO, and Scopus. The study selection process followed predetermined inclusion and exclusion criteria, and the results of included studies were systematically analyzed. Results: A total of 20 studies were analyzed. Most studies show that SCFAs can protect the gastrointestinal mucosa through a healthy microbiota balance and a proper diet, including a high-fiber diet. Conclusion: A high-fibre diet can produce SCFAs that regulate metabolic/inflammatory genes, improve intestinal mucosal function, enhance glucagon-like peptide-1 (GLP-1) secretion, improve glycemic/appetite control, and reduce the brain's response to high-calorie foods. It also lowers high-sensitivity C-reactive protein (hs-CRP)), improving stress, anxiety, and mental health.

Contribution to Sustainable Development Goals (SDGs):

SDG 3- Good Health and Well-Being

SDG 4:- Quality Education

SDG 12 – Responsible Consumption and Production

1. INTRODUCTION

1.1. Research Background

The intestinal mucosa is a crucial component in maintaining homeostasis of the digestive tract through its barrier, immunological, and metabolic functions. Interactions among intestinal epithelial cells, the immune system, and the gut microbiota strongly influence mucosal integrity. One of the main

mediators in this interaction is short-chain fatty acids (SCFAs), especially acetate, propionate, and butyrate, which are produced by the gut microbiota during fermentation of dietary fibre. SCFAs play a crucial role in maintaining intestinal mucosal function, particularly as an energy source for colonocytes, regulating epithelial cell proliferation and differentiation, and modulating intestinal barrier function and immune responses [1], [2]. In addition to local effects, SCFAs also regulate the gut-brain axis through neuroimmune and neuroendocrine mechanisms, thereby influencing central nervous system function and mental health.



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SCFA production is strongly influenced by dietary patterns, particularly by the consumption of fibre-rich foods. A high-fibre diet promotes gut microbiota diversity and increases SCFA production, whereas a low-fibre diet is associated with impaired gut mucosal function and disruption of the gut-brain axis [3].

High-fibre dietary interventions, such as prebiotic supplementation, have been shown to modulate gut-brain axis communication by influencing the composition and function of the gut microbiota. This study demonstrated that inulin administration to overweight individuals resulted in significant changes in the gut microbiota, specifically an increase in bacteria capable of producing short-chain fatty acids (SCFAs). Although no significant changes in systemic SCFA levels were detected, these shifts in the microbiota profile were associated with changes in brain activity as measured by fMRI, particularly a decreased response in brain areas involved in the reward system to high-calorie food stimuli. These findings indicate that the effects of a high-fibre diet on brain function are likely mediated by microbiota metabolites, including SCFAs, through gut-brain axis mechanisms that are not always reflected in circulating SCFA levels.^{3,4} Furthermore, increasing SCFA-producing bacteria indirectly supports the stability of the gut mucosal environment, given the role of SCFAs, particularly butyrate, in maintaining epithelial integrity and intestinal barrier function. Overall, these results strengthen the concept that high-fibre dietary patterns can influence neurological function and eating behaviour by modulating the gut microbiota and the gut-brain axis, with SCFAs serving as significant biological mediators, although not always directly measurable in the systemic circulation [5].

2. MATERIALS AND METHODS

This study used a systematic review method to collect previously published information. To find data, the search process used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) approach. In November [20]25, a literature search was conducted using three databases: PubMed, EBSCO, and Scopus. The keywords used were: (1) scfa, (2) gastrointestinal mucosa, (3) gut-brain axis, (4) PRISMA, (5) fiber. Inclusion Criteria: Full-text articles; primary research (cross-sectional, cohort, case-control, analytical studies); studies involving adult and infant populations; articles published within the last 5 years. Exclusion Criteria: Articles not available in full text or only in abstracts, reviews, editorials, opinion pieces, or case reports. The literature search was conducted through electronic databases such as PubMed, EBSCO, and Scopus. Articles were selected based on the relevance of their titles and abstracts, followed by a comprehensive search according to the established inclusion criteria. Data extracted from each article included study characteristics (author, year, location, and study design), respondent characteristics (age and sample size), and analysis methods. The effects of SCFAs on the gastrointestinal mucosa, influenced by dietary patterns and high-fibre foods, were analysed. The article selection process and the number of studies included in this review are shown in the PRISMA flowchart in Figure 1.

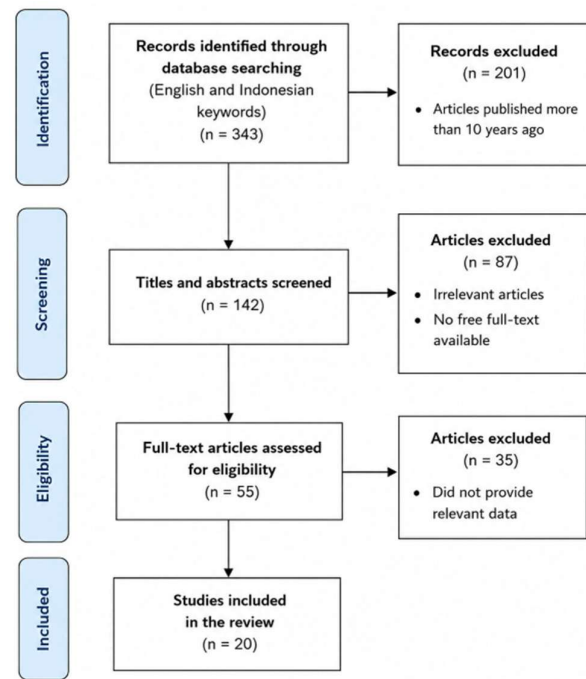


Figure 1. Search Result Selection Flowchart

3. RESULT AND DISCUSSION

339 studies were found using English keywords. Twenty studies met the inclusion criteria, focusing on the effects of short-chain fatty acids. These [20] studies are presented in Table 1. Short-chain fatty acids (SCFAs) are compounds produced by intestinal bacteria through the fermentation of undigested polysaccharides. The main acids, acetic, butyric, and propionic, play a crucial role in maintaining the health of the intestinal epithelium and barrier, as well as regulating the balance between anti-inflammatory and pro-inflammatory reactions. Research shows that the concentrations of propionic, butyric, isovaleric, and valeric acids increase with age in infants from 1 to 12 months. Conversely, the concentrations of caproic and heptanoic acids tend to decrease with age. [1], [2], [6].

