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Konjac glucomannan-mediated microbiota cross-feeding yields valeric acid for colitis mitigation

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ABSTRACT: Ulcerative colitis is closely linked to gut dysbiosis, and konjac glucomannan (KGM) can ameliorate symptoms by modulating the gut microbiota. However, the specific microbial interactions driving these therapeutic effects remain unclear. This study aimed to identify a KGM-mediated microbial interaction and its role in alleviating colitis. Through in vitro fermentation, we discovered that KGM mediates a mutualistic interaction where *Roseburia intestinalis* NSP017 promotes the growth of *Bacteroides xylanisolvens* NSP016, leading to enhanced production of the metabolite valeric acid. These findings were validated in vivo using a DSS-induced colitis mouse model. Treatment with KGM and the two bacterial strains synergistically reduced disease severity, protected the intestinal barrier, and modulated the gut microbiota. Crucially, valeric acid production was dependent on the presence of *R. intestinalis* NSP017 and correlated with disease amelioration. Our findings establish a novel axis that KGM facilitates a functional interaction between *R. intestinalis* NSP017 and *B. xylanisolvens* NSP016, resulting in the generation of valeric acid, which functions as a key metabolite contributing to the improvement of colitis outcomes in mice.

Keywords: *R. intestinalis*, *B. xylanisolvens*, Valeric acid, Cross-feeding, Colitis, Konjac glucomannan

1. Introduction

Ulcerative colitis (UC), a major type of inflammatory bowel disease (IBD), is characterized by a complex pathogenesis involving genetics, immunity, environmental, and microbial factors^[1,2]. A hallmark of UC is gut dysbiosis, marked by reduced microbial diversity and an imbalance in key taxa, including a decrease in beneficial *Bifidobacteria* and butyrate-producers like *Faecalibacterium*, *Eubacterium*, and *Roseburia*, and an increase in proinflammatory candidates like *Enterobacteriaceae*^[3]. This dysbiosis environment contributes to chronic intestinal inflammation, making the restoration of a healthy microbiota a key therapeutic strategy. Interventions with prebiotics, such as dietary fibers, have shown promise in preventing and treating UC by selectively promoting beneficial bacteria and their metabolites^[4,5].

The efficacy of these prebiotics is often rooted in complex microbial interactions, such as cross-feeding, where metabolic byproducts from one species serve as substrates for another^[6,7]. For instance, *Bacteroides*

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uniformis degrades β -glucan to produce nicotinamide, which is then utilized by *Lactobacillus johnsonii*^[8]. *Bifidobacterium bifidum* can utilize fructooligosaccharides to interact with *Faecalibacterium prausnitzii*, thereby promoting the production of butyric acid^[9]. Furthermore, *Bifidobacterium adolescentis* utilizes starch to produce lactic acid, a substrate that butyric acid-producing bacteria *Eubacterium hallii* and *Anaerostipes caccae* can further metabolize into butyric acid^[10]. Konjac glucomannan (KGM) is a soluble dietary fiber derived from konjac tubers and is one of the most extensively studied glucomannans; it is characterized by a main chain of β -(1 $\rightarrow$ 4)-linked D-glucosyl and D-mannosyl residues with branches formed through β -(1 $\rightarrow$ 6)-glucosyl units^[11,12]. Recently, the health benefits of KGM have gained increasing recognition, including improvements in glucose metabolism^[12] and the alleviation of colitis^[13,14], effects that are potentially attributed to its modulation of the gut microbiota^[15,16]. However, despite being an excellent bioactive polysaccharide, most studies have focused on the regulatory effects of KGM on the overall microbial community, without analyzing specific microbe-microbe interactions mediated by KGM.

Therefore, this study aimed to identify and characterize a KGM-mediated microbial interactions. We first utilized an *in vitro* fermentation model to screen for interacting bacteria and verified their mutualism through transcriptomic and metabolite analyses. These findings were then validated *in vivo* using a DSS-induced colitis mouse model to determine if this interaction could restore microbial function and ameliorate disease.

2. Materials and methods

2.1 Chemicals and reagents

Yeast extract-casein hydrolysate-fatty acid medium (YCFA) was purchased from Hope Bio-Technology Co., Ltd. (China). L-cysteine hydrochloride anhydrous, hemin chloride, vitamin K₁, short chain fatty acid standard, and sodium valerate were purchased from Shanghai Aladdin Biochemical Technology Co., Ltd. Spermine was purchased from MedChemExpress (China). The bacterial genomic DNA extraction kit was purchased from Tiangen Biochemical Technology (Beijing) Co., Ltd. Takara PrimeSTAR® HS DNA Polymerase, PrimeScriptMFAST RT reagent kit with gDNA Eraser, and TRIzol were purchased from Takara Bio Inc. The Mouse TNF- α , IL-6, and IL-10 ELISA kit was purchased from Nanjing Fcmacs Biotech Co., Ltd. The SOD activity detection kit (WST-8 method) and lipid oxidation (MDA) detection kit were purchased from Shanghai Beyotime Biotechnology Co., Ltd. The myeloperoxidase (MPO) assay kit (colorimetric method) was purchased from Nanjing Jiancheng Bioengineering Institute.

2.2. Preparation of KGM

KGM was extracted and purified as described in our previous research^[17]. The resulting KGM was then characterized for its neutral sugar^[18], uronic acid^[19], and protein^[20] contents, as well as its molecular weight and monosaccharide composition, using established methods.

2.3. Bacterial strain and medium

The strains used in this study were originally isolated and purified from the fecal samples of healthy

adults and are maintained in the State Key Laboratory of Food Science and Resources. For routine recovery, bacteria were cultured from cryovials in conventional YCFA medium supplemented with 1 g/L-cysteine hydrochloride, 0.05 g/L hemin chloride and 0.001 g/L vitamin K₁. To investigate KGM utilization and cross-feeding, strains were cultured in carbon-free YCFA medium, either alone or supplemented with 0.2% of a carbohydrate source (eg. KGM or glucose).

2.4 Screening for bacteria cross-feeding on KGM

A total of 24 bacterial strains, comprising 10 *Bacteroides* (1 *Bacteroides xylanisolvens*, 1 *Bacteroides caccae*, 1 *Bacteroides fragilis*, 1 *Bacteroides thetaiotaomicron*, 1 *Bacteroides stercoris*, 1 *Bacteroides koreensis*, 1 *Bacteroides ovatus*, 1 *Bacteroides salyersiae*, 1 *Bacteroides intestinalis*, 1 *Bacteroides vulgatus*) and 14 Firmicutes (1 *Roseburia intestinalis*, 1 *Roseburia faecis*, 1 *Enterococcus hirae*, 1 *Ruminococcus gnavus*, 1 *Lactocaseibacillus rhamnosus*, 1 *Faecalibacterium prausnitzii*, 1 *Parasutterella excrementihominis*, 1 *Dorea longicatena*, 1 *Ligilactobacillus ruminis*, 1 *Alistipes indistinctus*, 1 *Akkermansia muciniphila*, 1 *Eubacterium rectale*, 1 *Eubacterium ventriosum*, 1 *Bifidobacterium pseudocatenulatum*), were screened for cross-feeding in pairwise combinations. Strains were inoculated (2% v/v overnight culture) individually or in pairs (ratio 1:1) into the YCFA media with either (i) KGM as the primary substrate, (ii) glucose as a positive control, or (iii) no carbohydrate as a negative control. Cultures were incubated anaerobically at 37 °C for 48 hours. To monitor growth, 200 µL samples were collected at 0, 6, 12, 24, 36, and 48 hours to measure optical density at 600 nm (OD₆₀₀). Samples from the 0- and 48-hour timepoints were also analyzed for bacterial quantification via quantitative PCR (qPCR)^[8] using the primers shown in Supplementary Table 1.

