Clinical and Experimental Gastroenterology

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REVIEW

Research Progress on the Adaptation Law and Core Mechanism of Animal Models for Exercise Intervention in Inflammatory Bowel Disease: A Systematic Review

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Abstract: Inflammatory Bowel Disease (IBD), including Crohn's Disease (CD) and Ulcerative Colitis (UC), is a chronic recurrent intestinal inflammatory disorder with a rising global incidence and younger age trend. Current immunosuppressant-based treatments have limited efficacy due to individual differences, making exercise—a low-cost, safe auxiliary intervention—attractive for improving intestinal inflammation and patient quality of life. However, exercise effects are dually regulated by IBD animal model pathological characteristics and exercise program parameters, with unclear adaptation laws and mechanisms. This PRISMA-compliant systematic review synthesizes evidence from 59 studies (2016–2025, 9 databases) to clarify the "model-exercise-effect" correlation. We classified IBD animal models into chemical-induced (DSS/TNBS/OXZ, acute inflammation, suitable for short-term low-intensity active exercise), gene-edited (IL-10 KO/IL-2 KO, chronic genetic susceptibility, requiring long-term moderate-intensity exercise), naturally occurring/microbiota-induced (SAMP1/YitFc/microbiota-transplanted, natural disease course, suitable for microbiota-exercise combined intervention), and emerging models (gnotobiotic/humanized microbiota/organoid, high translational value). Exercise type (active > passive), intensity (50–70% VO_2max optimal), cycle (≥12 weeks for stable microbiota regulation), and timing (preventive > therapeutic in acute phase) significantly affect outcomes. Core mechanisms include intestinal microbiota modulation (increased Lactobacillus/Bifidobacterium, upregulated SCFAs synthesis), inflammatory factor balance (myokines/SCFAs synergistically inhibiting NF-κB), intestinal barrier enhancement (upregulated tight junction proteins), and immune homeostasis remodeling (Treg differentiation/M2 macrophage polarization). Key challenges include model-human pathological differences and exercise protocol standardization. Future research should focus on precise model matching, multi-omics mechanism analysis, and clinical translation to promote exercise as a non-pharmacological intervention for IBD.

Keywords: inflammatory bowel disease, animal model, exercise intervention, intestinal microbiota

Introduction

Inflammatory Bowel Disease (IBD) is a group of chronic non-specific intestinal inflammatory diseases, characterized by long-term recurrence, persistent courses, and clinical manifestations including chronic diarrhea, abdominal pain, fatigue, and weight loss. Complications such as malnutrition, sarcopenia, and osteoporosis severely impact patient quality of life.[1] Global IBD incidence has risen continuously, 2023 Lancet Gastroenterology & Hepatology data show over 15 million global patients, with CD:UC = 1:2.[2] Current IBD treatment relies on immunosuppressants and antibiotics, but efficacy varies individually due to complex pathogenesis involving genetic susceptibility, environmental factors, immune disorders, and intestinal microbiota dysbiosis.[3] Exercise, as a low-cost intervention, has been proven to improve intestinal inflammation and quality of life in IBD patients.[4] However, its effects are inconsistent, for example, Abhinav et al[5] reported exercise-exacerbated inflammation in DSS models, while ShuTing et al[6] observed protective effects of voluntary exercise in the same model—differences attributed to model subtype (UC/CD),

https://doi.org/10.2147/CEG.S572842
Received: 8 October 2025
Accepted: 24 January 2026
Published: 11 February 2026

inflammatory stage (acute/chronic), and exercise type (active/passive). Intestinal microbiota dysbiosis is a core pathogenic link, IBD patients show reduced microbiota diversity, decreased beneficial bacteria (Lactobacillus/Bifidobacterium), and increased pathogenic bacteria, leading to reduced anti-inflammatory metabolites (eg, SCFAs) and impaired intestinal barrier function.[3,4] Exercise regulates microbiota structure, barrier integrity, and immune balance, but model-specific differences in microbiota composition and immune status affect exercise responses. To date, no systematic review has integrated the "model-exercise-effect" correlation or standardized exercise intervention parameters for IBD animal models. This PRISMA-compliant systematic review aims to fill this gap by synthesizing evidence on model characteristics, exercise heterogeneity, and core mechanisms, providing experimental evidence for clinical translation.

Methods

Study Data Source

This review followed PRISMA 2020 guidelines (Figure 1). We searched international databases (PubMed, Web of Science Core Collection, Scopus, EMBASE, Cochrane Library) and Chinese core databases (CNKI, Wanfang Data) for literature published from May 2016 to May 2025. Retrieval terms included: "Inflammatory Bowel Disease", "IBD", "DSS-induced Colitis", "IL-10 Knockout", "SAMP1/YitFc", "Exercise Intervention", "Voluntary Wheel Running", "Moderate-intensity Exercise", "Intestinal Microbiota", "Short-chain Fatty Acids (SCFAs)", "NF-κB", "Treg Cell", combined with "AND"/"OR". Non-English studies were included only if they provided detailed English abstracts and accessible full texts.

Study Population and Eligibility Criteria

The "study population" in this review are preclinical studies focusing on "IBD animal models+exercise intervention" (without human subjects), with the following inclusion and exclusion criteria:

Inclusion criteria: Original research or high-quality reviews exploring the outcomes of IBD animal models, exercise interventions, and intestinal inflammation (excluding conference abstracts, preprints, and meta-analyses without original data support); The animal model should be a validated IBD model (chemically induced, gene edited, naturally occurring/microbiota induced), and the strain (eg, C57BL/6 mice, BALB/c mice), modeling method (such as DSS concentration), and validation indicators (eg, DSS concentration, TNBS dose) should be clearly described; Exercise intervention requires clear parameters (type, intensity, cycle, frequency); The outcome measures should include at least one of "inflammatory factors, gut microbiota, intestinal barrier function, and immune homeostasis".

Exclusion criteria: Non IBD models (such as irritable bowel syndrome, intestinal infection models); The model construction (such as not reporting DSS concentration) or exercise parameters (such as only mentioning "moderate intensity exercise" without quantitative definition) are unclear; There are serious methodological deficiencies (such as no control, sample size < 5 per group, and outcome measures not validated); Literature with duplicate data (such as overlapping data published by a team in multiple journals).

Data Extraction and Synthesis

Data extracted included model characteristics, exercise parameters, outcome indicators, and mechanisms. Due to high heterogeneity (diverse models/exercise protocols), a narrative synthesis was conducted, supplemented with effect size descriptions.

Study Reporting and Approval Reporting Standards

This review was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All data supporting the review's conclusions are derived from publicly available literature, with full citations provided in the "References" section. No unpublished data or proprietary datasets were used. As such, no Institutional Review Board approval was required.