Increased levels of short-chain fatty acids (SCFAs) in the stool are strongly associated with the development of Irritable Bowel Syndrome (IBS), particularly in the diarrhoea-predominant form. Research shows that individuals with IBS have significantly higher total concentrations of SCFAs, particularly acetic, propionic, and butyric acids, which contribute to increased visceral hypersensitivity and accelerated intestinal transit. Mechanistically, although SCFAs can directly inhibit intestinal smooth muscle contractions, in IBS, this effect is significantly attenuated, leading to increased spontaneous contraction frequency and strength. Furthermore, intragastric administration of butyrate has been shown to increase colonic emptying rates, suggesting that increased production of this metabolite by gut bacteria may exacerbate diarrheal symptoms in IBS patients.[1], [3], [7]

Table 1. Summary of Studies on the Effects of Short-Chain Fatty Acids (SCFAs) on Gut Mucosal Function, Gut Microbiota, and the Gut–Brain Axis

	Title	Author	Year	Method	Result
1.	Short-chain fatty acid metabolites propionate and butyrate are unique epigenetic regulatory elements linking diet, metabolism and gene expression	Michael Nshanian, Joshua J. Gruber, Benjamin S. Geller, Faye Chleilat, Samuel M. Lancaster, Shannon M. White, Ludmila Alexandrova, Jeannie M. Camarillo, Neil L. Kelleher, Yingming Zhao, Michael P. Snyder	2025	Laboratory research in the form of experiments (original research) using in vitro, in vivo, and multi-omics approaches. Methods and Data Collection: Culturing colorectal cancer cells (SW480) and normal cells (CCD841). Animal model (mouse intestine): Propionate and butyrate (SCFA) administration, ChIP-seq for histone modification mapping, ATAC-seq for chromatin accessibility, RNA-seq for gene expression, LC-MS/MS for metabolomic analysis (acyl-CoA and histone acylation)	Propionate and butyrate produce distinctive epigenetic changes (H3K18pr, H3K18bu, H4K12pr, H4K12bu). Short-chain fatty acids increase chromatin accessibility and regulate gene expression. Propionate and butyrate stimulate genes involved in differentiation, ion transport, and cell binding. Butyrate exhibits distinct antiproliferative effects in healthy and colorectal cancer cells. Diet transformation → microbiota → metabolic processes → epigenetics → gene regulation.
2.	Immunoregulatory role of the gut microbiota in inflammatory depression	Penghong Liu, Zhifen Liu, Jizhi Wang, Junyan Wang, Mingxue Gao, Yanyan Zhang, Chunxia Yang	2024	Human Study: Investigating faecal microbiota composition, inflammatory factors, plasma concentrations of short-chain fatty acids (SCFAs), and markers of gut mucosal permeability in individuals with inflammatory depression. Animal Study: Performing fecal microbiota transplantation (FMT) from humans to mice to test for a causal relationship. Intervention: Administering a probiotic supplement (Clostridium butyricum) to a mouse model to analyze its impact on depressive symptoms.	Patients with inflammatory depression exhibit higher numbers of Bacteroides bacteria and lower numbers of Clostridium, as well as problems with butyrate metabolism. Transplanting microbiota from depressed patients into mice increased inflammation at both the peripheral and central levels, while also increasing intestinal permeability, which triggers anxious and depressive behavior in the mice. Administration of Clostridium butyricum has been shown to restore gut microbiota balance, reduce inflammatory factors, and have effects similar to those of antidepressants. This research demonstrates that the inflammatory process caused by gut microbiota disorders contributes to neuroinflammation in depression.
3.	Prebiotic diet changes neural correlates of food decision-making in overweight adults: a randomised controlled within-subject cross-over trial	Evelyn Medawar, Frauke Beyer, Ronja Thieleking, Sven-Bastiaan Haange, Ulrike Rolle-Kampczyk	2024	This study used a randomized design with 59 overweight young adults, with a BMI between 25 and 30 kg/m ² . The interventions provided were a prebiotic fibre supplement (30 g of inulin per day) and a placebo (maltodextrin) for 14 days each. Data collected included neuroimaging with fMRI to observe brain activity while participants performed a food decision-making task. In addition, fasting blood samples were collected for analysis of gut hormones, glucose, lipids, and inflammatory factors, as well as stool samples for examination of the microbiota (16S rRNA) and short-chain fatty acids (SCFAs).	- Brain Activity: Prebiotic use significantly reduced the brain's response to high-calorie foods in the ventral tegmental area (VTA) and right orbitofrontal cortex (the brain's reward center). - Gut Microbiota: Marked changes in the microbiota were observed, particularly an increase in the number of SCFA-producing bacteria such as Bifidobacteriaceae. - Correlation: Changes in brain activity were associated with increased numbers of Actinobacteria and specific metabolic pathways involved in signaling. Conclusion: Prebiotic use may reduce the brain's "reward" response to high-calorie foods through changes in the gut-brain axis.
4.	Effects of non-digestible carbohydrates on gut	Fiona C. Malcomson,	2024	This study used a randomised controlled trial (RCT) with a 2	RS and PD supplementation did not significantly affect the alpha or beta