For pairs exhibiting significant growth enhancement in co-culture compared to monoculture, alterations in pH and residual content^[21] was analyzed. The promoter and recipient roles were determined by separately cultivating each strain with the cell-free supernatant from its partner. These supernatants were harvested from partner cultures grown in YCFA medium with KGM at 6, 12, and 24 hours post-inoculation. Growth was assessed by measuring the change in OD₆₀₀, pH, and residual sugar content after 48 hours of incubation (Fig. 1c-f).

2.5 Transcriptomic analysis

Draft genomes for *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 were generated to serve as references for transcriptomic analysis. Sequencing was performed by Shanghai Majorbio Bio-pharm Technology Co., Ltd. on an Illumina NovaSeq 6000 platform.

Total RNA was extracted from bacterial cells collected at mid-log phase using CTAB method and genomic DNA was removed. High-quality RNA sample was used to construct sequencing libraries with the Illumina® Stranded mRNA Prep, Ligation kit (San Diego, CA). Paired-end sequencing was performed on an the Illumina Novaseq 6000 (Illumina Inc., San Diego, CA, USA). Bioinformatic analyses were performed on the Majorbio Cloud Platform (<http://cloud.majorbio.com>). Cleaned reads were aligned to the reference genome using Bowtie 2 (<http://bowtie-bio.sourceforge.net/index.shtml>), and gene expression levels were

calculated using RSEM (<http://deweylab.github.io/RSEM/>). Differentially expressed genes (DEGs) were identified with the DESeq2 (<http://bioconductor.org/packages/release/bioc/html/DESeq2.html>) package. GO functional enrichment of DEGs was performed using Goatools (<https://github.com/tanghaibao/GOatools>) and Fisher's exact test, with p-values adjusted using the Benjamini-Hochberg FDR method. Significantly enriched GO terms were defined as those with an adjusted *P*-value ≤ 0.05 .

2.6 Animal experiments

Male SPF-grade C57BL/6J mice (6 weeks old, 18 g–20 g, purchased from GemPharmatech Co., Ltd.) were housed under standard conditions ($(25 \pm 0.5)^\circ\text{C}$, $(50 \pm 5)\%$ humidity, 12h light/dark cycle) with free access to standard diet (SPF-grade growth maintenance feed for mice and rats, Beijing Keao Xieli Feed Co., Ltd.) and water. Mice were acclimated for 7 days prior to the intervention.

Experiment 1: Effect of the Cross-Feeding Involved Bacteria on DSS-Induced Colitis (Fig 3a)

Mice were randomly assigned to seven groups ($n = 8$): Normal Control (NC), Model (M), KGM group (KGM), *B. xylanisolvens* NSP016 group (*B.x*), *R. intestinalis* NSP017 group (*R.i*), KGM+*B.x*, KGM+*R.i*. Prior to colitis induction, groups *B.x*, *R.i*, KGM+*B.x*, and KGM+*R.i* underwent a 7-day course of broad-spectrum antibiotics^[8], while the rest received sterile saline. Starting from day 8, all groups except NC received 3% DSS in drinking water for 7 consecutive days to induce colitis. During this period, daily interventions were administered by oral gavage as follows: the NC and M groups received sterile saline; the KGM, KGM+*B.x*, and KGM+*R.i* groups received KGM (250 mg/kg·BW); the *B.x* and KGM+*B.x* groups received *B. xylanisolvens* NSP016 (1×10^8 CFU); the *R.i* and KGM+*R.i* groups received *R. intestinalis* NSP017 (1×10^8 CFU).

Experiment 2: Effect of Valeric Acid on DSS-Induced Colitis (Fig 6a)

Mice were randomly divided either a model group (M) or a sodium valeric treatment group (SV). Colitis was induced in both groups by administering 3% DSS solution in their drinking water for 7 consecutive days. During this period, the M group received a daily oral administration of sterile saline, while the SV group received a daily oral administration of sodium valeric at a dose of 100 mg/kg·BW^[22].

Mouse body weight was monitored daily throughout the study. At the endpoint, mice were humanely euthanized, and serum, fecal, colon, and spleen samples were collected for analysis. All procedures were approved by the Experimental Animal Care and Use Committee of Nanchang University and followed the National Institutes of Health Guide for the Care and Use of Laboratory Animals (NCULAE-20250529001).

2.7 Disease active index (DAI) and organ index

Disease severity was assessed daily using methods adapted from previous research^[23]. Body weight loss, stool consistency, and rectal bleeding were each scored on a scale of 0 to 4. The DAI was calculated as the average of these three scores. At the experimental endpoint, the length of the colon (from cecum to rectum)

and the weight of the spleen were measured. The spleen index was calculated as the ratio of spleen weight (g) to final body weight (kg).

2.8 ELISA

Colon tissues were homogenized in PBS buffer (1:10 w/v), and centrifuged at 13,000 g for 15 min. Total protein levels in the supernatant were measured by BCA kit (Beyotime Biotechnology) for data normalization. The levels of inflammatory cytokines TNF- α , IL-6, IL-10, and oxidative stress markers superoxide dismutase (SOD), myeloperoxidase (MPO), and malondialdehyde (MDA) in the colon tissue were further determined using corresponding ELISA kit according to the manufacturer's instructions.

2.9 RNA extraction and gene expression analysis

Total RNA was extracted from colon tissue using TRIzol reagent. For cDNA synthesis, total RNA was reverse-transcribed using the PrimeScript RT Kit and spermine, followed by quantification of the cDNA on a Nanodrop spectrophotometer. The expression of tight junction proteins (ZO-1, Claudin-1, and Occludin) were then determined by quantitative real-time PCR (RT-qPCR) with primers specified in Supplementary Table 2. β -actin served as the endogenous control, and relative mRNA abundance was calculated using the $2^{-\Delta\Delta Ct}$ method^[8].

2.10 H&E staining and histopathological grading

A 1 cm segment of distal colon was placed in 4% paraformaldehyde solution for 24 hours to obtain fixed colon tissue samples. Following fixation, the tissue underwent standard processing, including dehydration, paraffin embedding, and sectioning. After deparaffinization and rehydration, 5 μ m sections were stained with hematoxylin and eosin (H&E)^[23]. The stained sections were digitally scanned, and histological scoring was performed on the captured images. An established protocol was used to grade three distinct parameters: Inflammation grade (0-4), Epithelial cell damage (0-4), Crypt damage (0-4). The overall histological score was calculated as the sum of these three individual scores^[8].

2.11 16S rRNA gene sequencing and data analysis

Total microbial genomic DNA was extracted from mouse fecal microbiota using the FastPure Stool DNA Isolation Kit (MJYH, Shanghai, China) according to manufacturer's instructions. The quality and concentration of DNA were determined by agarose gel electrophoresis and a NanoDrop® ND-2000 spectrophotometer (Thermo Scientific Inc., USA). The bacterial 16S rRNA V3-V4 region were amplified with primers 338F (5'-ACTCCTACGGGAGGCAGCAG-3') and 806R (5'-GGACTACHVGGGTWTCTAAT-3')^[24] on an T100 Thermal Cycler (BIO-RAD, USA). After gel purification, libraries were prepared with the NEXTFLEX Rapid DNA-Seq Kit (Bioo Scientific, USA) and sequenced on an Illumina NextSeq 2000 PE300 platform. Raw reads were filtered with fastp (v0.19.6)^[25], merged with FLASH (v1.2.11)^[26], denoised into amplicon sequence variants (ASVs) using DADA2^[27] plugin in the Qiime2^[28] (version 2020.2). ASVs were

taxonomically assigned using SILVA 16S rRNA database (v138.2).