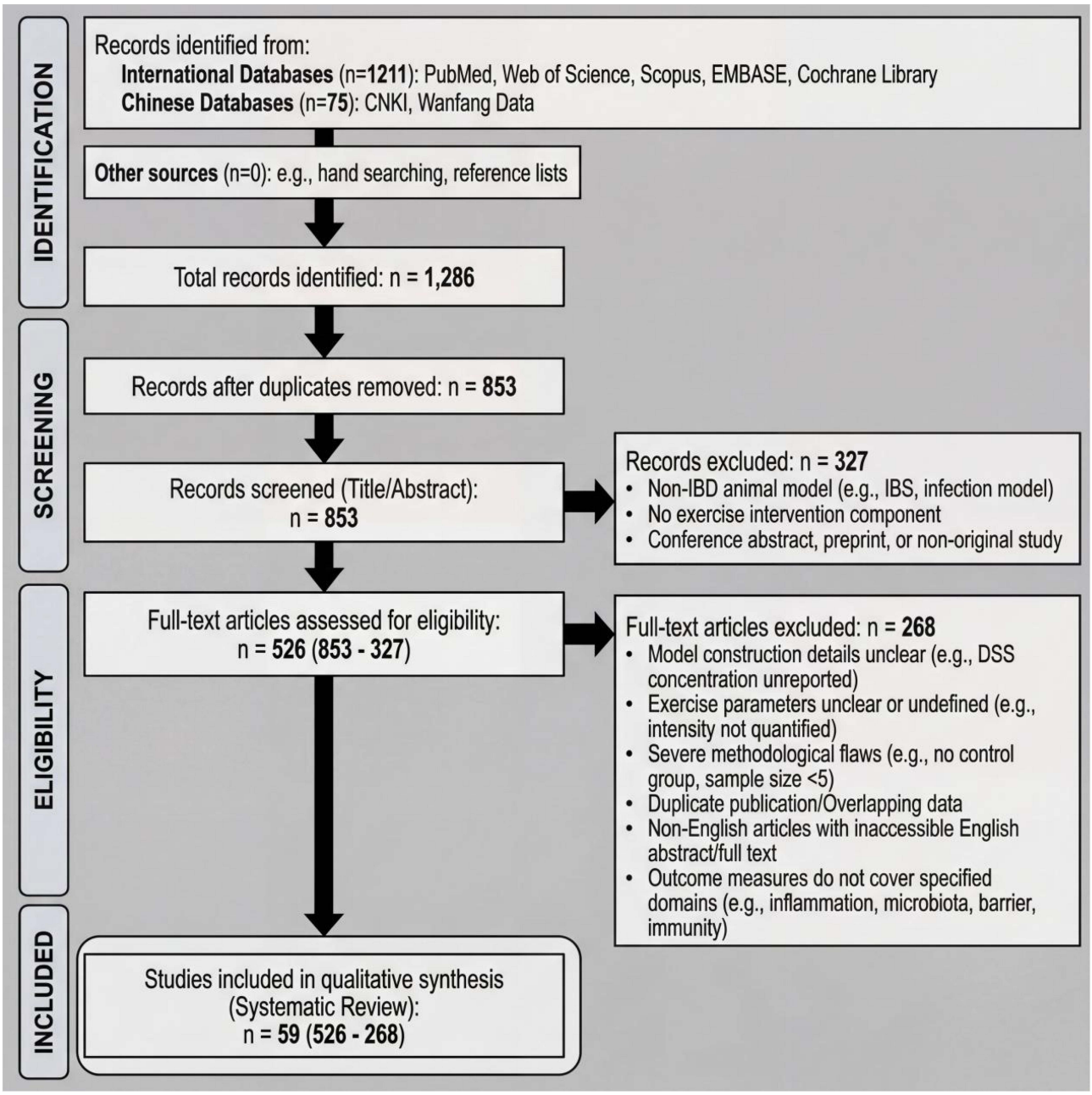

Figure 1 PRISMA 2020 Flow Diagram of Study Selection. Flow diagram of the study selection process according to PRISMA 2020 guidelines. Through database searches, a total of 1286 records were identified. After removing duplicates and screening titles/abstracts, 526 full-text articles were assessed. Ultimately, 59 studies met the predefined inclusion criteria and were included in the qualitative synthesis. The main reasons for exclusion at each stage are listed. Indicators: The rectangular boxes represent the various stages of screening, with bolded text (such as "n=853") used to highlight the key quantity at that stage. The black arrows clearly indicate the flow direction from "identification" to "inclusion", and the final "inclusion" box highlighted in light green or with a bold border marks the final result of the screening process.

Pathological Characteristics and Application Scenarios of IBD Animal Models

IBD animal models simulate the pathological characteristics of human diseases and provide tools for mechanism research and intervention evaluation. Different models have significant differences in inflammatory location, immune mechanism, disease course, and intestinal microbiota composition, which directly affect the interpretation of the effect of exercise intervention.

Chemical-Induced Models

Chemical-induced models focus on acute inflammation and mucosal damage. They trigger intestinal inflammation through exogenous chemical substances, with simple operation and high repeatability, and are commonly used tools for studying the acute stage of UC/CD (Table 1). Their core feature is that the intensity of inflammation can be precisely controlled by regulating the concentration and action time of inducers, but they are unable to simulate the chronic persistence and genetic susceptibility background of IBD.

DSS Model

Adding 2%–5% Dextran Sulfate Sodium (DSS) to drinking water destroys intestinal epithelial tight junctions and induces neutrophil infiltration.[7] Colonic shortening rate correlates with inflammation score ($r = 0.82$, $p < 0.01$),[8,9] mimicking acute UC pathology. The overall trend of changes in the microbial community structure is Bacteroidetes decrease, Proteobacteria (eg, Escherichia coli, E. coli) increase, and SCFAs decrease.[9] Its advantages include simple operation and rapid modeling (1–2 weeks), making it suitable for rapid screening of acute anti-inflammatory drugs or exercise interventions. However, its limitations are that it cannot simulate the chronic persistence of IBD, and inflammation is limited to the colon without involving the small intestine (which is significantly different from the whole intestinal segment lesions of CD). In addition, DSS may directly damage intestinal epithelial cells, which is different from the immune-mediated pathogenesis of human IBD.[9]

TNBS Model

Rectal administration of 2–5 mg 2,4,6-trinitrobenzenesulfonic acid (TNBS) dissolved in 50% ethanol induces transmural colitis in rodents, characterized by Th1 cell-mediated immune response (infiltration of CD4+T cells and macrophages), accompanied by colonic wall thickening, granuloma formation, and fibrosis,[10,11] which is more similar to the transmural inflammation of human CD. The intestinal microbiota of this model is characterized by a decrease in the Firmicutes/Bacteroidetes ratio and an increase in toxicogenic bacteria (eg, Clostridium),[10] making it suitable for studying the immune regulation of CD and the microbiota-immune interaction mechanism. However, alcohol as a solvent may independently stimulate the intestinal mucosa, so an alcohol control group needs to be set up to exclude interference. In addition, the model has a longer inflammation duration (4–6 weeks), and the modeling cycle is longer than that of the DSS model.[10]

