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Modulation of SCFA-Producing Bacteria by the Combination of Intermittent Fasting and Probiotics in the Aging Gut Microbiota

Taha CEYLANI[1], Sevcan KABAYER[2], Vesila YILDIRIM[2], Enes ESMERTAS[2] Hikmet Taner TEKER[3]

[1]*Department of Molecular Biology and Genetics, Muş Alparslan University, Muş, TÜRKİYE*
t.ceylani@alparslan.edu.tr —ORCİD 0000-0002-3041-6010
[2]*Institute of Science, Muş Alparslan University, Muş, TÜRKİYE*
kabayersevcan@gmail.com —ORCİD 0009-0006-8826-6787
vesilayildirim771@gmail.com —ORCİD 0009-0007-7900-8791
enes.esmertas.44@gmail.com —ORCİD 0009-0007-3379-0706
[3]*Department of Medical Biology and Genetics, Ankara Medipol University, Ankara, TÜRKİYE*
h.tanerteker@gmail.com—ORCİD 0000-0002-6621-3071

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Corresponding Author: Hikmet Taner TEKER

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RESEARCH ARTICLE

Modulation of SCFA-Producing Bacteria by the Combination of Intermittent Fasting and Probiotics in the Aging Gut Microbiota

Taha CEYLANI[1], Sevcan KABAYER[2], Vesila YILDIRIM[2], Enes ESMERTAS[2], Hikmet Taner TEKER*[3]

[1]*Department of Molecular Biology and Genetics, Muş Alparslan University, Muş, TÜRKİYE*
[2]*Institute of Science, Muş Alparslan University, Muş, TÜRKİYE*
[3]*Department of Medical Biology and Genetics, Ankara Medipol University, Ankara, TÜRKİYE*

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ABSTRACT

Aging is accompanied by profound alterations in gut microbiota composition, often leading to a dysbiotic state characterized by reduced abundance of short-chain fatty acid (SCFA) producers. Intermittent fasting (IF) and probiotics (Prb) have emerged as dietary strategies with potential to counteract these changes. Twenty-four-month-old Sprague Dawley rats were assigned to control (Cnt), intermittent fasting (IF), probiotic (Prb), or combined IF+Prb groups. Cecal contents were subjected to 16S rDNA sequencing, and the relative abundance of key SCFA-producing taxa was determined. Correlation analyses (Spearman and Pearson) and heatmap visualizations were applied to examine ecological relationships and group-specific shifts. The control group displayed a dysbiotic profile with diminished representation of butyrate- and propionate-producing taxa. In contrast, IF, Prb, and IF+Prb interventions consistently promoted the enrichment of core SCFA producers such as *Anaerostipes hadrus*, *Roseburia intestinalis*, *Butyrivibrio fibrisolvens*, and *Akkermansia muciniphila*. Additional taxa including *Intestinimonas butyriciproducens, Coprococcus catus*, and *Clostridium hylemonae* also showed increased abundances under intervention conditions. Correlation analyses revealed coordinated ecological restructuring, supporting restoration of microbial networks linked to SCFA production. These findings demonstrate that intermittent fasting and probiotics, independently or in combination, mitigate age-associated dysbiosis by selectively enhancing SCFA-producing bacterial communities. Such interventions may represent promising nutritional strategies to restore gut microbial balance and improve host metabolic health in aging.

***Corresponding Author:** h.tanerteker@gmail.com
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1. INTRODUCTION

Intermittent fasting (IF) is a nutritional strategy that has garnered significant research attention due to its potential impact on metabolic health and healthy aging [1]. IF encompasses various protocols, including time-restricted feeding, alternate-day fasting, and periodic fasting, each of which has been demonstrated to exert multifaceted physiological effects. These effects include the reprogramming of energy metabolism, reduction of oxidative stress and inflammation, and promotion of mitochondrial biogenesis [2]. A substantial portion of these effects is intricately linked to structural and functional alterations in the gut microbiota. During the aging process, a decline in microbiota diversity, irregularities in the production of metabolites such as short-chain fatty acids (SCFAs), and the weakening of mucosal barrier functions contribute to systemic inflammation and tissue degeneration [3]. Consequently, IF is posited to play a pivotal role in enhancing survival and functional well-being in elderly organisms by reorganizing gut ecology [4].