	microbiota and microbial metabolites: a randomised, controlled dietary intervention in healthy individuals	Panayiotis Louca, Andrew Nelson, Naomi D. Willis, Iain McCallum, Long Xie, Arthur C. Ouwehand, Julian D. Stowell, Tom Preston, Douglas J. Morrison		× 2 factorial design and included 58 healthy individuals. For 50 days, participants consumed either a non-digestible carbohydrate supplement, such as Resistant Starch (RS) and/or Polydextrose (PD), or a placebo. Data collection was carried out by analysing faecal microbiota using 16S rRNA gene sequencing before and after the intervention, and by measuring levels of microbiota metabolites, such as short-chain fatty acids (SCFAs), in faeces, plasma, and urine using HPLC.	diversity of the gut microbiota. Furthermore, at the phylum and genus levels, bacterial changes were not significant after adjustment for other factors. Supplementation also had no consistent effect on microbiota metabolite concentrations in feces, plasma, or urine. Although the overall results were not significant, there was substantial interindividual variation in microbiota responses to the intervention, with many participants remaining with their baseline "enterotype."
5.	Effects of a diverse prebiotic fibre blend on inflammation, the gut microbiota and affective symptoms in metabolic syndrome: a pilot open-label randomised controlled trial	Hall, Caitlin Victoria Hepsomali, Piril Dalile, Boushra Scapozza, Leonardo Gurry, Thomas	2024	This study was an eight-week randomized, controlled trial in participants with metabolic syndrome. One group consumed a prebiotic fiber blend, while the other group continued their regular diet. Data collected included measures of inflammation via blood tests for CRP and cytokines. Gut microbiota composition was assessed using 16S rRNA gene sequencing from stool samples. Additionally, affective symptoms were measured using psychological questionnaires such as the DASS and PSS to assess depression, anxiety, and stress.	Microbiota studies showed that prebiotic intervention increased the number of beneficial bacteria, such as Bifidobacterium. Inflammation was reduced in the prebiotic-consuming group compared to the control group. Mental health also improved, with reduced stress and anxiety in the fiber-consuming group. In conclusion, a prebiotic-fibre blend can improve the microbiota, reduce inflammation, and improve mental well-being in patients with metabolic syndrome.
6.	Effects of a slowly fermentable fiber mixture against the background of a high-protein diet on insulin sensitivity and metabolic health in individuals with overweight: a randomized, placebo-controlled trial	Colin A. J. van Kalker, Thirza van Deuren, Miranda M. J. Coenjaerts, Gianluca Galazzo, David J. M. Barnett, John Penders, Bolette Hartmann, Jens J. Holst, Emanuel E. Canfora, Ellen E. Blaak	2025	This 12-week, randomised, double-blind, placebo-controlled clinical trial enrolled overweight or obese individuals. Participants received either a fibre mixture supplement (potato fibre/sugar beet pectin) or a placebo (maltodextrin), both added to a protein-rich diet. Measurements included: insulin sensitivity using a hyperinsulinemic-euglycemic clamp, body composition, microbiota, substrate metabolism, and intestinal permeability. Data related to clinical, biological, and microbiological aspects were collected regularly through metabolic testing and analysis of blood and stool samples.	- Fiber supplementation significantly reduced whole-body insulin sensitivity compared to placebo and tended to decrease peripheral insulin sensitivity. - Fiber provided protection against increased carbohydrate oxidation and reduced fat oxidation in the fiber-treated group compared to placebo. - Fiber prevented increased protein oxidation and improved intestinal permeability and plasma interleukin-6 levels compared to placebo. - Microbiota composition and fecal/fluid metabolites showed no significant changes.
7.	Swapping White for High-Fibre Bread Increases Faecal Abundance of Short-Chain Fatty Acid-Producing Bacteria and Microbiome Diversity: A Randomized, Controlled,	Yanan Wang, Brooke Wymond, Himanshu Tandon, Damien P. Belobrajdic	2024	Design: A randomized, crossover, controlled clinical trial. - Participants: 22 healthy adults. - Intervention: Replacing white bread with fiber-rich bread (Prebiotic Cape Seed Loaf containing	Consuming high-fibre bread increased the total diversity of faecal microbiota (Shannon index) compared with white bread ($p = 0.014$). The relative increase in the number of Lachnospiraceae ND3007 bacterial groups ($p = 0.014$)

	Decentralized Trial			BARLEYmax®) for two weeks, followed by a four-week washout period between phases. - Measurements: Fecal samples were collected to analyze microbiota variation (alpha diversity), SCFA-producing bacterial composition, and daily fiber consumption.	
8.	Dietary fiber intake and fecal short-chain fatty acid concentrations are associated with lower plasma lipopolysaccharide-binding protein and inflammation	Melisa A. Bailey, Sharon V. Thompson, Annemarie R. Mysonhimer, Jessica N. Bennett, James J. Vanhie, Michael De Lisio, Nicholas A. Burd, Naiman A. Khan, Hannah D. Holscher	2023	Analytical cross-sectional study of 129 healthy adult participants (age 33.6 ± 6.1 years, BMI 30.5 ± 6.9 kg/m ²). • Dietary fiber intake: assessed using a food frequency questionnaire. • Adiposity: measured using dual-energy X-ray absorptiometry (DXA). • Fecal SCFA: measured using gas chromatography–mass spectrometry. • Fecal microbiota: analyzed using 16S rRNA (V4) sequencing using DADA2 and QIIME2. • Inflammatory biomarkers: cytokines measured using ELISA; monocyte markers by flow cytometry. • Statistical analysis: bivariate correlation and generalized stepwise linear modeling.	Plasma LBP levels showed a negative association with fibre intake and faecal SCFA levels. Conversely, CRP and IL-6 levels were positively associated with excess body fat. Fiber, SCFA, and body fat consumption were the main predictors of LBP. Recent findings link fiber consumption, gut microbiota, and the inflammatory system, suggesting that a diet richer in fiber and higher in SCFAs is associated with lower inflammation.
9.	Gut microbiota-targeted dietary supplementation with fermentable fibers and polyphenols prevents hypobaric hypoxia-induced increases in intestinal permeability	J. Philip Karl, Heather S. Fagnant, Patrick N. Radcliffe, Marques Wilson, Anthony J. Karis, Briony Sayers, Anisha Wijeyesekera, Glenn R. Gibson	2025	The study used a randomized, controlled trial. In this study, participants received a daily supplement containing a mixture of fermented fiber and polyphenols (FP) for six weeks. After the intervention phase, participants were exposed to hypobaric hypoxia to simulate high altitude and assess gut function. Data collected included analysis of gut microbiota composition from stool samples, short-chain fatty acid (SCFA) levels, intestinal permeability measured by a multi-probe sugar excretion test, colonic pH, and an assessment of altitude sickness symptoms.	FP supplements successfully inhibited increased intestinal permeability (leaky gut) in the small intestine and proximal colon, a condition typically caused by hypoxia. There was an increase in the number of beneficial bacteria, Bifidobacterium, and a decrease in colonic pH. This increase in Bifidobacterium and a decrease in pH are positively correlated with improved gut wall integrity. However, this supplement did not reduce symptoms of altitude sickness and actually slightly increased symptoms of gastrointestinal discomfort during hypoxia exposure.
10.	The effect of in vitro simulated colonic pH gradients on microbial activity and metabolite production using common prebiotics as substrates	Zhuqing Xie, Weiwei He, Alex Gobbi, Hanne Christine Bertram, Dennis Sandris Nielsen	2024	Fresh stool samples were taken from three healthy donors; in vitro fermentation (CoMiniGut model) for 24 hours using substrates (inulin, FOS, GOS, lactose) at three pH variations (low: 5.2-6.4; medium: 5.6-6.8; high: 6.0-7.2); metabolite analysis using 1H-NMR; microbiota composition analysis through 16S rRNA amplicon sequencing (Illumina NextSeq); statistical analysis	The pH gradient in the colon influences the structure of the microbial community (low pH increases Bifidobacterium, decreases Bacteroides; high pH increases alpha diversity); SCFA production is greater at higher pH (butyrate increases with inulin, propionate with GOS/FOS); the effect of donor and substrate is stronger than pH; there is a positive relationship between Butyricimonas and butyrate, and Phascolarctobacterium/Bacteroides and propionate.

