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Short-Chain Fatty Acids as Postbiotics in Colorectal Cancer Management: A Meta-Analysis of Preclinical Evidence

Cinzia Zolfanelli[1], Vincenzo Lauciello[1], Alessio Di Ciancia[1], Alessio Vagliasindi[1], Theodoros Varzakas[2], Teresa D'Amore[1,3,*]

[1] IRCCS CROB, Centro di Riferimento Oncologico della Basilicata, Rionero in Vulture, Italy; [2] Dep of Food Science and Technology, University of the Peloponnese, Antikalamos, 24100, Greece, [3] Dep. of Pharmacy, University of Naples - Federico II, Naples, Italy, *current: Istituto Superiore di Sanità—ISS, Rome, Italy; **teresa.damore@iss.it**.

Introduction and Aim

Short-chain fatty acids (SCFAs) are postbiotic metabolites produced by microbial fermentation of dietary fibers (Fig. 1). Their immunomodulatory and anticancer effects have been widely documented in colorectal cancer (CRC) models. However, a cross-model synthesis of their efficacy is lacking. Despite extensive preclinical data, no clinical trials have yet assessed SCFAs as therapeutic agents in CRC, highlighting an urgent translational gap.

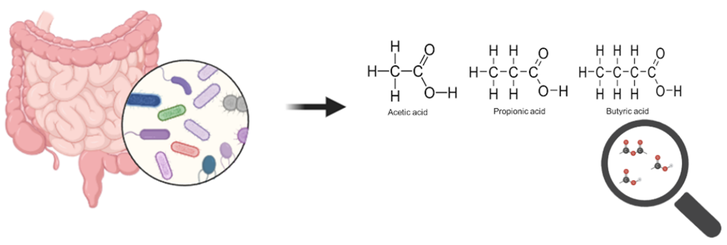
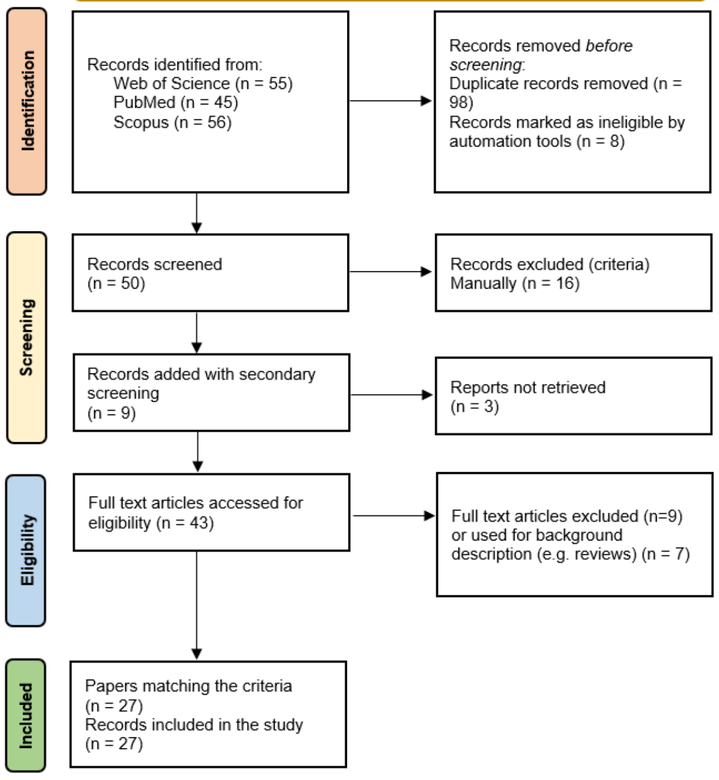


Fig 1. Principal SCFAs: acetate, propionate, butyrate.

This study aims to systematically assess the role of SCFAs in CRC prevention and therapy across multiple preclinical models and to evaluate their mechanisms of action using meta-analytic and qualitative synthesis.