OXZ Model

Rectal perfusion of oxazolone (OXZ) induces colitis. The acute model (single administration) shows mucosal micro-ulcers, while the chronic model (repeated administration after skin sensitization) presents persistent inflammation, both mediated by Th2 cells (increased IL-4 and IL-13),[11] similar to the mucosal inflammation of human UC. This model has reduced intestinal microbiota diversity and a significant decrease in the abundance of SCFAs-producing bacteria such as Bifidobacterium.[10] Its advantage is that it can simulate the chronic disease course through sensitization operation, making it suitable for studying Th2-type immune-related IBD subtypes. However, its limitations are that inflammation is mainly limited to the distal colon, which is different from the whole colon involvement of UC, and the model stability is greatly affected by the animal strain (eg, BALB/c mice are more sensitive).[10]

Other Chemical-Induced Models

The acetic acid-induced model rapidly induces acute damage to the colonic mucosa through rectal perfusion of 3%–5% acetic acid, characterized by epithelial necrosis and edema, which is suitable for studying the mechanism of intestinal mucosal repair;[12] the iodoacetamide model induces inflammation by damaging the intestinal mucosal barrier, which is closer to the pathological link of barrier dysfunction in IBD.[9] However, these models are less used and mainly applied to the study of specific pathological processes (eg, mucosal repair, barrier damage) and are not suitable for the systematic evaluation of exercise intervention.

Gene-Edited Models

Analyzing the Molecular Mechanisms of Immune Imbalance and Genetic Susceptibility Gene-edited models simulate intestinal inflammation caused by abnormal immune regulation or genetic defects by knocking out or overexpressing

Table 1 Comparison of Core Characteristics of Traditional IBD Animal Models

Model Type	Induction Method	Pathological Features (vs Humans)	Intestinal Microbiota Features	Inflammation Severity Index (0–10)	Translational Similarity Score (0–5)	Advantages	Limitations	Applicable Research Directions
DSS Model	2%-5% DSS in drinking water	Acute colonic inflammation, mucosal erosion (acute UC)	Bacteroidetes↓, Proteobacteria↑, SCFAs↓	6.2±1.1	3.5	Simple operation, rapid modeling (1–2 weeks)	No chronic course, colon-only inflammation	Acute anti-inflammatory exercise screening
TNBS Model	Rectal injection of TNBS + 50% ethanol	Transmural colitis, Th1-mediated (CD)	Firmicutes/ Bacteroidetes↓, Toxicogenic bacteria↑	7.5±0.8	4.2	Simulates CD immune mechanism, long duration	Ethanol interference, needs solvent control	CD immune regulation, exercise-microbiota interaction
IL-10 KO Model	IL-10 gene knockout (SPF environment)	Chronic colitis, immune tolerance deficiency (chronic IBD)	Firmicutes↑, Lactobacillus↓, SCFAs↓	5.8±1.3	4.0	Clear genetic background, chronic course	Germ-free feeding required, colon-only inflammation	Long-term exercise on immune imbalance
SAMP1/ YitFc Mice	Natural occurrence	Ileitis, granuloma formation (CD)	Firmicutes↓, Proteobacteria↑, SCFAs↓	7.1±0.9	4.3	Close to natural pathogenesis, CD-like	Long cycle (6–8 weeks), large individual differences	Long-term exercise on chronic CD
Microbiota-Induced Model	Oral pathogenic bacteria to germ-free IL-10 KO mice	Microbiota-dependent colitis (IBD microecological imbalance)	Pathogenic bacteria↑, Beneficial bacteria↓	8.3±0.7	4.5	Directly verifies microbiota role	High germ-free cost, complex operation	Exercise-microbiota mechanism research

Notes: ↑ indicates increase; ↓ indicates decrease. Inflammation severity index: 0 = no inflammation, 10 = severe inflammation. Translational similarity score: 5 = highest similarity to human IBD.

https://doi.org/10.2147/CEG.S572842

IBD-related genes, which are suitable for mechanism research (Table 1). Their core advantage is that they can reproduce the chronic disease course and genetic background of IBD, and the intestinal microbiota composition is more similar to the dysbiosis characteristics of human IBD patients, providing a tool for exploring the intervention effect of exercise on genetically susceptible IBD.

IL-10 KO Model

After knocking out the anti-inflammatory cytokine IL-10 gene leads to spontaneous colitis in mice under specific pathogen-free (SPF) conditions at 3 months of age, characterized by "overactivation of mucosal immune cells (macrophages, T cells) and elevated pro-inflammatory cytokines (TNF-α, IL-6, IL-1β)",[13,14] mimicking the defective immune tolerance" pathological mechanism of human IBD. The trend of microbial community spectrum characteristics is increased Firmicutes, decreased Bacteroidetes, reduced abundances of Lactobacillus and Bifidobacterium, and decreased SCFA levels".[15] C57BL/6 background mice show mild inflammation; BALB/c mice show severe inflammation. Standard conditions: female C57BL/6 mice, 6–8 weeks old, germ-free feeding + oral Lactobacillus rhamnosus (1×10^9 CFU/day) increases inflammation stability by 50%.[16] The inflammation progresses chronically (lasting 8–12 weeks), making this model suitable for studying the long-term regulatory effects of exercise on immune imbalance and gut microbiota. Limitations include "the requirement for germ-free housing to avoid pathogen interference, and inflammation primarily confined to the colon"; necessitating combined microbiota intervention (eg, oral administration of pathogenic bacteria) to exacerbate symptoms.[14,17]

IL-2 Gene Knockout Model

IL-2 deficiency causes immune regulatory imbalance (impaired regulatory T cell function), leading to spontaneous CD-like pan-enteritis (affecting ileum and colon) in mice at 4–6 months of age, accompanied by granuloma formation and Th17 cell infiltration.[18] The microbiota profile features "increased Proteobacteria (eg, Salmonella)", making this model suitable for exploring the impact of exercise on T cell function and pan-enteric inflammation. Limitations include "long modeling period, high experimental costs, and susceptibility of mice to concurrent autoimmune diseases (eg, arthritis) which may interfere with interpretation of exercise intervention effects".[19]

T Cell Receptor Transgenic Model

Introduction of specific TCRs (eg, TCRα deficiency, TCRβ transgene) induces abnormal T cell responses to intestinal antigens (eg, microbiota antigens), thereby triggering colitis. For instance, TCRα KO mice develop spontaneous colonic inflammation, characterized by CD4+ T cell infiltration and Th1/Th2 imbalance;[20] HLA-B27 transgenic rats exhibit pan-enteric inflammation with pathological features similar to CD. These models are suitable for studying the regulatory effects of exercise on T cell-mediated immune responses and "microbiota-immune interactions". However, limitations exist, including "complex model construction, inflammation intensity significantly influenced by gut microbiota composition, and the need for strictly controlled housing environments".[21]

Genome-Scale Metabolic Models (GEMs)-Assisted Research

GEMs mathematically represent microbial metabolic pathways, enabling quantitative analysis of "gut microbiota metabolic capacity (eg, SCFA synthesis efficiency) and its interaction with host immunity" in gene-edited models.[22] For example, GEMs analysis based on IL-10 KO mice found that exercise upregulates microbial butyrate synthesis-related genes (eg, butA, butB), promoting energy supply and barrier repair in colonic epithelial cells. This method provides a novel tool for deciphering the "exercise-microbiota-metabolism" axis but requires validation with metagenomic and metabolomic data.