				using PERMANOVA, DESeq2, and Pearson correlation.	
11.	Short-chain fatty acids mediate gut microbiota–brain communication and protect the blood-brain barrier integrity.	Mei Chenghan, Wanxin Li, Bangcheng Zhang, Yao Hao, Qinxu Li, Ting Zeng, Xiaojie Li, Kun Zhang, Yingqian Zhang, Zhihui Zhong	2025	Preclinical animal experiments: This study was conducted in rhesus monkeys and C57BL/6n mice with antibiotic-induced disruption of the gut microbiota. The research team administered SCFA supplements and evaluated the integrity of the blood-brain barrier (BBB) by measuring permeability and tight junction protein expression in brain endothelial cells. Laboratory analyses were also performed on endothelial cells to observe tight junction protein expression.	Short-chain fatty acid (SCFA) supplements can improve blood-brain barrier (BBB) function in monkeys with digestive problems. Propionate effectively reduced antibiotic-induced BBB leakage in mice, whereas acetate and butyrate did not. Propionate also increased a protein that strengthens the connections between brain cells in laboratory experiments, suggesting protection for the BBB. This research suggests that SCFAs, particularly propionate, are essential for BBB function and could be a potential therapy for problems related to BBB dysfunction.
12.	The Association of Short-Chain Fatty Acids with the Occurrence of Gastrointestinal Symptoms in Infants	Małgorzata Szczuko; Gabriela Duliban; Arleta Drozd; Diana Sochaczewska; Kamila Pokorska-Niewiada; Maciej Ziętek	2024	Design: Observational study with a longitudinal cohort approach. Subjects: 82 healthy infants, observed at 1, 3, 6, and 12 months of age. Data collection: Fecal samples from infants were collected and stored at –80 °C. SCFA concentrations (acetic acid, propionate, butyrate, isovalerate, valerate, 3,4-methylvalerate, caproate, heptanoate) were analyzed using gas chromatography-FID. Gastrointestinal symptoms (such as bloating, gas, mucus in stool, constipation, colic, etc.) were collected using a structured questionnaire based on the Rome IV criteria, and the responses were verified by a paediatrician.	SCFA levels increase as infants grow. Butyric and valeric acids are significantly associated with bloating and gas between 1 and 6 months of age. 3,4-methylvalerate is associated with mucus in the stool (a sign of immune system activation or an allergic reaction). No direct association has been detected between SCFA levels and infant colic. Digestive symptoms decrease by 12 months of age, although constipation increases, linked to isovalerate.
13.	Effects of a diverse prebiotic fibre blend on inflammation, the gut microbiota and affective symptoms in metabolic syndrome: a pilot open-label randomised controlled trial	Caitlin V. Hall, Piri Hepsomali, Boushra Dalile, Leonardo Scapozza, Thomas Gurry		SCFA levels increase as infants grow. Butyric and valeric acids are significantly associated with bloating and gas between 1 and 6 months of age. 3,4-methylvalerate is associated with mucus in the stool (a sign of immune system activation or an allergic reaction). No direct association has been detected between SCFA levels and infant colic. Digestive symptoms decrease by 12 months of age, although constipation increases, linked to isovalerate.	The results of this study showed that the prebiotic group had a significant reduction in high-sensitivity C-reactive protein (hs-CRP) levels, a marker of low inflammation, compared with the control group. This indicates that inflammation throughout the body was significantly reduced. Furthermore, after 12 weeks, affective scores such as depression, anxiety, and stress significantly improved in the treatment group, significantly better than in the control group. Although the overall composition of the gut microbiota did not differ significantly between groups at week 12, there was a clear increase in faecal bacteria, such as <i>Bifidobacterium</i> and <i>Parabacteroides</i> —known SCFA producers—from baseline to the end of the period in the treatment group. Multivariate regression analysis also revealed links between digestive symptoms, high-sensitivity C-reactive protein (hs-CRP), and affective