Probiotics are defined as live microorganisms that confer health benefits to the host and are recognized as a crucial biological tool for reshaping the gut ecosystem [5]. The colonization of species such as La*ctobacilli, Bifidobacteria*, and *Akkermansia* within the gastrointestinal environment enhances the production of SCFAs, including butyrate, propionate, and acetate, fortifies epithelial integrity, and contributes to the regulation of immune responses [6], [7]. Recent studies have reported that probiotic interventions may mitigate age-related physiological deteriorations and, in particular, may exert beneficial effects on metabolic balance, neuroinflammation, and immune homeostasis [8]. Furthermore, when administered in conjunction with IF, probiotics are anticipated to synergistically enhance microbiota diversity and support the production of functional metabolites [6].

In this study, we examined the effects of a 30-day intermittent fasting protocol on the abundance profiles of SCFA-producing bacteria in the cecal microbiota of 24-month-old Sprague Dawley rats. Our hypothesis posits that IF will partially reverse age-related microbial imbalances and, specifically, will create a selective ecological pressure favoring an increased capacity for SCFA production, particularly butyrate. In this context, it is anticipated that the study's findings will elucidate the biological basis for the reprogramming of gut ecology in aging, thereby enhancing the translational potential of IF and probiotic interventions.

2. MATERIAL METHOD

2.1. Animal studies

In this research, 24-month-old male Sprague-Dawley rats (n=28) served as the model organisms. They were divided into four groups: a control group (n=7), a group undergoing intermittent fasting (IF) for 30 days (n=7), a group receiving probiotics for 30 days (n=7), and a group receiving both probiotics and IF for 30 days (n=7). Rats in the IF groups had their food access limited to 6 hours daily, from 9 a.m. to 3 p.m., while water was available without restriction. All rats were provided with a standard rodent diet, and their body weight, as well as water and food intake, were tracked. The probiotic supplement used was Essential Probiotics XI (500 ml H.S. Code: 2206.00.7000) from SCD Probiotics, which included species such as *Bacillus subtilis, Bifidobacterium bifidum, Bifidobacterium lognum, Lactobacillus acidophillus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus fermentum, Lactobacillus plantarum, Lactococcus lactis, Saccharomyces cerevisiae,* and *Streptococcus thermophilus*. This was administered orally in daily doses of 3 mL (1 x 108 CFU), split into two 1.5 mL doses after feeding [5]. One day post-experiment, the animals were lightly anesthetized with ether and euthanized. Cecum contents were collected, frozen using dry ice, and stored at -80°C for processing within two weeks. The study adhered to standard animal care protocols and received approval from the Saki Yenilli Experimental Animal Production and Practice Laboratory Ethics Committee (Approval No: 2021/05).

2.2. DNA isolation

Genomic DNA was extracted from cecal content using the Quick-DNA™ Fecal/Soil Microbe Miniprep Kit (Cat. No. D6010). The concentration and purity of the extracted DNA were assessed fluorometrically using the Qubit system, as in our previous study [4].

2.3. Amplification of the 16S rRNA V3-V4 region

PCR conditions for the 16S V3–V4 regions involved an initial denaturation at 95°C for 10 minutes using a high-specificity (HS) enzyme. This was followed by 35 cycles of amplification, each consisting of a 45-second denaturation at 95°C, a 45-second annealing at 50-55°C, and a 60-second elongation at 72°C. A final elongation step was conducted at 72°C for 3 minutes, after which the reaction was cooled to 4°C to conclude the PCR process, as described in our previous study [9].