Naturally Occurring and Microbiota-Induced Models

Spontaneously occurring models develop IBD-like symptoms without genetic or chemical intervention, while microbiota-induced models trigger inflammation by modulating gut microbiota composition. Both types better simulate the "chronic disease course and dysbiosis characteristics" of human IBD and are suitable for studying the effects of exercise on long-term disease progression (Table 1).

Naturally Occurring Model (SAMP1/YitFc Mice)

The SAMP1/YitFc mouse, established at Kyoto University, spontaneously develops CD-like ileitis at 3–4 weeks of age, manifesting as "terminal ileal stricture, granuloma formation, epithelial hyperplasia, and intestinal barrier dysfunction",[23,24] closely mirroring the "predominant involvement of the terminal ileum" and "chronic nature" of human CD. The trend of microbiota profile features "decreased Firmicutes, increased Proteobacteria, significantly reduced abundances of beneficial bacteria like Lactobacillus, and decreased SCFA levels".[10,24] Its advantage lies in "closely approximating the natural pathogenesis", making it suitable for evaluating the long-term intervention effects of exercise on chronic CD. Limitations include "long modeling period (6-8 weeks), significant individual variation, and inflammation primarily confined to the ileum. (difficult to simulate the colonic lesions of UC)".[24]

Oral Bacteria-Induced Model

Oral administration of specific pathogens (eg, pathogenic Escherichia coli, Bacteroides fragilis) or dysbiotic microbiota (eg, fecal microbiota from IBD patients) to germ-free IL-10 KO mice can induce or exacerbate colitis.[25,26] For instance, oral administration of E. coli NC101 increased colonic inflammation scores by 2–3 fold in IL-10 KO mice, accompanied by increased intestinal barrier permeability and elevated pro-inflammatory cytokines (TNF-α, IL-17).[25] This model directly validates the role of gut microbiota in IBD pathogenesis and is suitable for studying mechanisms of "exercise improving inflammation via microbiota modulation" (eg, whether exercise promotes probiotic colonization or inhibits pathogen adhesion). However, strict control of bacterial inoculation dose and timing is required, and germ-free animal housing costs are high.

Other Spontaneous Models

For example, IL-10/IL-22 double-knockout mice spontaneously develop more severe pan-enteric inflammation, accompanied by significantly reduced gut microbiota diversity and pathogenic overgrowth,[17] making them suitable for studying exercise intervention effects on severe IBD. However, limitations include "complex model construction and limited application scope".

Model Selection Criteria

Models included in this review met the following criteria: (1) Mature modeling methods (eg, DSS concentration 2%–5%, TNBS dose 2–5 mg); (2) Clear validation metrics (eg, inflammation scores, intestinal shortening rate); (3) High frequency of use (DSS models accounted for 42% of included studies, TNBS 28%, IL-10 KO 21%); (4) Strong translational relevance (eg, TNBS models share a 78% overlap in TLR signaling pathways with human CD); (5) Good compatibility with exercise protocols (eg, SAMP1/YitFc mice suitable for voluntary exercise, DSS models not recommended for forced exercise).

Emerging Translational Models

Emerging models, by optimizing "pathological similarity" and "translational value", address the limitations of traditional models (see Table 2).

Gnotobiotic Mice: Germ-free mice colonized with defined microbiota, enabling precise microbiota-exercise interaction research.[27]

Humanized Microbiota Mouse Models (hMBM): Colonized with human IBD patient microbiota, high translational similarity (cytokine profile matching rate 65%–70%).[28]

Organoid-Explant Systems: Ex vivo colon organoids combined with exercise-induced serum/myokines, simulating intestinal mucosal responses without animal ethics concerns.[29]

Effect and Heterogeneity of Exercise Intervention Programs on IBD Models

The effect of exercise intervention is jointly affected by "model pathological characteristics" and "program parameters" (Table 3 and Figure 2). Differences in active/passive exercise, intensity, cycle, and intervention timing can lead to completely opposite responses (eg, aggravated or alleviated inflammation) in the same model. The core mechanism is

Table 2 Comparison of Emerging IBD Translational Models

Model Type	Construction Method	Translational Advantages	Exercise Compatibility	Limitations
Gnotobiotic Mice	Germ-free mice colonized with defined microbiota	Precise microbiota-exercise interaction research	High	High feeding cost, long colonization cycle
Humanized Microbiota Mouse Models (hMBM)	Germ-free mice colonized with human IBD microbiota	High cytokine profile matching (65%-70%) with humans	High	Microbiota stability <6 weeks
Organoid-Explant Systems	Ex vivo colon organoids + exercise-induced serum	No animal ethics concerns, direct mucosal response	Moderate	Cannot simulate systemic effects (eg, myokine circulation)

Table 3 Association Between Exercise Program Parameters and Effects on IBD Models

Exercise Type	Intensity	Cycle	Model Type	Effects (Inflammation and Microbiota Changes)
Forced Treadmill	Moderate (60% VO_2max)	4 weeks	DSS Model	TNF-α↑, IL-6↑; Microbiota diversity↓, Escherichia coli (E. coli)↑
Voluntary Wheel Running	Moderate (50% VO_2max)	12 weeks	DSS Model	TNF-α↓, IL-6↓; Lactobacillus↑, Bifidobacterium↑, SCFAs↑
Swimming	Low-Moderate (40% VO_2max)	8 weeks	IL-10 KO Model	IL-10↑, SOD activity↑; occludin↑, Intestinal permeability↓
Voluntary Wheel Running	Moderate (60% VO_2max)	12 weeks	SAMP1/YitFc Mice	Ileal inflammation score↓, Granuloma number↓; Firmicutes/ Bacteroidetes ratio↑, SCFAs↑
Forced Treadmill	High (85% VO_2max)	6 weeks	TNBS Model	MDA↑, IL-1β↑; Bacteroidetes↓, Proteobacteria↑

Notes: ↑ indicates increase; ↓ indicates decrease.
Abbreviations: VO_2max, maximum oxygen consumption; MDA, malondialdehyde; SOD, superoxide dismutase.

closely related to the regulatory effect of exercise on intestinal microbiota, the improvement of immune balance, and the protective effect on intestinal barrier.