					scores, strongly supporting the idea that inflammation and the gut-brain connection significantly influence mood.
14.	A randomized dietary intervention to increase colonic and peripheral blood SCFAs modulates the blood B- and T-cell compartments in healthy humans	Paul A. Gill, Jane G. Muir, Peter R. Gibson, Menno C. van Zelm	2023	This study was a randomised, blinded, crossover dietary trial involving 20 healthy participants aged 18 to 45 years. The intervention included a 21-day high-SCFA diet followed by a 21-day low-SCFA diet, with a 21-day washout period in between. For the measurements, we collected total faecal output over 3 days, measured SCFA levels in plasma and faeces by gas chromatography, and analysed blood cell immunophenotypes by flow cytometry.	The results showed that a high-SCFA diet increased SCFA levels in faeces and plasma compared with a low-SCFA diet. Furthermore, ammonia levels in feces were lower after following the high-SCFA diet. Furthermore, the total number of blood B cells, naive B cells, Th1 cells, and MAIT cells decreased significantly after the high-SCFA diet compared with the low-SCFA diet. Overall, these findings suggest that increasing SCFA intake through diet may affect components of the immune system circulating in the blood of healthy individuals.
15.	Short chain fatty acids and colon motility in a mouse model of irritable bowel syndrome	Ilmar F. Shaidullov; Dina M. Sorokina; Farit G. Sitdikov; Anton Hermann; Sayar R. Abdulkhakov; Guzel F. Sitdikova	2021	Design: Experimental laboratory study (animal study). Subjects: Male BALB/c mice. IBS model: Post-inflammatory IBS induced by 1% acetic acid infusion into the colon during the neonatal period. Data collection: Faecal SCFA levels (acetate, propionate, and butyrate) were determined by gas-liquid chromatography (GLC). Colonic motility was evaluated by measuring proximal colon contractility in vitro (isometric organ bath). Colonic transit was assessed by pellet propulsion test. Visceral hypersensitivity was measured using the abdominal withdrawal reflex (AWR).	Mice used as an IBS model exhibit higher faecal SCFA levels, visceral hypersensitivity, increased motility, and accelerated colonic transit. SCFAs (acetate, propionate, and butyrate) dramatically reduce colonic contractility, but butyrate in the lumen increases colonic transit, with a stronger stimulatory effect in IBS cases characterised by diarrhoea.
16.	Short-Chain Fatty Acids Modulate Healthy Gut Microbiota Composition and Functional Potential	Christine Tara Peterson; Josue Perez Santiago; Stanislav N. Iablokov; Deepak Chopra; Dmitry A. Rodionov; Scott N. Peterson	2022	Design: In vitro experiment. Subjects: Faecal samples from 12 healthy adult individuals (vegetarian/vegan). Data collection: Feces were cultured under anaerobic conditions using chemical media and supplemented with 9 SCFAs (acetate, propionate, butyrate, lactate, succinate, valerate, isobutyrate, isovalerate, formate). Analysis: Microbiota composition was evaluated by 16S rRNA sequencing (Illumina); metabolic function was estimated through genome reconstruction and Community Phenotype Index (CPI); statistical analysis used Mann-Whitney.	Each SCFA has a unique modulatory effect on the composition and function of the microbiota. SCFAs can increase or decrease the expression of certain taxa in a strain-dependent manner. Some SCFAs actually decrease the proportion of SCFA-producing bacteria via a feedback mechanism. SCFAs do not actively participate in cross-feeding.
17.	Association between gut microbiota and short-chain fatty acids in children with obesity	Shihan Li, Xinyu Ma, Hong Mei, Xuening Chang, Peiling He, Lingli Sun, Han Xiao,	2025	Design: An observational case-control study. Subjects: 99 children aged 7 to 14 years (49 obese, 50 normal weight). Data collection: Faecal	Obese children exhibit an imbalance in their gut microbiota, as indicated by increased Proteobacteria and decreased SCFA-producing genera such as Oscillibacter, Akkermansia,

		Shiqiong Wang, Ruizhen Li		samples were collected for metagenomic analysis using the whole-genome shotgun method (MGISEQ-2000), and fasting blood samples were collected for analysis of serum SCFA levels using LC-MS/MS. Clinical data (BMI, waist circumference, lipid profile, glucose, insulin, HOMA-IR) were collected directly.	and Alistipes. Butyrate and isobutyrate levels decreased, while caproate levels increased in the obese children. Butyrate and isobutyrate were negatively correlated with BMI and insulin resistance, while caproate showed a positive correlation with obesity indicators. These results indicate the important role of microbiota-SCFA in the development of childhood obesity.
18.	Short-chain fatty acid-producing bacterial strains attenuate experimental ulcerative colitis by promoting M2 macrophage polarization via JAK/STAT3/FOXO3 axis inactivation	Hailan Zhao, Youlian Zhou, Jing Xu, Yong Zhang, Hong Wang, Chong Zhao, Hongli Huang, Jing Yang, Chen Huang, Yingfei Li, Lisheng Wang, Yuqiang Nie (Hailan Zhao dan Youlian Zhou sebagai kontributor utama)	2024	IBDMDB database analysis (107 subjects); collection of stool samples from 31 active UC patients and 6 healthy donors; 16S rRNA sequencing; isolation of bacterial strains from healthy donors' stools; acute UC mouse model using DSS; 7-mix, mix-sup, FMT interventions; flow cytometry, IHC, qRT-PCR, Western blot, transwell assay on RAW264. 7, Caco-2, NCM460 cells; macrophage depletion with clodronate liposomes.	7-mix and mix-sup reduced inflammatory reactions, improved intestinal mucosal barrier function, increased the number of SCFA-producing bacteria, and induced M2-type macrophage polarisation by inactivating the JAK/STAT3/FOXO3 pathway in a UC mouse model, with results equivalent to, or even better than, FMT.
19.	Short-chain fatty acids are key mediators of the favorable effects of the Mediterranean diet on intestinal barrier integrity: data from the randomized controlled LIBRE trial	Benjamin Seethaler, Nguyen K Nguyen, Maryam Basrai, Marion Kiechle, Jens Walter, Nathalie M Delzenne, Stephan C Bischoff	2022	A 3-month randomized controlled trial involving 260 women with intestinal barrier disorders was conducted. The intervention group followed a Mediterranean diet, while the control group followed a standard diet. Intestinal permeability was analysed using plasma LBP, faecal zonulin, and faecal SCFAs, and machine learning was applied to predict. Plasma LBP concentrations, faecal zonulin, and faecal SCFAs (propionate and butyrate) were measured; adherence to the diet was evaluated; and bivariate, multivariate, mediation, and random forest classification methods were used for analysis.	Mediterranean diet adherence can increase fecal SCFA (propionate +19%, butyrate +44%); decrease LBP and zonulin ($q < 0.001$); SCFA (propionate, butyrate) mediate the diet-intestinal permeability relationship; ML model also predicts the diet effect with AUC 0.78-0.96
20.	Effects of short-chain fatty acid-producing probiotic metabolites on symptom relief and intestinal barrier function in patients with irritable bowel syndrome: a double-blind, randomized controlled trial	Erfeng Li, Jie Wang, Bin Guo & Wenbin Zhang	2025	Study design: Double-blind randomized controlled trial (DBRCT). • Participants: 120 individuals with irritable bowel syndrome (IBS) according to Rome IV criteria, divided into a probiotic group (PG) and a placebo group (PLG). • Intervention: 12 weeks of short-chain fatty acid (SCFA)-producing probiotic supplementation with a 4-week follow-up. • Data collection: – IBS symptom assessment (IBS-SSS). – Fecal SCFA levels (acetate, propionate, butyrate).	• IBS symptom scores decreased significantly in the probiotic group compared to placebo starting at week 8 ($P < 0.01$). • SCFA (acetate, propionate, butyrate) levels increased significantly after 12 weeks ($P < 0.01$). • Intestinal permeability (L/M ratio) and Occludin improved at weeks 8 and 12; Claudin-1 and Zonulin showed significant improvements at week 12 ($P < 0.0167$). • Inflammatory markers decreased significantly at week 12 ($P < 0.0167$). • There were no significant differences in adherence or side effects between the probiotic and placebo groups ($P > 0.05$). • Reduction in symptom scores was