Further data analysis and visualization was performed on the Majorbio Cloud platform (<https://cloud.majorbio.com>). Alpha diversity (Chao 1, Shannon and Simpson) was calculated in Mothur v1.30.2^[29], while beta diversity was assessed by Bray-curtis-based principal coordinate analysis (PCoA) and PERMANOVA test using R Vegan package (version 3.3.1). Differentially abundant taxa were identified using the linear discriminant analysis (LDA) effect size (LEfSe)^[30] (<http://huttenhower.sph.harvard.edu/LEfSe>) (LDA score > 2, $P < 0.05$).

2.12 *In vitro* fermentation

To prepare the fecal inoculum, samples from DSS-treated mice were homogenized (1:9 w/v) in sterile PBS. The homogenate was filtered through a 100 µm cell strainer within an anaerobic glove box. The resulting filtrate was then combined 1:1 with a sterile 50% glycerol solution supplemented with 1 g/L cysteine hydrochloride to generate a fecal bacterial suspension for storage at -80 °C. In parallel, pre-activated cultures of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 were concentrated. Four experimental inocula were generated by adding these cultures to the fecal slurry individually, at final concentrations of 10⁷ (low dose, L) or 10⁸ (high dose, H) CFU/mL. These inocula were then introduced at a 2% (v/v) ratio into a YCFA medium containing KGM as the sole carbon source. For controls, fermentations were established with fecal slurry alone in YCFA medium containing KGM, as well as with all the experimental inocula including fecal slurry alone in YCFA medium lacking any carbon source. After 48 hours of anaerobic cultivation, samples were collected for short-chain fatty acid (SCFA) analysis (Fig 5a).

2.13 Determination of SCFAs

SCFA concentrations (acetic, propionic, isobutyric, butyric, isovaleric, and valeric acids) were quantified using gas chromatography with an external standard method.

For bacteria fermentation samples cultured for 48 hours or 24 hours^[31], 1 mL of broth was centrifuged at 13,000 r/min for 5 minutes. For fecal samples from mice (100 mg-200 mg)^[32], the material was homogenized in 1×PBS (1:10 w/v) with zirconia grinding beads at 70 Hz for three 1-minute cycles, then centrifuged at 13,000 r/min for 5 minutes.

The resulting supernatants from both sample types were filtered through a 0.22 µm aqueous filter. An aliquot (0.5 mL-0.7 mL) of the filtrate was acidified with 0.2 mL of 10% sulfuric acid, vortex, and then extracted with 10 µL of 10 mmol/L internal standard solution and 0.4 mL of anhydrous diethyl ether. After a 2-minute incubation and centrifugation at 13,000 r/min for 2 min, the organic layer was filtered through a 0.22 µm organic filter and proceed to instrument analysis. Chromatographic analysis was performed using an Agilent 7890 N gas chromatograph equipped with an HP-FFAP column, using conditions adapted from previous research^[32].

2.14 Statistical analysis

All statistical analyses were performed using GraphPad Prism (version 8.0) and IBM SPSS Statistics (version 27.0). Data are expressed as mean $\pm$ standard error of the mean (SEM). For comparisons between two groups, an unpaired t-test was used when samples were normally distributed; the Mann-Whitney U test was used when samples were not normally distributed. For comparisons involving more than two groups, one-way analysis of variance (ANOVA) and Tukey's post hoc test were used when samples were normally distributed; the Kruskal-Wallis test was used when samples were not normally distributed. $P < 0.05$ was considered statistically significant, with $^*P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$, and $^{****}P < 0.0001$.

3. Results

3.1. Physical and Chemical Properties of KGM

Chemical characterization of the extracted KGM revealed a composition of $(86.80 \pm 7.08)\%$ neutral sugars, $(6.53 \pm 0.53)\%$ uronic acids, and $(2.79 \pm 1.85)\%$ protein, indicating high polysaccharide purity (Table 1). Monosaccharide analysis showed that KGM primarily consisted of mannose ($59.50 \pm 1.56\%$) and glucose ($38.35 \pm 1.59\%$), with a minor component of glucuronic acid ($2.16 \pm 0.35\%$) (Table 2). The weight-average molecular weight (Mw) of KGM was determined to be 1676 kDa by HPGPC (Supplementary Fig. 1a).

Table 1 Monosaccharide composition of KGM

Glucose (%)	Mannose (%)	Glucuronic acid (%)
38.35 ± 1.59	59.50 ± 1.56	2.16 ± 0.35

Table 2 Sugar and protein content of KGM

Neutral sugar content (%)	Sugar-aldehyde content (%)	Protein content (%)
86.80 ± 7.08	6.53 ± 0.53	2.79 ± 1.85

3.2. Cross-feeding of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 via KGM

Preliminary screening for mutualistic interactions, assessed by alterations in OD₆₀₀ and bacterial counts, identified three promising strain pairs: *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 (Fig. 1a-b), *Bacteroides caccae* XN001 and *Roseburia intestinalis* NSP017 (Supplementary Fig. 1b-c), and *Bacteroides fragilis* XN002 and *Roseburia faecis* NX001 (Supplementary Fig. 1d-e). Among these, the *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 pair demonstrated the strongest evidence of a synergistic relationship and was therefore chosen for subsequent experiments.