2.4. Library preparation and sequencing

For library preparation and sequencing, the 16S rRNA V3-V4 amplicon libraries were created using the Nextera XT DNA Library Prep Kit (Illumina, Cat. No: FC-131-1096), with indexing done using the TG Nextera XT Index Kit v2 Set A (96 Indices, 384 Samples; Cat. No: TG-131-2001). PCR purification was performed with AMPure XP beads (Beckman Coulter). Sequencing was executed on Illumina's MiSeq platform, producing paired end (PE) reads of 2x150 bases. A minimum sequencing depth of 30,000 reads per sample was maintained, as in our previous study [6]. Metagenome sequencing took place at Ficus Biotechnology (FicusBio), Ankara, Turkey.

2.5. Bioinformatics analysis of raw data

The raw sequencing data (FastQ files) underwent bioinformatics analysis, starting with quality control to improve the accuracy of microbial diversity analysis and eliminate sequencing artifacts, such as low-quality and contaminated reads. Quality checks and trimming, if necessary, were conducted using FastQC v0.10.1. The Kraken metagenomic system was then used to classify and cluster the

sequence data into operational taxonomic units (OTUs). Heatmaps were generated using GraphPad Prism 10.0.1 (GraphPad Software, USA) software, as in our previous study [11]. All raw reads from the samples have been deposited at NCBI under the BioProject ID PRJNA887213.

2.6. Statistics

All statistical evaluations were carried out using the GraphPad Prism software package (version 10.5; GraphPad Software, USA). Data are reported as the mean values accompanied by their standard error of the mean (SEM) in order to provide a reliable estimate of variability across groups. Comparative analyses were performed between the experimental cohorts, namely control (Cnt), intermittent fasting (Fst), probiotic supplementation (Prb), and the combined treatment group receiving both probiotics and intermittent fasting (FstPrb). Group differences were initially assessed through one-way analysis of variance (ANOVA), followed by pairwise comparisons using unpaired t-tests with a one-tailed probability approach to detect directional differences in abundance and diversity metrics. Levels of statistical significance were annotated using the following thresholds: $p < 0.05$, $**p < 0.001$, and $***p < 0.0001$, respectively. In addition to diversity analyses, visualization of taxonomic distribution patterns was achieved through the construction of heatmaps, generated from normalized metagenomic count data at the family, genus, and species levels, also implemented within GraphPad Prism 10.5.

3. RESULTS

3.1 Correlation analyses of SCFA-producing species

Initial correlation analyses were conducted to assess the relationships among selected short-chain fatty acid (SCFA)-producing taxa across the experimental groups. The Spearman correlation heatmap (Fig. 1) revealed strong positive monotonic associations among butyrate- and propionate-producing species, notably *Anaerostipes hadrus, Butyrivibrio fibrisolvens, Roseburia intestinalis*, and *Akkermansia muciniphila*. These taxa consistently exhibited covariation in abundance under dietary and probiotic interventions, suggesting coordinated ecological shifts. Additionally, Pearson correlation analysis (Fig. 2) confirmed linear associations among several of these taxa, thereby reinforcing the robustness of the observed microbial interactions. While the Spearman analysis captured broader monotonic dynamics, the Pearson correlation highlighted linear co-occurrence, and together, both approaches validated the reliability of the observed microbial clustering.

The comparative analysis of SCFA-producing taxa revealed a disbiotic pattern in the control group, where several butyrate- and propionate-producing species were present at markedly reduced or imbalanced levels. For instance, *Intestinimonas butyriciproducens, Coprococcus catus*, and *Ruminococcus torques* exhibited relatively low and inconsistent abundances in controls, suggesting impaired fermentative capacity of the cecal microbiota. In contrast, animals subjected to intermittent fasting (IF), probiotic supplementation (Prb), or their combination (IF+Prb) displayed a more balanced and coordinated enrichment of these taxa. This shift was particularly evident for *Intestinimonas* and *Coprococcus*, which reached abundances comparable to other dominant SCFA producers under intervention conditions. Collectively, these findings indicate that dietary and probiotic interventions restore ecological balance among SCFA-producing communities, counteracting age-associated dysbiosis and reestablishing a functional microbial network conducive to host metabolic health.