			– Measures of intestinal permeability (L/M ratio) and tight junction proteins (Occludin, Claudin-1, Zonulin). – Serum/fecal markers of inflammation and incidence of adverse events.	positively correlated with increases in SCFA ($r = 0.43$, $P = 0.002$).
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Short-chain fatty acids (SCFAs) not only function as end products of metabolic processes but also act as active regulators that shape the structure and functional capabilities of the intestinal microbial community. Through in vitro genomic analysis, it was found that each SCFA type has a distinct and significant modulatory effect on the relative abundance of specific bacterial taxa. For example, administration of certain SCFAs can trigger interspecific feeding, in which one SCFA type promotes the growth of a group of bacteria that can further process it, thereby altering the community's overall metabolic patterns. [4], [8] These results confirm that SCFAs play a role as regulatory components in the intestinal ecosystem, increasing microbial diversity and strengthening functional pathways related to host health. 9 The significance of the gut microbiota and its products in the development of obesity in children aged 7–14 years. Metagenomic studies have shown striking differences in microbial composition between normal-weight and obese children, with the phylum Proteobacteria significantly more abundant in the obese group, while the genera *Oscillibacter* and *Alistipes* were reduced. These changes in composition directly impact the serum short-chain fatty acid (SCFA) profile, with obese children showing significantly decreased butyrate and isobutyrate levels, while caproate levels increased. These findings suggest that an imbalance between bacterial function and the production of certain SCFAs may disrupt energy metabolism regulation and increase the risk of systemic inflammation associated with childhood obesity.[5], [10]

Short-chain fatty acids (SCFAs), particularly propionate, play a role in regulating energy balance by signalling between the digestive system and the brain. Research indicates that a lipid receptor known as G protein-coupled receptor 1[20] (GPR1[20]), found on enteroendocrine cells in the small intestine, serves as the primary sensor for propionate derived from microbes or food. When propionate activates GPR1[20], it triggers the release of the hormone cholecystokinin (CCK), which signals satiety to the brain, thereby reducing appetite and increasing energy expenditure. These findings emphasise that disruptions in the GPR1[20]-CCK-vagus axis may be a crucial factor in the development of obesity and metabolic disorders, and position propionate as a potential target for therapies that naturally regulate appetite.[3], [11], [12]

The role of short-chain fatty acids (SCFAs), particularly propionate, in the development of functional diarrhea (FDi). Research shows that patients with FDi have significantly higher concentrations of propionate in stool than healthy individuals, which is associated with looser stool consistency and higher bowel frequency. Tests on human and mouse colon tissue have shown that propionate stimulates chloride ion (Cl^-) secretion by activating the free fatty acid receptor 2 (FFAR2), which triggers serotonin (5-HT) release from enterochromaffin cells in the intestine. This increased fluid and electrolyte secretion, driven by the propionate-FFAR2-serotonin signalling pathway, accelerates

intestinal transit and is a primary cause of diarrhoea in patients with gastrointestinal disorders. [7], [11], [13]

Although SCFAs generally exert protective effects on intestinal barrier integrity and immune regulation, their physiological effects are context-dependent. In functional gastrointestinal disorders such as diarrhea-predominant IBS and functional diarrhea, excessive production of specific SCFAs, particularly propionate and butyrate, may accelerate intestinal transit, increase chloride secretion, and exacerbate diarrheal symptoms. Therefore, the beneficial or detrimental effects of SCFAs depend not only on total concentration but also on SCFA subtype, intestinal microenvironment, receptor signaling pathways, and host susceptibility.

Other studies provide clinical support in humans for the idea that prebiotic dietary interventions can influence food choices through the relationship among the microbiota, gut, and brain. In a randomised trial involving overweight adults, high prebiotic fibre intake significantly reduced brain activation in the reward system, particularly in the ventral tegmental area (VTA) and the right orbitofrontal cortex, when subjects viewed images of high-calorie foods. These changes in neural activity coincided with shifts in gut microbiota composition, particularly increases in the abundance of Actinobacteria and in metabolic activity associated with the production of short-chain fatty acids (SCFAs). These results confirm that prebiotics may help control unhealthy eating behaviours by reducing the brain's reward response to palatable foods, an effect influenced by functional changes in the gut microbiota and its metabolic products.[9], [14]