Fig. 1

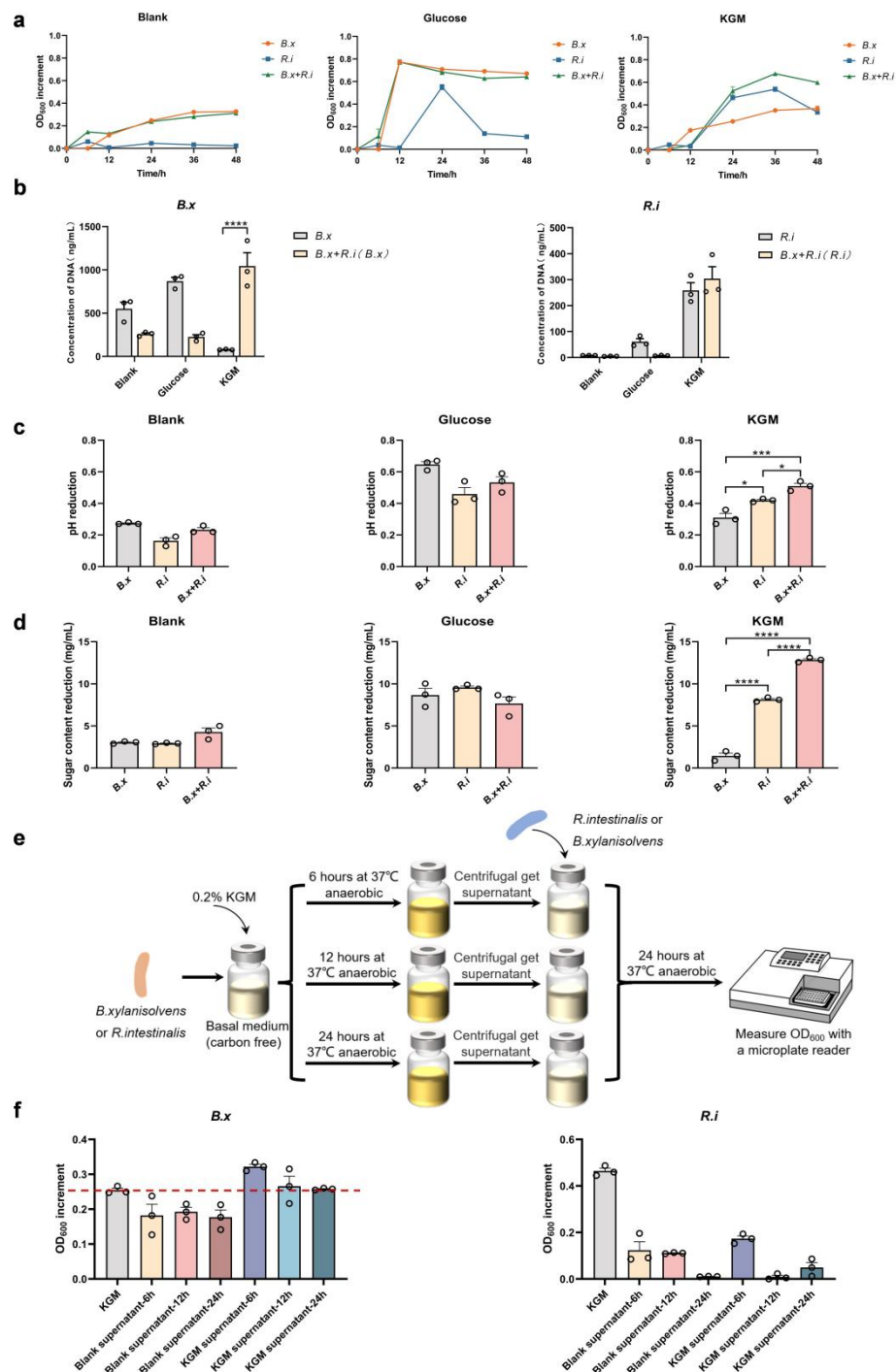


Fig. 1 Cross-feeding between *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 on KGM. (a) Growth curve (OD₆₀₀) of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 during 48-hour co-culture. (b) Relative abundance of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 after 48-hour co-culture, quantified by qPCR. (c) pH and (d) sugar content alterations after 48-hour co-culture. (e) Schematic of the supernatant cultivation assay for identifying promoter and recipient strains. (f) Growth promotion (OD₆₀₀) of recipient strains after 24 hours incubation with cell-free supernatant from the partner strain. Note: * indicates significant difference, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$.

Experiments based on pH and sugar content revealed a synergistic relationship between *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017, particularly on KGM. While both strains utilized glucose effectively, the co-culture produced less acid than *B. xylanisolvens* NSP016 monoculture, and sugar consumption in the co-culture was equivalent to that of the individual cultures. In contrast, in KGM medium, *R. intestinalis* NSP017 was the more efficient degrader, causing a larger pH drop and greater sugar reduction than *B. xylanisolvens*

NSP016. Critically, when co-cultured on KGM, the strains exhibited the highest level of sugar consumption and acid production, surpassing either monoculture (Fig. 1c-d).

Although both *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 grew well in YCFA-KGM medium, the supernatant of *R. intestinalis* NSP017, culture with KGM as sole carbon source, significantly promoted the growth of *B. xylanisolvens* NSP016. This effect was time-dependent, with the 6-hour supernatant showing the most potent promotion; the resulting increase in OD₆₀₀ surpassed that observed for *B. xylanisolvens* NSP016 grown directly on KGM (Fig. 1f). Notably, the supernatant of *B. xylanisolvens* NSP016 cultures, harvested at 6, 12, or 24 hours from medium with either carbon-free or KGM as sole carbon source, did not enhance the growth of *R. intestinalis* NSP017 (Fig. 1f). This result indicates that the symbiotic relationship is dominated by the promotion of *B. xylanisolvens* NSP016 growth by *R. intestinalis* NSP017.

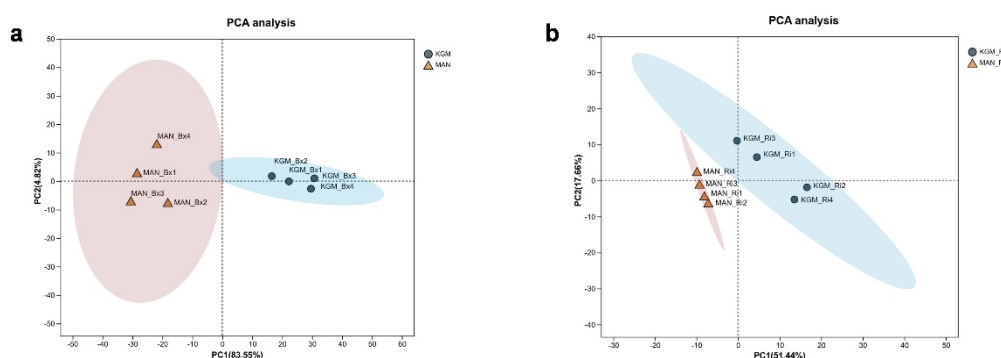
3.3. Transcriptomic Response of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 on KGM

The major monosaccharide of KGM was used for comparative analysis of the transcriptomic response of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017, and significant differences were witnessed by the principal component analysis (Fig. 2a-b).

For *B. xylanisolvens* NSP016, comparison of the KGM and mannose groups identified 1,655 upregulated and 1,244 downregulated DEGs (Fig. 2c). GO enrichment analysis of these DEGs highlighted upregulation of molecular functions (MF) related to cell wall remodeling (e.g., peptidoglycan muralytic activity). The corresponding biological processes (BP) were enriched for catabolism of glycosaminoglycan and peptidoglycan (Fig. 2e).

In contrast, analysis of the *R. intestinalis* NSP017 groups revealed 646 upregulated and 233 downregulated DEGs (Fig. 2d). The GO enrichment profile here pointed towards a different biological response, with significant upregulation of terms related to translation and protein synthesis. This was evident across all categories: molecular functions (e.g., structural constituent of ribosome), cellular components (e.g., ribosomal subunit), and biological processes (e.g., translation, protein metabolic process) (Fig. 2f). Carbohydrate metabolism was also detected, as indicated by carbohydrate metabolic process (BP) and hydrolase activity (acting on glycosyl or O-glycosyl compounds, MF).