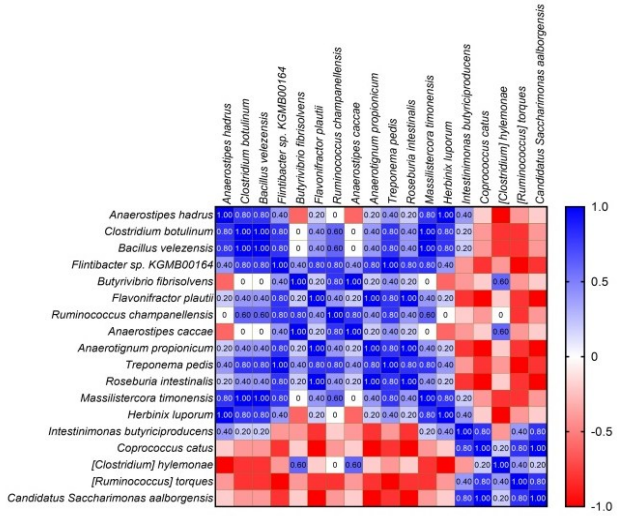

Fig. 1. Spearman correlation matrix of SCFA-producing bacterial species across experimental groups. Matrix plot shows Spearman's rank correlation coefficients (r) between dominant microbial taxa and key physiological variables. Correlation values were two-tailed tested and visualized using a color gradient from –1 (strong negative, blue) to +1 (strong positive, red). Only correlations with $|r| \geq 0.6$ and $p < 0.05$ are displayed. Non-significant associations are shown in grey. Data were analyzed using GraphPad Prism 10.1 and confirmed by Benjamini–Hochberg correction for multiple testing.

3.2 Relative abundance profiles of core SCFA producers

To further examine group-specific differences, the relative abundance of twelve representative short-chain fatty acid (SCFA)-producing taxa was depicted in a heatmap (Fig. 3). The control group demonstrated an imbalanced distribution, with most taxa present at significantly lower levels compared to the intervention groups. In contrast, the IF, Prb, and combined IF+Prb treatments facilitated the enrichment of key species such as *A. muciniphila, A. hadrus, B. fibrisolvens, and R. intestinalis*. Additional taxa, including *Flavonifractor plautii, Anaerostipes caccae,* and *Ruminococcus champanellensis*, also increased under intervention conditions, albeit to varying degrees. Notably, *Treponema pedis*, which was nearly absent in the control group, exhibited detectable enrichment in the intervention groups.