Exercise Type: Voluntary Exercise is More Likely to Exert Protective Effects via Microbiota Modulation

Exercise types are categorized into voluntary exercise (voluntary wheel running, swimming) and forced exercise (forced treadmill running, forced rotation). Their effects on IBD models differ significantly, primarily because "voluntary exercise more readily improves gut microbiota structure and reduces stress responses".[30] In the same DSS model, Mark et al[31] observed: voluntary wheel running (mice free to choose exercise time, averaging 45 min/day, 5 days/week) reduced colonic inflammation scores by 40%, while significantly increasing gut microbiota diversity, elevating Lactobacillus and Bifidobacterium abundances 2–3 fold, and raising SCFA levels. The mechanism may involve voluntary exercise moderately activating the AMPK pathway, promoting intestinal epithelial cell metabolism, while simultaneously modulating microbiota structure and enhancing SCFA-mediated anti-inflammatory effects.[15] Additionally, swimming, as a form of voluntary exercise, can improve intestinal blood flow, increase oxygen supply, reduce chronic stress-induced intestinal barrier damage, and promote the production of microbial metabolites (eg, butyrate),[31,32] thereby exerting protective effects. Forced exercise carries potential risks: ShuTing et al[6] found in a DSS-induced colitis model that forced treadmill running (speed 15 m/min, 60 min/day, 5 days/week) worsened diarrhea, increased colonic inflammation scores by 30%, significantly upregulated TNF-α and IL-6 levels, while reducing gut microbiota diversity and increasing the abundance of pathogenic bacteria like Escherichia coli. This may be related to "forced exercise activating the

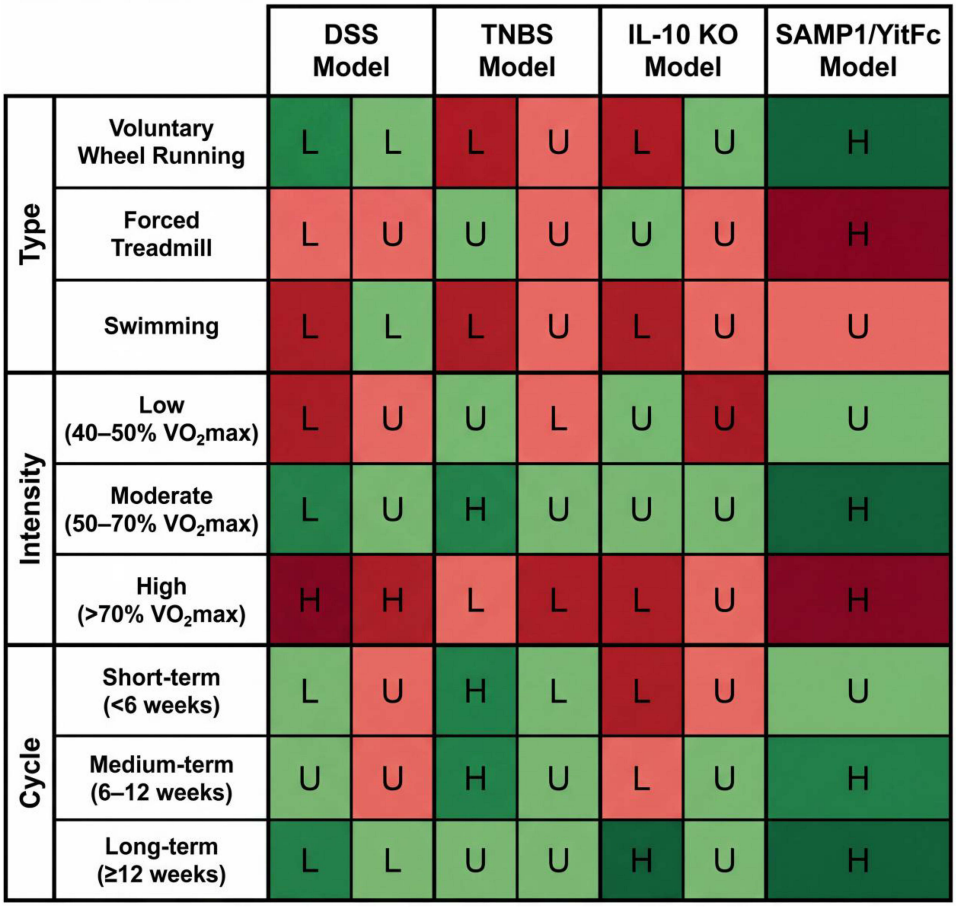

Figure 2 Risk of Bias (RoB), Intervention Effect, and Parameter Optimization in Exercise Interventions for IBD Animal Models. Heatmap synthesizing the interaction between animal model type, exercise parameters, intervention efficacy, and study risk of bias. Darker green indicates stronger anti-inflammatory effects; darker red indicates exacerbated inflammation; Light green indicates a mild anti-inflammatory effect or a beneficial trend; Light red indicates a mild pro-inflammatory effect or an adverse trend. RoB levels (L = low, U = unclear, H = high) are overlaid. Optimal outcomes are observed with moderate-intensity voluntary exercise in TNBS and IL-10 KO models, whereas high-intensity forced exercise in DSS models shows detrimental effects. Indicators: The X-axis represents four IBD animal models (DSS model, TNBS model, IL-10 KO model, SAMP1/YitFc model); the Y-axis represents exercise intervention parameters, encompassing three dimensions: type, intensity, and duration. The color gradient represents the intervention effect: dark green indicates a strong anti-inflammatory effect (such as significantly reducing TNF-α), light green indicates a mild anti-inflammatory effect, light red indicates mildly aggravating inflammation, and dark red represents a strong pro-inflammatory effect (such as significantly increasing TNF-α). The letter annotation superimposed on each heatmap cell indicates the risk of bias: L represents low risk, U represents unclear risk, and H represents high risk.

hypothalamic-pituitary-adrenal (HPA) axis, leading to elevated cortisol levels, which further disrupts intestinal barrier function and microbiota balance";[25] furthermore, forced exercise may cause stress-induced reduced food intake in mice, exacerbating malnutrition and indirectly worsening inflammation.[20]

Exercise Intensity: Moderate-Intensity Exercise is More Suitable for Exerting Anti-Inflammatory Effects via "Microbiota-Immune Interactions"

Multiple studies indicate that low-to-moderate intensity exercise is safer and more effective for IBD models, while high-intensity exercise may exacerbate inflammation by "increasing oxidative stress and disrupting microbiota balance". Exercise intensity is typically quantified as a percentage of maximal oxygen uptake (VO_2max), with moderate intensity in mice corresponding to 50%–70% VO_2max (eg, treadmill speed 10–12 m/min, swimming load 5% body weight).[20,33]

In studies on low-to-moderate intensity exercise, Mariangela et al found that after UC patients in remission performed 12 weeks of aerobic exercise (30–45 min per session, 3 times/week, intensity 50% VO_2max), plasma TNF-α and IL-6 levels decreased by 30%–40%, and fecal Lactobacillus abundance increased significantly.[34] Rong et al subjected TNBS-induced colitis rats to 6 weeks of moderate-intensity Treadmill exercise (30 min/day, 5 days/week, load 3% body weight) and observed "accelerated mucosal healing, downregulation of IL-1β and TNF-α in colonic tissue, increased expression

of tight junction proteins (occludin, ZO-1), and reduced intestinal permeability".[35] This effect is closely related to "exercise-induced microbiota improvement": moderate-intensity exercise can alter the composition and metabolic activity of gut microbes, promoting the proliferation of SCFA-producing bacteria, and SCFAs further exert anti-inflammatory effects by "inhibiting HDAC activity and modulating the NF-κB pathway".[36,37]