Fig. 2



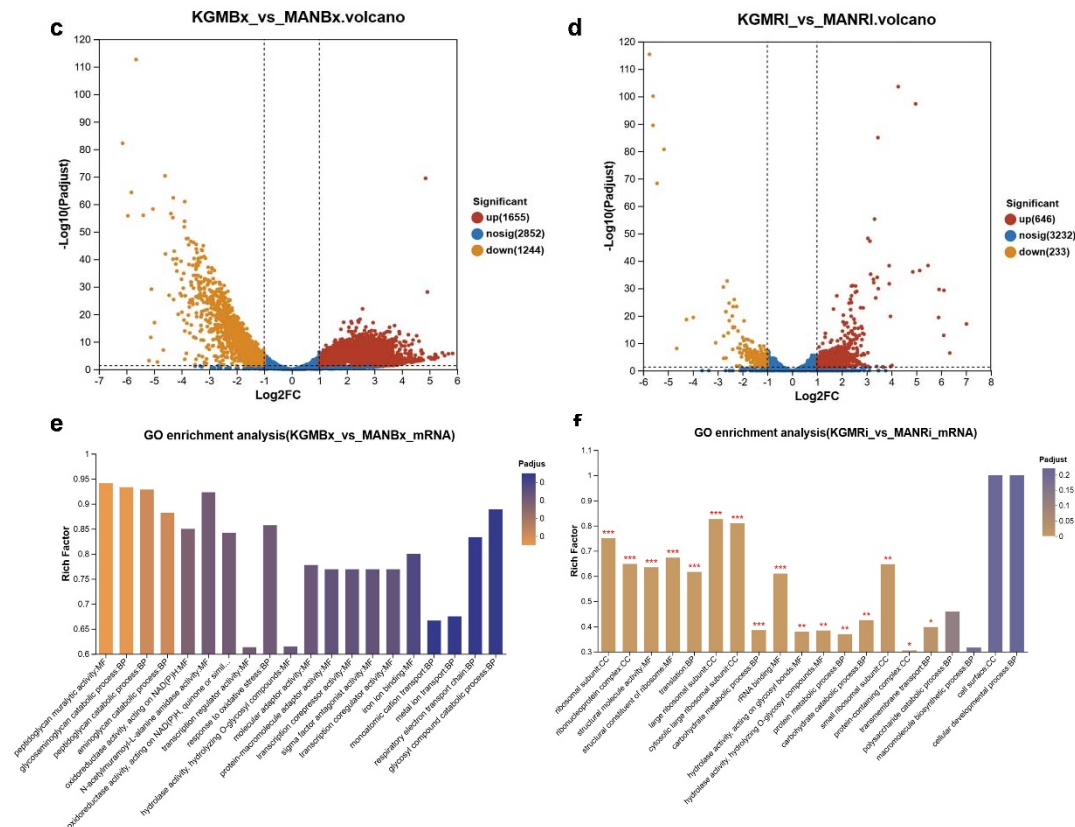


Fig. 2 Transcriptomic response of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 to KGM versus mannose (MAN). Principal component analysis (PCA) of transcriptomes for (a) *B. xylanisolvens* NSP016 and (b) *R. intestinalis* NSP017 grown on KGM or mannose. Volcano plots showing DEGs in (c) *B. xylanisolvens* NSP016 and (d) *R. intestinalis* NSP017 when grown on KGM versus mannose. GO enrichment analysis of DEGs in (e) *B. xylanisolvens* NSP016 and (f) *R. intestinalis* NSP017.

To specifically identify enzymes involved in carbohydrate metabolism, the DEGs were annotated using the CAZy database (www.cazy.org/). In *B. xylanisolvens* NSP016, 225 DEGs encoded glycoside hydrolases (GHs) and 78 encoded glycosyltransferases (GTs), while in *R. intestinalis* NSP017, 91 were GHs and 41 were GTs (Supplementary Tables 3, 4). Further data mining of upregulated genes identified the specific KGM-degrading enzymes. In *R. intestinalis* NSP017, these included β -mannanase, β -mannosidase, and exo- β -1,4-mannobiohydrolase, β -1,4-mannosylglucose phosphorylase, β -1,4-mannooligosaccharide phosphorylase, β -glucosidase, and glucan 1,4- β -glucosidase, corresponding to the GH families GH26, GH130, GH2, and GH3 (Table 3). In *B. xylanisolvens* NSP016, the upregulated enzymes included all Cazymes but notably lacked β -mannanase, corresponding to the GH families GH2, GH130, and GH3.

3.4. *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 mitigate colitis symptoms in mice

During the colitis modeling period, interventions in the KGM, *B.x*, *R.i*, KGM+*B.x*, and KGM+*R.i* groups significantly alleviated body weight loss, reduced DAI scores, prevented colon shortening, and lowered the spleen index in mice (Fig. 3b-e, Supplementary Fig. 2a-b). In contrast, the DSS model (M) group showed a significant increase in inflammatory damage and oxidative stress compared to the normal control (NC) group, evidenced by elevated colonic levels of proinflammatory cytokines (TNF- α and IL-6), MPO, and MDA, alongside decreased levels of the anti-inflammatory cytokine IL-10 and the antioxidant enzyme SOD (Fig. 3f-

k). All five interventions effectively reversed these molecular changes.