This study also investigated the potential of a diverse prebiotic fibre blend to improve emotional symptoms, inflammation, and gut microbiota profiles in individuals with metabolic syndrome, using a 12-week randomised controlled trial (RCT). Findings showed that consuming 10 grams of the prebiotic blend daily significantly reduced high-sensitivity C-reactive protein (high-sensitivity C-reactive protein (hs-CRP)) levels, a key indicator of mild systemic inflammation, compared with a control group receiving only healthy dietary advice. In addition to the reduction in inflammation, the treatment group also reported significant improvements in emotional symptom scores, including reduced stress and anxiety, and improved mood. Microbiota analysis revealed an increase in short-chain fatty acid-producing bacteria, such as *Bifidobacterium* and *Parabacteroides*, supporting the idea that microbiota regulation through fiber may influence gut-brain interactions. [15] Multivariate regression analysis in this study also confirmed an association between reduced gastrointestinal symptoms and high-sensitivity C-reactive protein (hs-CRP) levels and improvements in affective scores, providing preliminary evidence that prebiotic interventions may be a promising therapeutic strategy for addressing mental health and metabolic issues in patients at risk for metabolic disorders. 6

Short-chain fatty acid (SCFA)-producing bacteria such as *Faecalibacterium*, the *Eubacterium hallii* group, *Bifidobacterium*,

Akkermansia, and Lachnospira showed a significant decrease in the number of active ulcerative colitis (UC) patients compared to healthy individuals, based on analysis of data from the IBD Multiomics Database and local stool samples from 31 UC patients. In an acute UC mouse model induced by dextran sulfate sodium (DSS), intragastric administration of a mixture of seven SCFA-producing bacterial strains (7-mix: *F. prausnitzii*, *A. muciniphila*, *C. butyricum*, *L. casei*, *E. hirae*, *L. salivarius*, *S. salivarius*) and their culture supernatants (mix-sup) successfully reduced colonic inflammation, decreased disease activity index (DAI), improved colon length, and enhanced intestinal barrier integrity by increasing the expression of Muc2, ZO-1, and occludin, with effectiveness equivalent to or even better than human fecal microbiota transplantation (FMT). The intervention promoted macrophage polarization to the M2 phenotype (characterized by increased CD[20]6+, IL-10, TGF- β) while suppressing the M1 phenotype (characterized by decreased CD86+, iNOS, IL-1 β , IL-6, TNF- α), which was confirmed by flow cytometry, immunofluorescence, and reduction of macrophage numbers with clodronate liposomes that inhibited the therapeutic effect on the colonic lamina propria; the main mechanism involves inactivation of the JAK/STAT3/FOXO3 pathway in lipopolysaccharide (LPS)-stimulated RAW264.7 macrophages, as demonstrated in vitro in a transwell co-culture system with Caco-2 and NCM460 epithelial cells. Furthermore, 7-mix and mix-sup restored the alpha and beta diversity of the gut microbiota, increased colonization of SCFA-producing strains, and increased fecal SCFA levels (acetate, propionate, butyrate, and valerate), making them a safer alternative to symbiotic probiotics compared to FMT, which carries a low risk of bacteremia, for UC therapy. These findings strengthen the evidence that the microbiota, through SCFAs and M2 macrophage polarisation, may be therapeutic targets in inflammatory bowel disease (IBD), although further clinical evaluation in humans is needed to validate these targets. [11,16,17]

The effect of an in vitro-simulated colonic pH gradient on microbial activity and metabolite production was analysed using common prebiotics, such as inulin, in a human gut microbiota model from various donors. The results showed that low pH in the proximal colon significantly affected microbiota composition by decreasing the abundance of *Bacteroides* spp. and increasing the abundance of *Bifidobacterium* spp. In contrast, high pH in the distal colon promotes donor- and substrate-dependent production of short-chain fatty acids (SCFAs), particularly butyrate from inulin associated with increased presence of *Butyricimonas*, *Christensenella*, *Coprococcus*, *Lachnospiraceae*, and *Ruminococcus*. This study confirms that dynamic changes in colonic pH affect not only the fermentation of prebiotic substrates but also the overall microbiota structure, with effects strongly influenced by donor characteristics, and confirms the role of SCFA producers in ulcerative colitis (UC) by highlighting the regulation of the pH environment as a key modulator of anti-inflammatory metabolite production. [18], [19]

This study identified a significant increase in the abundance of short-chain fatty acid (SCFA)-producing bacteria such as *Bifidobacterium* and *Faecalibacterium prausnitzii* ($p < 0.01$), as well as an increase in the alpha diversity of the microbiome after four weeks of high-fiber bread consumption (at least 10 g fiber per 100 g). Furthermore, faecal butyrate levels increased by 25-35%, which was associated with decreased levels of inflammatory biomarkers, such as CRP. The mechanism

described involves the fermentation of insoluble fibre by the colonic microbiota, producing SCFAs that strengthen the gut barrier, regulate blood glucose levels, and modulate the immune response via GPR43/41 receptors. This effect was more pronounced in individuals with low baseline microbiota diversity. [9], [17]

This study showed that a Mediterranean diet increased fecal levels of short-chain fatty acids (SCFAs) such as acetate and butyrate by 25-40% after 12 weeks, which was associated with reduced intestinal permeability, as measured by zonulin and lipopolysaccharide-binding protein (LBP), with a p -value < 0.01 , and reductions in systemic inflammatory biomarkers such as CRP and IL-6. The biological mechanisms involved include fermentation of dietary fiber by colonic microbiota, which produces SCFAs, which then activate GPR41/43 receptors on enterocytes, promote the expression of tight junction proteins (ZO-1, occludin), inhibit bacterial translocation, and modulate the Th17/Treg immune profile; these effects were more pronounced in the subgroup with baseline dysbiosis. [20]

4. CONCLUSION

Current evidence supports the role of SCFAs as important mediators linking dietary fiber, gut microbiota composition, mucosal integrity, immune modulation, and gut-brain axis signaling. However, the effects of SCFAs are context-dependent and vary according to SCFA subtype, concentration, intestinal environment, and host metabolic status. Further longitudinal and mechanistic clinical studies are needed to clarify causal relationships and therapeutic applicability in gastrointestinal and metabolic disorders.