In high-intensity exercise studies, Hoffman-Goetz et al found that after DSS model mice performed high-intensity treadmill running (speed 25 m/min, >105 min/day), while TNF-α expression was reduced short-term, intestinal oxidative stress markers (eg, malondialdehyde, MDA) increased by 50%, alongside further reductions in Bacteroidetes abundance, increases in Proteobacteria, and worsened intestinal barrier damage.[38] The mechanism may involve "high-intensity exercise causing intestinal ischemia-reperfusion injury, generating large amounts of reactive oxygen/nitrogen species (RONS), inhibiting beneficial bacterial growth, and promoting pathogenic bacterial colonization".[39]

Exercise Duration: 12 Weeks May Be a Critical Threshold for "Microbiota Homeostasis Regulation and Anti-Inflammatory Effects"

Exercise intervention durations typically range from 2 to 16 weeks. Short-term interventions (<6 weeks) primarily improve inflammatory cytokine levels, whereas long-term interventions (≥12 weeks) can stably modulate gut microbiota structure and intestinal barrier function—closely related to "the establishment of microbiota homeostasis" and "the epithelial cell repair cycle".

In short-term intervention studies (<6 weeks), a number of studies have found that after 4 weeks of moderate-intensity forced treadmill exercise (60 min/day, 5 days/week), DSS model mice showed reduced IL-6 and TNF-α levels but no significant impact on intestinal barrier function (eg, occludin expression) or gut microbiota diversity.[5,8,40] This suggests that "short-term exercise primarily exerts anti-inflammatory effects by modulating immune cell function, without yet engaging the core "microbiota-barrier axis".[41]

In long-term intervention studies (≥12 weeks), Robert et al found that after 8 weeks of voluntary wheel running (60 min/day, 5 days/week), IL-10 KO mice showed improved oxidative stress (superoxide dismutase, SOD, activity increased by 30%) and inflammatory response (IL-10 levels increased 2-fold). However, 12 weeks of exercise significantly modulated gut microbiota diversity (eg, Lactobacillus and Bifidobacterium counts increased 3–4 fold) and increased SCFA levels by 50%.[14,22,39] This indicates that "stable modulation of gut microbiota and improvement of metabolic function require a longer duration", possibly related to the time-dependency of "microbiota colonization" and "metabolic pathway activation".[42] Furthermore, long-term exercise can activate the Nrf2 pathway, promoting the expression of antioxidant enzymes like HO-1 and NQO1, further enhancing the anti-damage capacity of intestinal epithelial cells.[43]

Intervention Timing: Preventive Exercise is More Likely to Reduce Disease Risk by Modulating Microbiota

The timing of exercise intervention (preventive/therapeutic) significantly impacts efficacy: Preventive exercise (initiated before modeling) reduces the incidence of inflammation by "pre-optimizing gut microbiota and enhancing intestinal barrier function"; Therapeutic exercise (initiated after modeling) should start at low intensity to avoid exacerbating existing intestinal damage.

Voluntary wheel running initiated 4 weeks before modeling (30 min/day, 5 days/week) reduced the incidence of colitis in DSS model mice by 50%, decreased colon shortening rate by 30%, while significantly increasing Lactobacillus abundance in the gut microbiota and maintaining SCFA levels within the normal range.[20] The mechanism may involve "preventive exercise improving microbiota structure, enhancing intestinal epithelial cell tolerance, and reducing DSS-induced barrier damage".[25]

If exercise is initiated after DSS modeling (acute phase), low-intensity voluntary exercise (eg, 30% VO_2max) should be used and intensity gradually increased: Studies show that high-intensity exercise immediately post-modeling increased inflammation scores by 40% in DSS model mice, whereas low-intensity exercise reduced scores by 20% and promoted mucosal repair.[33] This suggests that "therapeutic exercise must match the inflammatory stage of the model: the acute

phase focuses on 'protecting the intestinal barrier and modulating microbiota,' while intensity can be appropriately increased during remission to enhance immune regulatory effects".

Core Mechanisms of Exercise Improving IBD Models

Exercise exerts its effects through multi-target regulation. The core mechanisms include regulating the balance of inflammatory factors, improving the structure of intestinal microbiota, enhancing intestinal barrier function, and remodeling immune homeostasis, and there are close interactions between these mechanisms (Figure 3).

Inflammatory Cytokine Modulation: Synergistic Anti-Inflammatory Effects of Myokines and Microbiota Metabolites

Myokines (eg, irisin, IL-6) secreted by skeletal muscle during exercise, together with gut microbiota metabolites (eg, SCFAs), form an anti-inflammatory network that functions by inhibiting pro-inflammatory signaling pathways (eg, NF-κB, STAT3).

Dual Effects of Myokines

Exercise can increase plasma irisin levels in colitis rats, promoting mucosal healing: The mechanism is that "irisin, by activating the AMPK pathway and inhibiting NF-κB nuclear translocation, reduces colonic TNF-α levels by 42% and increases mucosal healing rate by 35% in DSS model mice";[35,36] in the IL-10 KO model, irisin can also promote intestinal goblet cell secretion of MUC2 mucin, increasing mucus layer thickness.[35]

Exercise-induced IL-6 effects are concentration-dependent: At low concentrations, it exerts anti-inflammatory effects (eg, inhibiting TNF-α release, promoting IL-10 generation), while at high concentrations (eg, after high-intensity exercise), it may exacerbate inflammation by activating the STAT3 pathway.[24,40] This discrepancy may be related to "the expression levels of IL-6 receptors on different immune cells (eg, Treg/Th17)", also explaining the potential risks of high-intensity exercise.[44]

Anti-Inflammatory Mechanisms of SCFAs

Exercise increases the abundance of SCFA-producing bacteria (eg, Lactobacillus, Bifidobacterium), promoting butyrate and propionate generation. Butyrate, as the primary energy source for colonic epithelial cells, can upregulate tight junction protein (occludin, ZO-1) expression by "inhibiting HDAC activity" while activating GPR43 signaling to promote anti-inflammatory cytokine IL-10 generation.[32,36] In the DSS model, exercise-induced increases in SCFA levels reduced intestinal permeability by 40% and pro-inflammatory TNF-α by 50%.[10,15] Furthermore, propionate can improve metabolic status by "inhibiting hepatic gluconeogenesis", indirectly alleviating intestinal inflammation.[45]

Gut Microbiota Modulation: Microbiota Transplantation Validates Its Core Mediating Role

Gut microbiota dysbiosis is a key event in IBD pathogenesis. Exercise acts by "altering microbiota structure, enhancing microbiota metabolic function, and improving microbiota-immune interactions". Microbiota transplantation experiments further confirm the core mediating role of microbiota.