Fig. 3

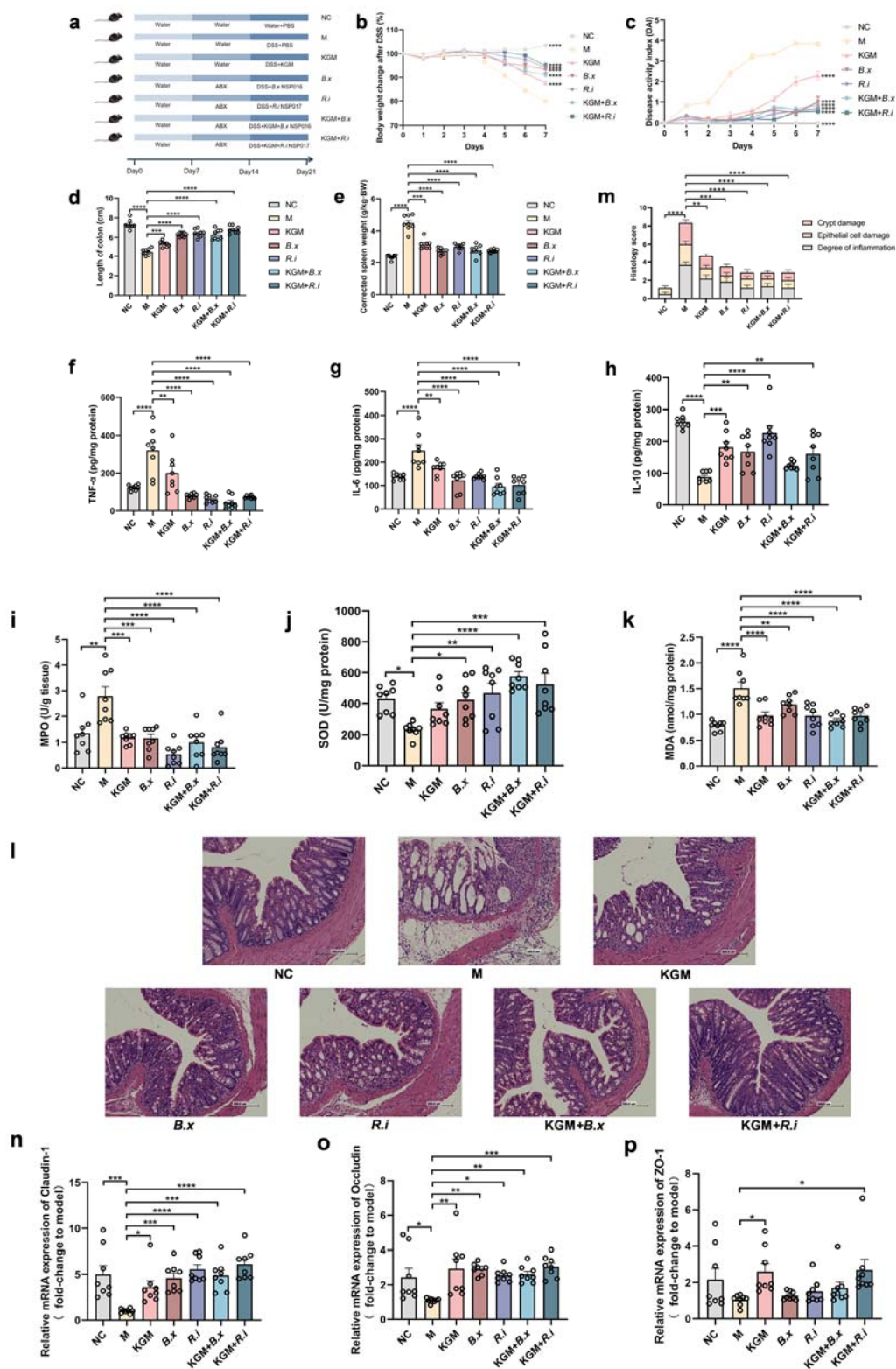


Fig. 3 *B. xylanisolvans* NSP016 and *R. intestinalis* NSP017 mitigate colitis symptoms in mice. (a) Experimental design. (b) Body weight, (c) DAI scores, (d) Colon length, and (e) spleen index of mice in each group. (f-h) Levels of inflammatory factors TNF- α , IL-6, and IL-10 in colon tissue. (i-k) Levels of oxidative stress factors MPO, SOD, and MDA in colon tissue; (l) Representative H&E-stained sections of the distal colon and (m) corresponding histopathological scores. Scale bars = 200 μ m. (n-p) Protein expression of colonic tight junction proteins Claudin-1, Occludin, and ZO-1 in colon tissue.

Note: * indicates significant difference, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$.

Histological evaluation corroborated these findings; the M group exhibited severe mucosal destruction,

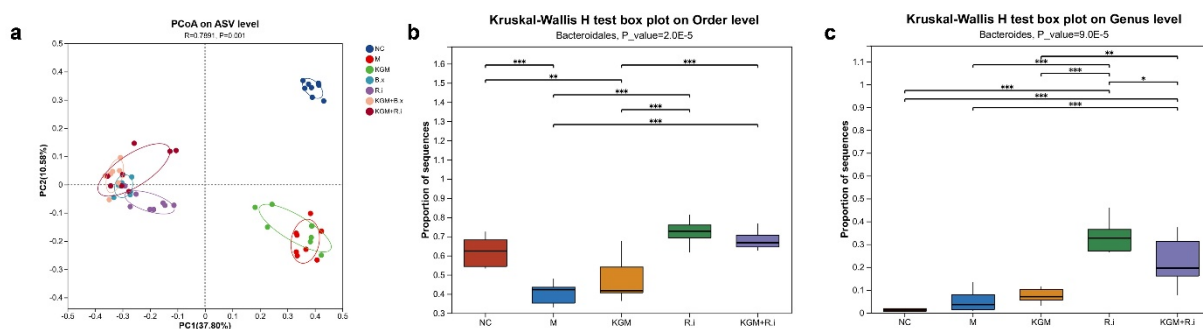
crypt loss, and massive inflammatory cell infiltration, while all treatments, especially KGM+*R.i*, markedly alleviated this damage, restoring colon morphology to near-normal levels (Fig. 3l, m). To investigate barrier integrity, a key factor in colitis, we measured tight junction proteins. DSS treatment significantly reduced the expression of Claudin-1, Occludin, and ZO-1. Conversely, all interventions up-regulated these proteins, with the KGM+*R.i* group showing the most potent restorative effect (Fig. 3n-p). In summary, these data indicate that KGM and both bacterial strains protect against DSS-induced colitis, with the combination of KGM and *R. intestinalis* NSP017 providing the most potent protection.

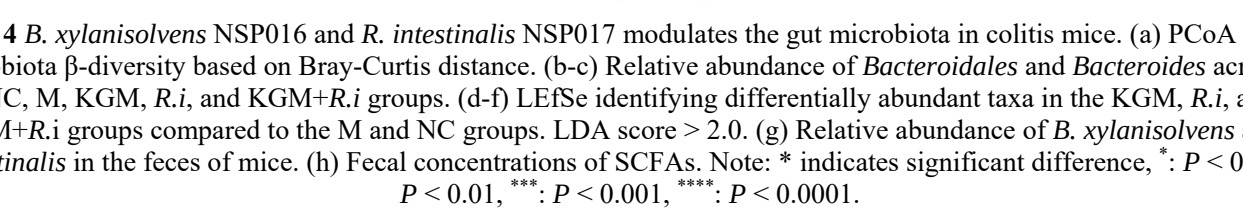
3.5 *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 modulates the gut microbiota in colitis mice

Analyses of α -diversity (Chao-1, Shannon, and Simpson index; Supplementary Fig. 3a), and β -diversity (PCoA; Fig. 4a) revealed significant alterations to the gut microbiota following treatments of KGM, *B.x*, *R.i*, and their combinations. At the phylum level, DSS treatment disrupted the microbial balance, significantly decreasing Bacteroidota while increasing Bacillota and Pseudomonadota compared to the NC group. Intervention with all treatments reversed the depletion of Bacteroidota, and groups receiving *B. xylanisolvens* NSP016 or *R. intestinalis* NSP017 (alone or with KGM) also showed a significant reduction in Bacillota (Supplementary Fig. 3b). LEfSe analysis provided higher-resolution insight, confirming that DSS enriched taxa such as *Clostridia* and *Lachnospiraceae* (Fig. 4d-f, Supplementary Fig. 3d-e). Conversely, the *B.x*, *R.i*, KGM+*B.x*, and KGM+*R.i* treatments significantly upregulated *Bacteroidales* and *Bacteroides* (Fig. 4b-c, Supplementary Fig. 3f-g). Crucially, qPCR analysis confirmed that oral administration of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 led to their successful colonization in the mice feces. Furthermore, supplementation of *R. intestinalis* NSP017 significantly enriched the abundance of *B. xylanisolvens* (Fig. 4g), a finding consistent with our *in vitro* data and demonstrating a clear cross-promotion effect *in vivo*.

Compared with the NC group, colitis induction in the M group significantly reduced the concentrations of all detected SCFAs, with propionic and valeric acid becoming undetectable. All intervention strategies effectively restored overall SCFAs levels. Notably, while isobutyric and isovaleric acid was generally low across the groups, valeric acid was exclusively detected in the NC, *R.i*, and KGM+*R.i* groups (Fig. 4h). This finding suggests that *R. intestinalis* NSP017 is capable of either producing valeric acid directly or restoring the capacity of the gut microbiota to do so. Furthermore, the co-administration of KGM appears to enhance this specific effect.

Fig. 4





3.6 Valeric acid may be a key metabolite induced by the symbiotic effect between *B. xylansolvens* NSP016 and *R. intestinalis* NSP017

To pinpoint the origin of valeric acid, we analyzed their metabolic output in isolation and in combination. In monoculture, *B. xylanisolvens* NSP016 produced a wide array of SCFAs, including acetic, propionic, isobutyric, and isovaleric acid, while *R. intestinalis* NSP017 produced only acetic and butyric acid (Fig. 5h-l). Notably, valeric acid was not detected in either monoculture. However, it was specifically and robustly produced when the two strains were co-cultured (Fig. 5m).