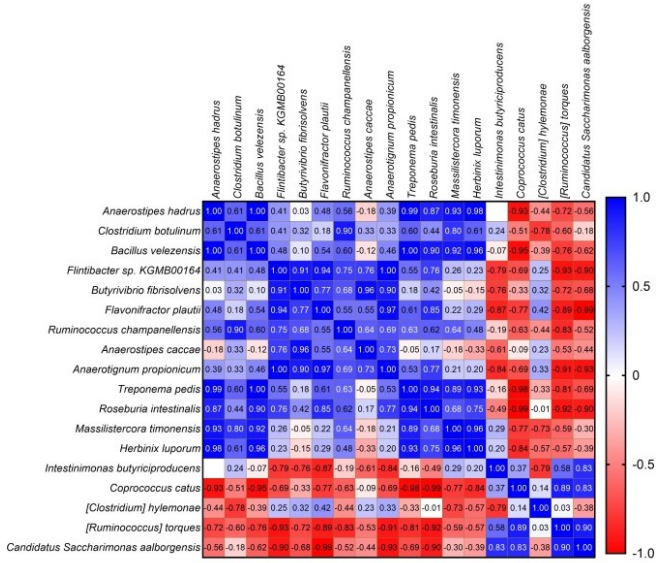

Fig. 2. Pearson correlation matrix of SCFA-producing bacterial species across experimental groups. Pearson's correlation matrix illustrating linear associations (r values) among dominant short-chain fatty acid (SCFA)–producing bacterial species identified across all experimental groups. Correlations were calculated using log-transformed relative abundance values to minimize compositional bias. The color scale represents the strength and direction of correlations, ranging from –1 (strong negative, blue) to +1 (strong positive, red). Only statistically significant correlations ($p < 0.05$) are visualized; non-significant relationships are shown in grey. The analysis highlights coordinated abundance patterns among key butyrate- and acetate-producing taxa, particularly under intermittent fasting and probiotic-supplemented conditions, suggesting shared ecological or metabolic responses. Data visualization was performed in GraphPad Prism 10.1 (GraphPad Software, USA).

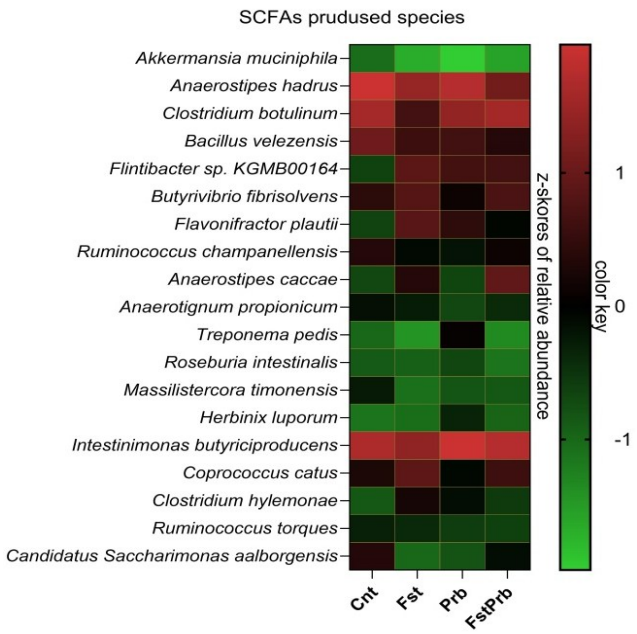

Fig. 3. Heatmap illustrating the relative abundance profiles of bacterial taxa (family and genus levels) across experimental groups. Data were normalized using log-transformed relative abundance values and row Z-score scaling to visualize inter-group differences. The color scale represents Z-scores ranging from –2 (blue, lower abundance) to +2 (red, higher abundance). Only taxa with a mean relative abundance >0.1% and present in at least 50% of samples were included. Hierarchical clustering was performed using the Ward.D2 method and Euclidean distance metric. Statistical significance among groups was assessed by one-way ANOVA followed by Tukey's post hoc test ($p < 0.05$).

4. DISCUSSION

Intermittent fasting (IF) has garnered increasing attention as a nutritional strategy with the potential to modulate gut microbiota composition and function, bearing significant implications for aging and metabolic health. In the present study, aged rats subjected to IF, probiotic supplementation (Prb), or their combination (IF+Prb) exhibited a consistent enrichment of short-chain fatty acid (SCFA)-producing taxa compared to controls, which displayed a dysbiotic microbial profile. This observation is consistent with previous findings that aging is associated with reduced microbial diversity and a decreased abundance of butyrate- and propionate-producing species, contributing to systemic inflammation and metabolic decline [11], [12]. Our data suggests that targeted nutritional interventions can restore ecological balance and reestablish microbial networks conducive to SCFA production in aged hosts.

Among the core taxa analyzed, *Anaerostipes hadrus*, *Butyrivibrio fibrisolvens*, *Roseburia intestinalis*, and *Akkermansia muciniphila* were consistently enriched under IF and probiotic treatments. These taxa are well-known butyrate producers, and their increase has been directly linked to improved colonic barrier integrity, reduced endotoxemia, and modulation of host energy metabolism [13], [14]. Notably, A. muciniphila has been associated with enhanced mucin degradation and improved host metabolic profiles, and its expansion under IF aligns with reports that caloric restriction and fasting promote the growth of mucin-degrading, health-associated taxa [15], [16]. The concurrent increase of *Roseburia* and *Anaerostipes* further underscores the restoration of butyrate-driven trophic chains within the aged gut ecosystem.