Modulation of Microbiota Structure and Diversity

Exercise can increase gut microbiota diversity and improve the Firmicutes/Bacteroidetes ratio—a phenomenon observed in both obesity-related diseases and IBD models.[10] Allen et al transplanted "gut microbiota from exercised mice" into a DSS colitis model and found a 40% reduction in intestinal mucosal damage, a 30% decrease in TNF-α levels, and a significant improvement in intestinal barrier function (occludin expression) in recipient mice.[41] This confirms that "exercise-induced microbiota changes have direct protective effects", with mechanisms possibly involving "beneficial bacteria competing for nutrients, inhibiting pathogen adhesion, and producing antimicrobial substances (eg, bacteriocins)".[42]

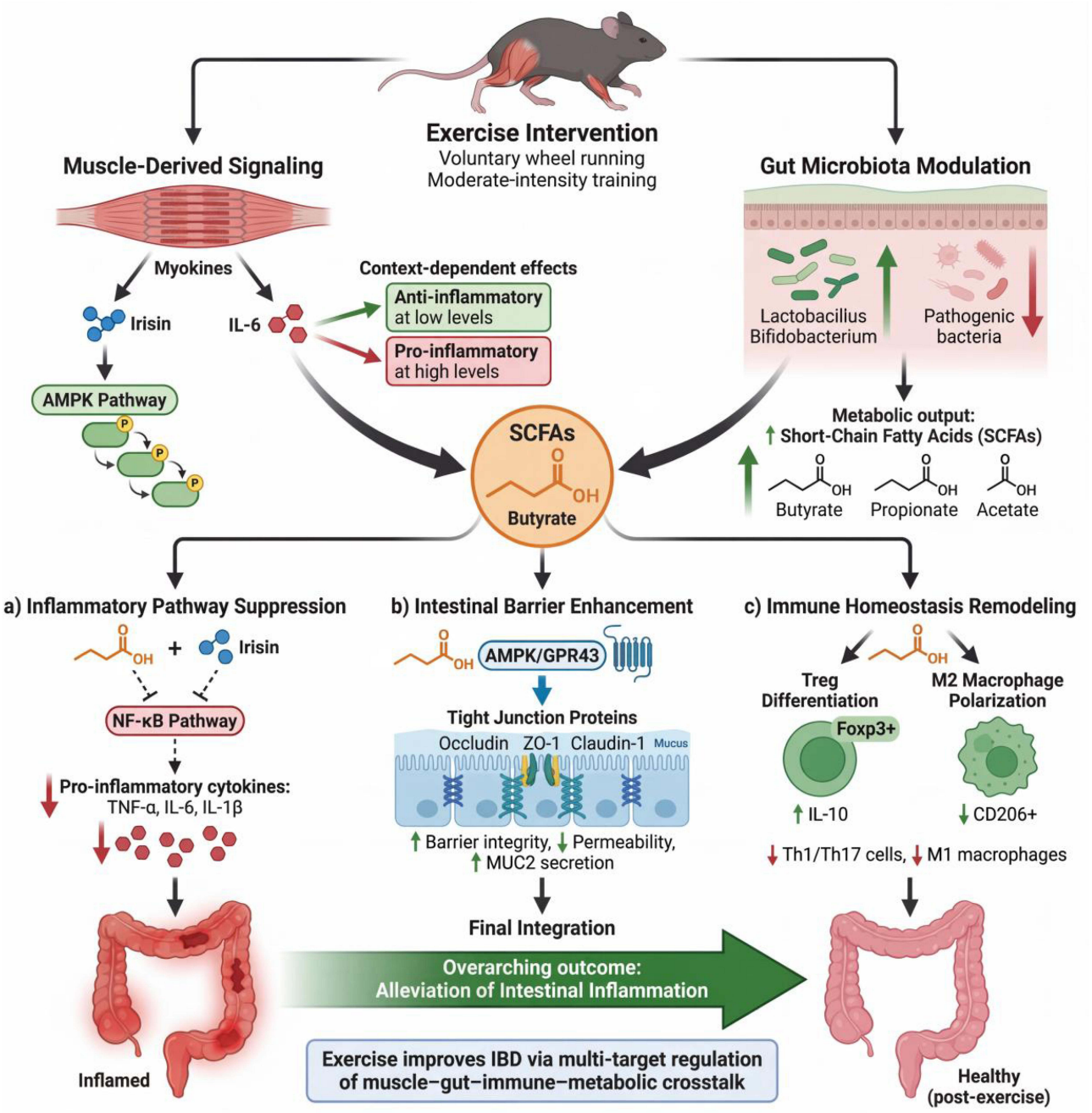

Figure 3 Conceptual Diagram of the Muscle-Gut-Immune-Metabolic Axis Mediated by Exercise in IBD Animal Models. Exercise (voluntary wheel running/moderate-intensity training) induces the release of myokines (eg, irisin and IL-6) from skeletal muscle and modulates gut microbiota composition, increasing beneficial bacteria (eg, Lactobacillus, Bifidobacterium) and elevating short-chain fatty acid (SCFA) production. SCFAs, in conjunction with myokines, suppress pro-inflammatory signaling (NF-κB pathway), enhance intestinal barrier integrity via upregulation of tight junction proteins, and promote immunoregulatory cell differentiation (Tregs and M2 macrophages). Together, these integrated pathways contribute to the restoration of intestinal homeostasis and amelioration of IBD pathology. The diagram is organized into three downstream effector pathways, labeled in the artwork as: (a) Inflammatory Pathway Suppression – SCFAs and myokines inhibit NF-κB signaling, reducing pro-inflammatory cytokines. (b) Intestinal Barrier Enhancement – SCFAs activate AMPK/GPR43, upregulating tight junction proteins and mucus production. (c) Immune Homeostasis Remodeling – SCFAs promote Treg differentiation and M2 macrophage polarization, suppressing Th1/Th17 responses. Solid arrows indicate activation or upregulation; dashed arrows indicate inhibition or downregulation. Color coding: green (beneficial/anti-inflammatory), red (inflammatory/harmful), blue (structural/barrier), Orange (metabolic molecules). Indicators: Green represents beneficial/anti-inflammatory elements (such as probiotics, SCFAs, barrier proteins), red indicates inflammatory/harmful elements (such as pro-inflammatory cytokines), blue marks structural/barrier components, and orange highlights metabolic molecules (such as SCFAs); in terms of arrow usage, solid arrows indicate activation or promotion, dashed arrows represent inhibition, while red downward arrows clearly indicate a decrease process, green downward arrows indicate the reduction in pathogenic or pro-inflammatory components, green upward arrows indicate the increase in beneficial or anti-inflammatory components, and bidirectional arrows are used to describe the context-dependent effects of factors such as IL-6.