Fig. 5

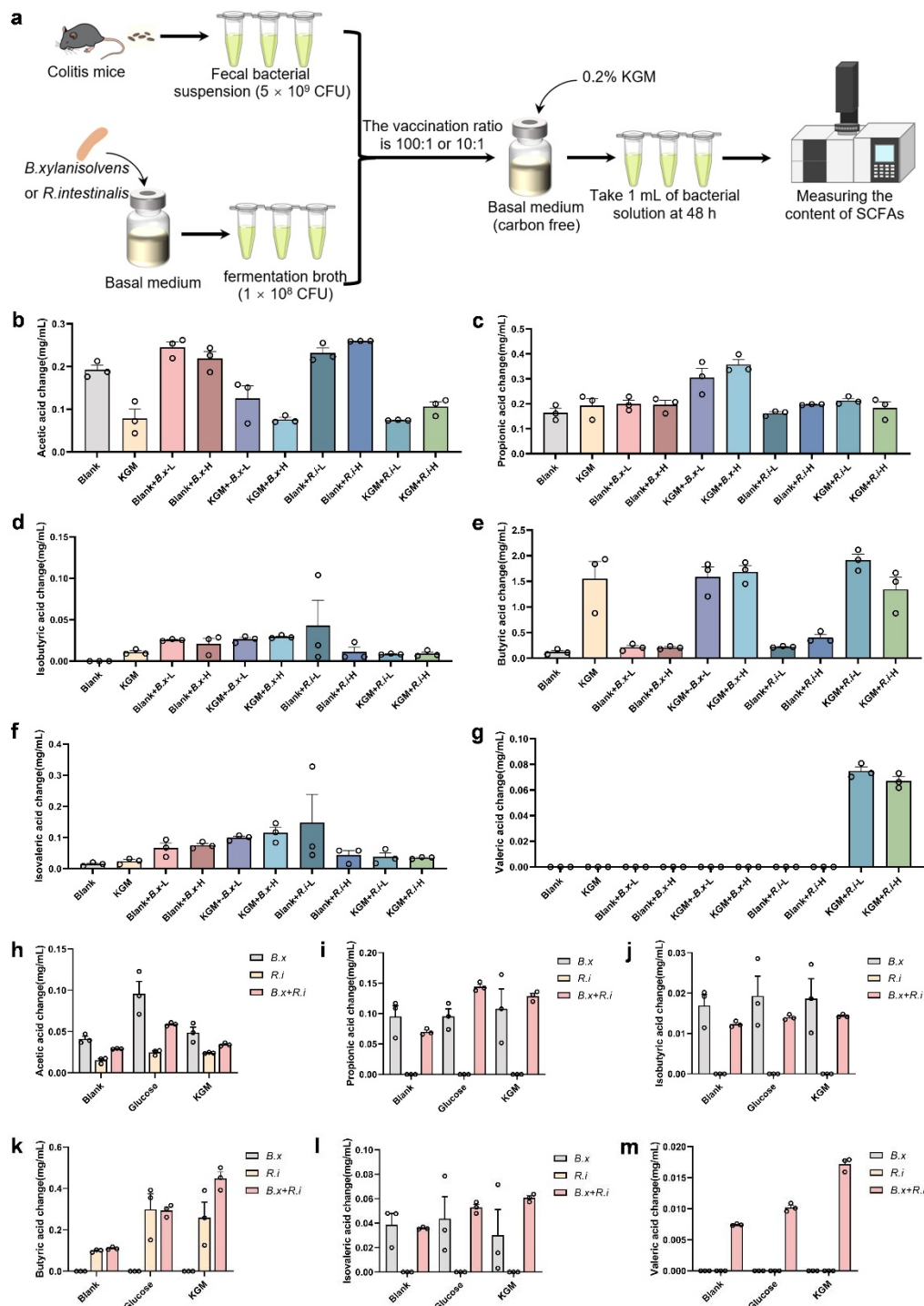


Fig. 5 Valeric acid may be a key metabolite induced by the symbiotic effect between *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017. (a) Schematic of the *in vitro* fecal fermentation assay. (b-g) Production of SCFAs (acetic, propionic, isobutyric, butyric, isovaleric, and valeric acid) during fecal fermentation. (h-m) Production of SCFAs (acetic, propionic, isobutyric, butyric, isovaleric, and valeric acid) during co-culture of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017.

3.7. Valeric acid alleviates DSS-induced colitis in mice

Supplementation of valeric acid was found to significantly counteract the pathological manifestations of colitis. Specifically, it attenuated body weight loss, reduced DAI scores, prevented colon shortening, and decreased the spleen index compared to the untreated colitis group (Fig. 6b-e, Supplementary Fig. 2c, d). A

molecular analysis of colonic tissues revealed that valeric acid treatment significantly downregulated the pro-inflammatory cytokines TNF- α and IL-6, as well as the lipid peroxidation product MDA. In contrast, the levels of the anti-inflammatory cytokine IL-10 and the antioxidant enzyme SOD were significantly upregulated (Fig. 6f-j), suggesting a suppression of both inflammation and oxidative stress. Consistent with these biochemical findings, histopathological analysis revealed that valeric acid treatment ameliorated colon tissue damage, characterized by preserved intestinal epithelial integrity and reduced inflammatory cell infiltration, culminating in significantly lower histopathological scores (Fig. 6k). Taken together, these results provide compelling evidence that valeric acid confers substantial protection against DSS-induced colitis in mice.