Methodology



A systematic review (SR) of existing literature on postbiotics and CRC was performed using PRISMA methodology and 27 records were included in the study. SCFA-focused studies were analyzed based on inclusion criteria targeting natural or synthetic SCFAs tested in CRC cell lines, animal models, or advanced platforms (e.g., organoids, organ-on-chip) (Fig. 2).

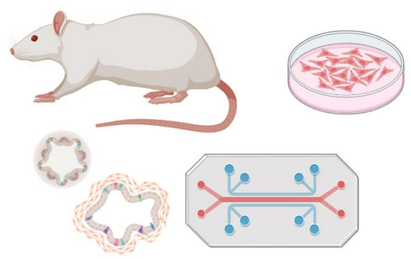


Fig 2. PRISMA flow diagram illustrating the selection process of studies (10.3390/microorganisms13061335).

Outcomes included apoptosis, proliferation, inflammation, and gut barrier integrity. Quantitative data were pooled where possible; model usage and mechanistic insights were summarized descriptively.

Results and discussion

Eight studies focused on SCFAs, either directly or indirectly (Table 1). Four studies investigated purified or directly quantified SCFAs in CRC models, while four additional studies evaluated SCFA-producing strains or cell-free supernatants (CFS) containing SCFAs alongside other metabolites. Collectively, these studies included five in vitro models (HT-29, HCT-116, Caco-2) and three in vivo models (AOM/DSS-induced CRC, xenografts). In addition, two studies using CFS on organoid-based systems were found. SCFAs consistently triggered apoptosis via caspase activation, modulated Wnt and MAPK signaling pathways, enhanced mucin expression, and reinforced tight junction proteins. Meta-analysis revealed a moderate-to-strong effect size for butyrate-induced caspase-3 activation in vitro (Cohen's d = 0.8, $p < 0.01$). Butyrate was also linked to autophagy induction via the LKB1–AMPK pathway (Fig. 3).

Importantly, most studies using cell-free supernatants or SCFA-producing strains lacked detailed compositional analysis. The absence of standardized metabolite profiling limits mechanistic interpretation and makes it difficult to determine which specific compounds are responsible for the observed biological effects. This issue is common across postbiotic research and represents a significant barrier to reproducibility, cross-study comparison, and clinical translation.

Table 1. Selected studies, following the SR, on postbiotic SCFAs in CRC preclinical models.

ID	Model	SCFA(s)	Microorganism / Source	Key Findings	Notes
1	In vitro (HCT-116, HT-29)	sodium butyrate	Synthetic	Induced autophagy via LKB1–AMPK	
2	In vitro (HT-29, HCT-116)	propionate, acetate	*Propionibacterium freudenreichii*	Increased pro-apoptotic gene expression (TRAIL-R2/DR5) and decreased anti-apoptotic gene expression (FLIP, XIAP); death receptors (TRAIL-R1/DR4, TRAIL-R2/DR5) and caspase activation (caspases-8, -9, and -3); Bcl-2 expression inhibition	propionate:30 mM) acetate: 15 mM
3	In vitro (LS174T)	butyrate	*Lactobacillus acidophilus* *Bifidobacterium longu*m	Increased mucin (MUC3, MUC4, and MUC12) MAPK signaling pathway	6 or 9 mM
4	In vivo (Sprague-Dawley rats)	acetate, propionate, butyrate	*Lactobacillus rhamnosus* MD14	Wnt/β-Catenin Pathway: downregulation of oncogenes (K-ras, β-catenin, Cox-2, NF-κB) and upregulation of the TP53 gene	active components in the metabiotic extract were characterized by LC-MS
5	In silico + In vitro (HT-29)	SCFA-rich supernatant	*Lactobacillus acidophilus* ATCC4356	Cell cycle arrest at G1 phase, anti-proliferative and anti-migration effects, and anti-proliferative activity (Wnt signaling - SFRP1, SFRP2, SFRP4, MMP7)	scRNA-seq analysis and DEGs analysis
6	In vitro (HT-29)	SCFA-rich supernatant	*Bifidobacterium breve* *Lactobacillus rhamnosus*	Apoptosis (Bax/Bcl-2), Wnt modulation	
7	In vivo (AOM/DSS CRC model)	Putrescine + SCFAs	*Escherichia coli* Nissle 1917	Reduced tumor burden, inflammation (cell proliferation; fecal Lcn-2, TNFα, IL6, and IL10; 16S rRNA amplicon sequencing)	
8	In vivo (AOM/DSS CRC model)	SCFA-stimulating EPSs	*Lactobacillus plantarum*-12	Activation of caspase cascade and NF-κB signaling (IκB-α, p65, p-p65, p38, and p-p38)	additional untargeted fecal metabolomic analysis