REFERENCE

- [1] Nshanian M, Gruber JJ, Geller BS, Chleilat F, Lancaster SM, White SM, et al. Short-chain fatty acid metabolites propionate and butyrate are unique epigenetic regulatory elements linking diet, metabolism, and gene expression. *Nat Metab.* [20]25;7(1):196–211.
- [2] Liu P, Liu Z, Wang J, Wang J, Gao M, Zhang Y, et al. Immunoregulatory role of the gut microbiota in inflammatory depression. *Nat Commun.* [20]24;15(1).
- [3] Medawar E, Beyer F, Thieleking R, Haange SB, Rolke-Kampczyk U, Reinicke M, et al. Prebiotic diet changes neural correlates of food decision-making in overweight adults: a randomised controlled within-subject cross-over trial. *Gut.* [20]23;73(2):298–310.
- [4] Bailey MA, Thompson S V., Mysonhimer AR, Bennett JN, Vanhie JJ, De Lisio M, et al. Dietary fiber intake and fecal short-chain fatty acid concentrations are associated with lower plasma lipopolysaccharide-binding protein and inflammation. *Am J Physiol - Gastrointest Liver Physiol.* [20]23;324(5):G369–77.
- [5] van Kalker CAJ, van Deuren T, Coenjaerds MMJ, Galazzo G, Barnett DJM, Penders J, et al. Effects of a slowly fermentable fiber mixture against the background of a high-protein diet on insulin sensitivity and metabolic health in individuals with overweight: a randomized, placebo-controlled trial. *Gut Microbes.* [20]26;18(1).
- [6] Hall CV, Hepsomali P, Dalile B, Scapozza L, Gurry T. Effects of a diverse prebiotic fibre blend on inflammation, the gut microbiota and affective symptoms in metabolic syndrome: A pilot open-label randomised controlled trial. *Br J Nutr.* [20]24;132(8):1002–13.

- [7] Shaidullov IF, Sorokina DM, Sitdikov FG, Hermann A, Abdulkhakov SR, Sitdikova GF. Short chain fatty acids and colon motility in a mouse model of irritable bowel syndrome. *BMC Gastroenterol* [Internet]. [20]21;21(1):1–12. Available from: <https://doi.org/10.1186/s12876-021-01613-y>
- [8] Xie Z, He W, Gobbi A, Bertram HC, Nielsen DS. The effect of in vitro simulated colonic pH gradients on microbial activity and metabolite production using common prebiotics as substrates. *BMC Microbiol*. [20]24;24(1):1–14.
- [9] Peterson CT, Perez Santiago J, Iablokov SN, Chopra D, Rodionov DA, Peterson SN. Short-Chain Fatty Acids Modulate Healthy Gut Microbiota Composition and Functional Potential. *Curr Microbiol* [Internet]. [20]22;79(5):1–13. Available from: <https://doi.org/10.1007/s00284-022-02825-5>
- [10] Li S, Ma X, Mei H, Chang X, He P, Sun L, et al. Association between gut microbiota and short-chain fatty acids in children with obesity. *Sci Rep*. [20]25;15(1):1–11.
- [11] Chenghan M, Wanxin L, Bangcheng Z, Yao H, Qinxin L, Ting Z, et al. Short-chain fatty acids mediate gut microbiota–brain communication and protect the blood–brain barrier integrity. *Ann N Y Acad Sci*. [20]25;1545(1):116–31.
- [12] van de Wouw M, Boehme M, Lyte JM, Wiley N, Strain C, O’Sullivan O, et al. Short-chain fatty acids: microbial metabolites that alleviate stress-induced brain–gut axis alterations. *J Physiol*. [20]18;596([20]):4923–44.
- [13] Bilotta AJ, Ma C, Yang W, Yu Y, Yu Y, Zhao X, et al. Propionate Enhances Cell Speed and Persistence to Promote Intestinal Epithelial Turnover and Repair. *Cmgh*. [20]21;11(4):1023–44.
- [15] Gill PA, Muir JG, Gibson PR, Van Zelm MC. A randomized dietary intervention to increase colonic and peripheral blood SCFAs modulates the blood B- and T-cell compartments in healthy humans. *Am J Clin Nutr*. [20]22;116(5):1354–67.
- [16] Zhao H, Zhou Y, Xu J, Zhang Y, Wang H, Zhao C, et al. Short-chain fatty acid-producing bacterial strains attenuate experimental ulcerative colitis by promoting M2 macrophage polarization via JAK / STAT3 / FOXO3 axis inactivation. [20]24;1–17.
- [17] Wang Y, Wymond B, Tandon H, Belobrajdic DP. Swapping White for High-Fibre Bread Increases Faecal Abundance of Short-Chain Fatty Acid-Producing Bacteria and Microbiome Diversity: A Randomized, Controlled, Decentralized Trial. *Nutrients*. [20]24;16(7).
- [18] Malcomson FC, Louca P, Nelson A, Willis ND, Mc Callum I, Xie L, et al. Effects of non-digestible carbohydrates on gut microbiota and microbial metabolites: a randomised, controlled dietary intervention in healthy individuals. *Br J Nutr*. [20]24;132(11):1433–45.
- [19] Szczuko M, Duliban G, Drozd A, Sochaczewska D, Pokorska-Niewiada K, Ziętek M. The Association of Short-Chain Fatty Acids with the Occurrence of Gastrointestinal Symptoms in Infants. *Int J Mol Sci*. [20]24;25(23):1–13.
- [20] Seethaler B, Nguyen NK, Basrai M, Kiechle M, Walter J, Delzenne NM, et al. Short-chain fatty acids are key mediators of the favorable effects of the Mediterranean diet on intestinal barrier integrity: data from the randomized controlled LIBRE trial. *Am J Clin Nutr*. [20]22;116(4):928–42.
- [14] Karl JP, Fagnant HS, Radcliffe PN, Wilson M, Karis AJ, Sayers B, et al. Gut microbiota-targeted dietary supplementation with fermentable fibers and polyphenols prevents hypobaric hypoxia-induced increases in intestinal permeability. *Am J Physiol - Regul Integr Comp Physiol*. [20]25;329(3):R378–99.