Fig. 6

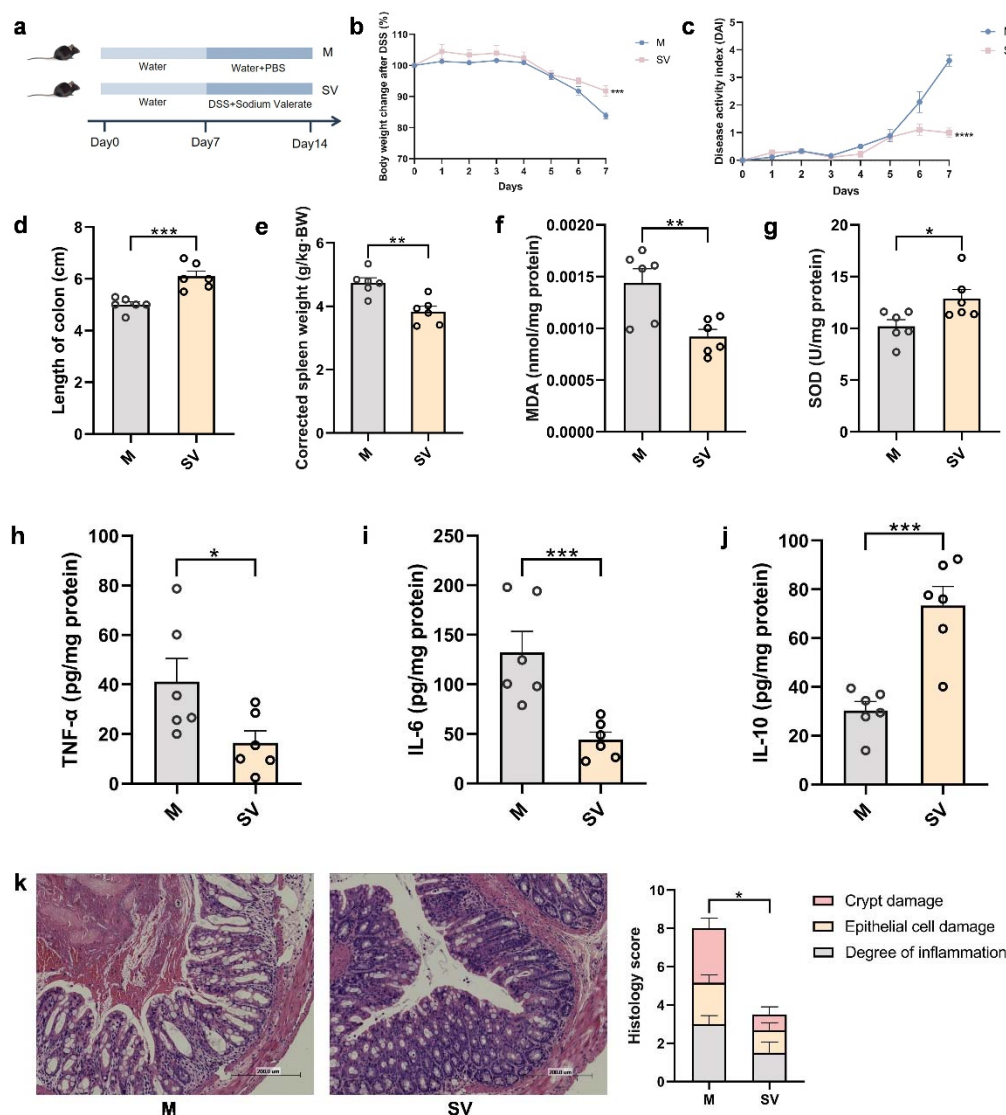


Fig. 6 Valeric acid alleviates DSS-induced colitis in mice. (a) Experimental design; (b) Body weight, (c) DAI scores, (d) colon length, and (e) spleen index of mice in each group. (f-g) Levels of oxidative stress factors MDA and SOD in colon tissue. (h-j) Levels of inflammatory factors TNF- α , IL-6, and IL-10 in colon tissue. (k) Representative H&E-stained sections of the distal colon and corresponding histopathological scores, scale bar = 200 μ m. Note: * indicates significant difference, *: $P < 0.05$, **: $P < 0.01$, ***: $P < 0.001$, ****: $P < 0.0001$.

4. Discussion

Dietary fibers such as KGM are well-established modulators of the gut microbiota and play a critical role in preventing and alleviating diseases such as UC^[33]. While extensive research has focused on how individual microbes utilize fiber^[34], the complex, cooperative interactions between microbes are less understood. This study elucidated how konjac glucomannan (KGM) drives mutualistic interactions among gut microbes and the mechanisms through which these interactions alleviate UC.

Our *in vitro* experiments first established a clear mechanistic basis for this interaction. KGM is the substrate basis for driving microbiota interactions and their consequent beneficial effects. We identified *R. intestinalis* NSP017 as a superior KGM degrader compared to *B. xylanisolvens* NSP016, a finding consistent with its known ability to break down glucan-mannans^[35]. Genomic and transcriptomic analyses revealed the molecular basis for this capability: only *R. intestinalis* NSP017 significantly upregulated the GH26 family of β -mannanases, the key enzymes for hydrolyzing the KGM backbone^[36]. Conversely, *B. xylanisolvens* NSP016 showed limited capacity to degrade intact KGM on its own, though its upregulation of GH2 family enzymes supported this basal growth. The critical insight emerged in co-culture, where *R. intestinalis* NSP017 acted as a primary degrader, creating oligosaccharides that fueled a significant increase in *B. xylanisolvens* NSP016 abundance. This synergy was enabled by the GH130 family of β -1,4-mannooligosaccharide phosphorylases identified in *B. xylanisolvens* NSP016, which guaranteed its ability to utilize the specific breakdown products from *R. intestinalis* NSP017. This cross-feeding dynamic reveals a potential role for *Roseburia* as a keystone degrader, challenging the conventional view that *Bacteroides* are always the primary fiber-utilizers in such mutualistic relationships^[8].

To translate the *in vitro* interaction into a physiological context, we assessed its therapeutic efficacy in a DSS-induced colitis model. While konjac polysaccharides, *B. xylanisolvens*, and *R. intestinalis* have all been reported to alleviate colitis individually^[37-39], our study elucidates a more sophisticated mechanism. We found that *R. intestinalis* NSP017 treatment enriched *Bacteroides* population, providing compelling *in vivo* evidence for the cross-feeding mutualism identified in our experiments. Critically, this treatment also restored the gut microbiota's capacity to produce valeric acid, an effect that was significantly potentiated when co-administered with KGM. This suggests that *R. intestinalis* NSP017 exerts its benefits by acting as a microbial regulator, reshaping the community to reinstate a key metabolic function.

The convergence of our data identifies valeric acid as a key effector molecule linking our *in vitro* and *in vivo* observations, though the potential contribution of other metabolites or microbial community shifts cannot be excluded. First, our controlled *in vitro* system showed that co-culture of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 was a prerequisite for valeric acid production, which was absent in monocultures. Second, this cooperative requirement was confirmed in a more complex system using fecal microbiota from colitis mice, demonstrating that *R. intestinalis* NSP017 is the essential initiator for valeric acid synthesis from KGM. Third, this exclusive production pattern was recapitulated *in vivo*; valeric acid was only detected in the colons of mice treated with *R. intestinalis* NSP017, and its abundance was further enhanced by KGM. Although without co-supplementation of *B. xylanisolvens* NSP016, qPCR analysis showed that *R. intestinalis* NSP017

treatment alone simultaneously induced valeric acid production and significantly upregulated native *B. xylanisolvens*. These results provide solid *in vivo* evidence of mutualistic interaction, even within a complex gut microbial community. Finally, to validate the therapeutic function of this metabolite, we demonstrated that direct supplementation with sodium valerate was sufficient to protect the intestinal barrier and reduce inflammatory cytokines, corroborating previous findings^[40].

Despite these insights, our study has limitations. While the interactive effects of *B. xylanisolvens* NSP016 and *R. intestinalis* NSP017 were demonstrated, the specific molecular mechanisms governing their cross-feeding and substrate uptake have not been fully resolved and warrant further investigation. A recent study has shown that certain butyrate-producing *Lachnospiraceae* synthesize valerate via the reverse β -oxidation pathway, utilizing exogenous propionate as precursors^[41]. This provides a valuable reference for deciphering the valerate production mechanism in our system, where the specific enzymatic steps and metabolic division of labor between *R. intestinalis* NSP017 and *B. xylanisolvens* NSP016 remain to be elucidated. Furthermore, our investigation was limited to KGM; a comparative analysis of other dietary fibers is necessary to ascertain their potential to promote this mutualism. It is important to acknowledge that while our multi-layered evidence strongly implicates valeric acid as a key mediator of the observed therapeutic effects, the current study does not establish it as the exclusive effector molecule. The microbial interaction we characterized likely reshapes the broader metabolic landscape of the gut, and other short-chain fatty acids, branched-chain fatty acids, or yet-unidentified metabolites may act in concert with valeric acid to alleviate colitis. Most critically, significant research is needed to translate these preclinical findings into clinical applications, requiring rigorous validation in human studies to assess the safety and efficacy of this therapeutic strategy for IBD.

5. Conclusion

Our findings reveal a KGM-mediated mutualistic interaction where *R. intestinalis* NSP017 acts as a keystone degrader, promoting the proliferation of *B. xylanisolvens* NSP016. This partnership restores the gut community's ability to produce the key anti-inflammatory metabolite, valeric acid. This synergistic interaction represents a promising therapeutic strategy that shifts the focus from targeting single organisms to restoring beneficial microbial functions within the gut ecosystem.

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Data availability

The 16S rRNA gene sequencing data (PRJNA1404849; <http://www.ncbi.nlm.nih.gov/bioproject/1404849>) and the transcriptomic data (PRJNA1404884; <http://www.ncbi.nlm.nih.gov/bioproject/1404884>) that support the findings of this study have been deposited in the NCBI database. Details are provided within the manuscript.

Conflict of interest statement

The authors declared no competing financial interests.

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