The analysis of additional taxa revealed similar trends. *Intestinimonas butyriciproducens* emerged as a particularly responsive species, demonstrating consistent enrichment across all intervention groups. This genus is recognized as a potent butyrate producer via amino acid fermentation, linking microbial activity to nitrogen metabolism [17]. Similarly, *Coprococcus catus* and *Clostridium hylemonae* exhibited intervention-driven increases, both of which are implicated in secondary bile acid metabolism and SCFA production [18]. Conversely, *Ruminococcus torques* and *Candidatus Saccharimonas aalborgensis*, while less consistent, also exhibited partial enrichment, suggesting broader ecological

restructuring under IF and Prb regimens. These taxa may contribute to cross-feeding interactions that sustain a balanced fermentative environment in the aging gut.

The functional implications of these microbial shifts are substantial. Butyrate serves as the primary energy source for colonocytes and exerts anti-inflammatory effects by modulating histone deacetylase activity, while propionate and acetate play critical roles in gluconeogenesis, appetite regulation, and lipid metabolism [19], [20]. The enrichment of SCFA producers observed in our study suggests a potential improvement in mucosal barrier function, reduced inflammatory tone, and enhanced host metabolic flexibility. These effects resonate with previous findings demonstrating that IF ameliorates age-associated metabolic decline partly via SCFA-mediated pathways [21].

In the present study, the probiotic formulation used contained multiple *Lactobacillus* and *Bifidobacterium* strains with complementary metabolic capacities, including SCFA production and mucosal immune modulation. While 16S rRNA sequencing enabled detection of shifts in community composition toward taxa affiliated with these genera, it does not allow for strain-level discrimination or confirmation of stable colonization. Nevertheless, the observed enrichment of *Lactobacillus*, *Bifidobacterium*, and other commensal taxa suggests that at least a subset of the administered strains or their functional analogues successfully persisted or promoted a supportive ecological niche. This pattern aligns with previous reports indicating that even transient colonization by probiotic strains can modulate gut microbiota architecture and metabolite output through cross-feeding and signaling interactions rather than permanent engraftment [6]. Future studies integrating shotgun metagenomics or strain-specific qPCR assays will be required to verify colonization dynamics and delineate the individual contribution of each probiotic strain to the overall ecological restructuring observed here.

Recent human studies corroborate many of the microbial shifts observed in our aged-rat model. Aging in humans is consistently associated with reduced alpha diversity, loss of beneficial SCFA-producing genera such as *Faecalibacterium, Roseburia*, and *Bifidobacterium*, and enrichment of pro-inflammatory pathobionts, leading to a state of "inflammaging" [11], [12]. Similarly, elderly cohorts exhibit decreased fecal concentrations of butyrate and propionate, paralleling the compositional decline of these taxa [24]. The restoration of SCFA-producing bacteria in our experimental groups thus mirrors microbial rejuvenation patterns reported in human probiotic and dietary intervention studies [24], [25]. These convergences suggest that the microbial remodeling induced by our interventions may have translational relevance for mitigating age-associated dysbiosis and systemic inflammation in humans.

Collectively, our findings provide strong evidence that IF and probiotic supplementation exert complementary ecological effects, restoring SCFA-producing bacterial populations that are diminished during aging. While our study focused on a targeted set of taxa, the consistent increase in butyrate, propionate, and acetate producers across intervention groups highlights a common mechanistic axis by which nutritional interventions promote gut homeostasis. Future studies integrating metatranscriptomics and metabolomic profiling will be required to confirm the functional consequences of these microbial changes, particularly in relation to systemic metabolic markers and host physiology. Nevertheless, the present results underscore the translational potential of IF and probiotics as strategies to counteract age-related dysbiosis and reinforce intestinal SCFA production.

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