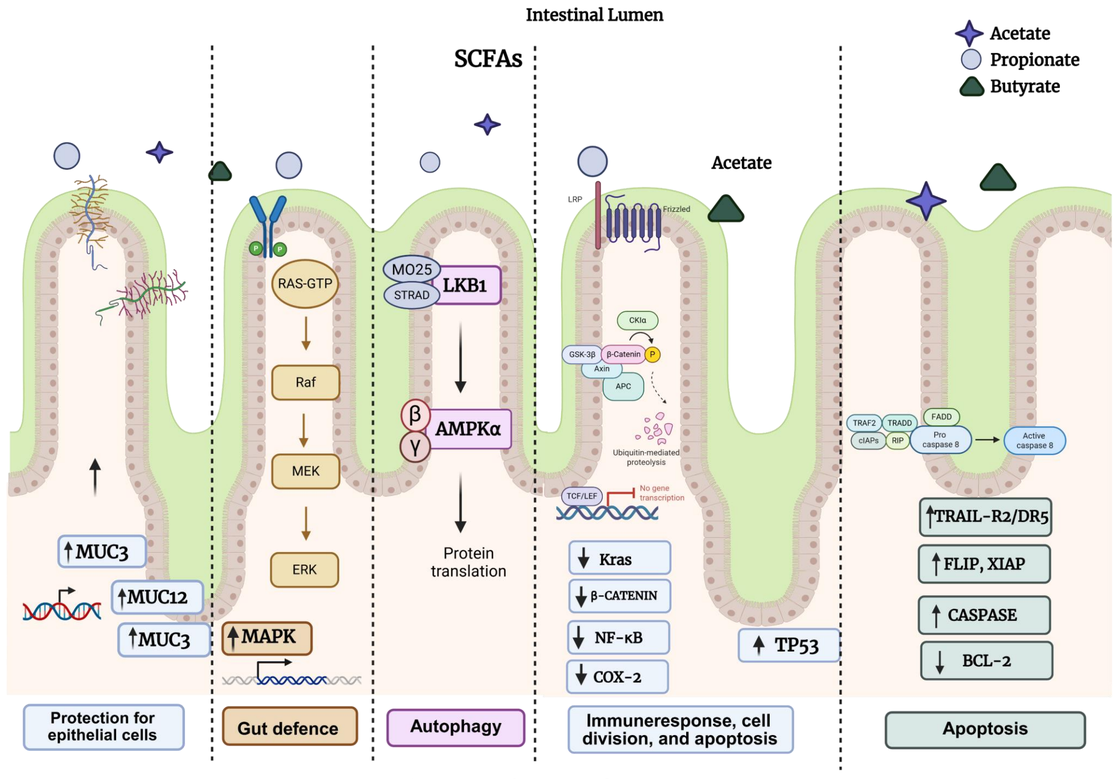


Fig 3. Mechanisms of action of SCFAs in CRC.

Conclusions and future perspectives

- ✓ SCFAs show consistent anticancer effects across in vitro, in vivo, and advance preclinical models.
- ✓ They induce apoptosis, modulate inflammation, and strengthen gut barrier integrity.
- ✓ Clinical validation is lacking — safety, dosage, and efficacy remain unexplored in humans.
- ✓ Future work should focus on standardized characterization, advanced human-relevant models, and early-phase clinical trials.
- ✓ SCFAs hold promise as microbiota-targeted agents for CRC prevention and therapy.

References and Acknowledgement

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