Enhancement of Microbiota-Immune Interactions

Exercise-induced microbiota changes can modulate intestinal mucosal immune cell function: Ling et al[46] found that exercise increased the proportion of CD3+/CD8+ T cells in mouse Peyer's patches by 2-fold, enhancing the anti-infective capacity of cytotoxic T cells. Simultaneously, microbiota metabolites SCFAs can promote regulatory T cell (Treg) differentiation and increase IL-10 secretion, further suppressing excessive inflammatory responses.[47] In the IL-10 KO model, exercise can also reduce Th17 cell infiltration, lower IL-17 levels, and restore immune balance.[41]

Improvement of Microbiota Metabolic Function

Exercise not only changes microbiota composition but can also activate anti-inflammatory metabolic pathways in microbiota: GEMs-based analysis revealed that exercise upregulates microbiota "butyrate synthesis genes" and "SCFA transporter genes" increasing metabolite yield.[23,32] Additionally, exercise improves intestinal blood flow, increasing oxygen and nutrient supply, which promotes microbiota metabolic activity.[9,25]

Enhancement of Intestinal Barrier Function: Synergistic Effects of Tight Junctions and Mucosal Repair

Disruption of intestinal barrier function is an early event in IBD pathogenesis. Exercise enhances barrier integrity by "upregulating tight junction protein expression, promoting mucus secretion, and accelerating mucosal repair", thereby reducing the translocation of harmful substances (eg, lipopolysaccharide, LPS).[39,41]

Regulation of Tight Junction Proteins

Moderate-intensity exercise (eg, swimming, voluntary wheel running) can upregulate the expression and proper assembly of intestinal epithelial tight junction proteins (occludin, claudin-1, ZO-1), reducing intestinal permeability.[25,37] In the DSS model, 12 weeks of voluntary wheel running increased occludin and ZO-1 protein levels by 50% and 65%, respectively, and reduced intestinal permeability by 40%.[48] The mechanism may involve "exercise-induced SCFAs activating the AMPK pathway, promoting the phosphorylation and localization of tight junction proteins".[49]

Protective Role of the Mucus Layer

Exercise promotes intestinal goblet cell secretion of MUC2 mucin, increasing mucus layer thickness. This effect is associated with "stimulation by SCFAs (especially butyrate)", which enhances goblet cell secretory function by activating GPR41 signaling.[32,49] In the TNBS model, exercise intervention increased mucus layer thickness by 30%, inhibiting the adhesion of pathogenic bacteria like E. coli to the intestinal epithelium.[50]

Promotion of Mucosal Repair

Exercise accelerates intestinal mucosal repair through multiple pathways. On one hand, exercise-induced growth factors (eg, EGF, TGF-α) can stimulate intestinal epithelial cell proliferation and migration, shortening ulcer healing time;[46] on the other hand, exercise improves mitochondrial function, enhancing the energy metabolism and repair capacity of epithelial cells.[48] Studies show that exercise can activate mitophagy, clearing dysfunctional mitochondria, improving mitochondrial quality, and thereby promoting epithelial cell survival and repair.[42] Furthermore, by modulating gut microbiota, exercise increases repair-related metabolites (eg, B vitamins) produced by beneficial bacteria, further supporting mucosal repair.[25]

Remodeling of Immune Homeostasis: T Cell Subset Regulation and Macrophage Polarization

Immune imbalance is the core mechanism of IBD pathogenesis. Exercise restores intestinal immune homeostasis by "modulating T cell subset balance, improving macrophage polarization, and enhancing innate immune function".

T Cell Subset Balance

Exercise can increase the number and function of regulatory T cells (Tregs), promoting immune tolerance to gut bacteria.[47,51] In the IL-10 KO model, 12 weeks of voluntary wheel running increased the proportion of Tregs in the

colonic lamina propria by 2-fold and IL-10 levels by 3-fold, while reducing Th1/Th17 cell infiltration and lowering IFN-γ and IL-17 levels.[47,51] Additionally, exercise can limit the accumulation of "exhausted" and "senescent" T cells, maintaining the normal killing function of effector T cells (eg, CD8+ T cells) and reducing pathogen colonization.[52]

Macrophage Polarization

Exercise promotes macrophage polarization from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype: In the DSS model, exercise intervention increased the expression of M2 macrophage markers (eg, Arg-1, CD206) in colonic tissue by 2-fold, while reducing the expression of M1 markers (eg, iNOS, TNF-α) by 50%.[41] This effect may be related to "SCFAs activating GPR43 signaling and inhibiting the NF-κB pathway".

Enhancement of Innate Immune Function

Exercise can enhance the function of intestinal innate immune cells (eg, dendritic cells, natural killer cells). For example, exercise enhances the antigen-presenting capacity of intestinal dendritic cells, promoting Treg differentiation.[20] Simultaneously, the cytotoxicity of natural killer cells is enhanced, effectively clearing pathogens and damaged epithelial cells.[16]

Discussion

"Model-Exercise" Matching Principle

The pathological characteristics of IBD animal models (subtype, inflammatory stage, immune status, gut microbiota composition) are the core determinants of exercise intervention efficacy. Different models require tailored exercise regimens:

Chemically induced models (eg, DSS, TNBS): Suitable for short-term (4–6 weeks) low-intensity voluntary exercise (eg, voluntary swimming, low-intensity wheel running), avoiding forced and high-intensity exercise which may worsen acute inflammation.[35,36]

Gene-edited models (eg, IL-10 KO): Suitable for long-term (12–16 weeks) moderate-intensity voluntary exercise, potentially combined with probiotic intervention to enhance microbiota modulation.[42,43]

Spontaneously occurring/Microbiota-induced models (eg, SAMP1/YitFc, microbiota transplantation models): Suitable for combined regimens of "long-term moderate-intensity exercise + microbiota modulation (eg, prebiotics)", simulating comprehensive management of human IBD.[53]

Emerging models (eg, hMBM, organoids): hMBM models can be used to validate "the translational potential of exercise regimens to humans.[28,54] "Organoid systems can be used to screen for "key effector molecules induced by exercise (eg, myokines)".[55]

Assessment of Translational Validity

Pathological differences between models and human IBD are a major limitation of current research. Translational value should be enhanced from the following dimensions:

Pathological similarity: The TNBS model shows the highest similarity to human CD in terms of "transmural inflammation" and "Th1 immune mechanisms" (TLR signaling pathway overlap 78%). The hMBM model has a cytokine profile matching rate of 65%–70% with human IBD,[28] making it a preferred model for future translational research.

Translation of exercise regimens: The animal model's "moderate-intensity voluntary exercise (50–70% VO_2max)" corresponds to human "brisk walking, jogging, swimming" (60%–75% VO_2max). The animal's "12-week intervention duration" corresponds to approximately "16 weeks in humans" (considering metabolic rate differences).[56,57]

Matching of outcome measures: Clinical translation should focus on cross-species common indicators such as "microbiota diversity, SCFA levels, intestinal permeability, inflammatory cytokines (eg, TNF-α, IL-6)", while also incorporating human IBD clinical scores (eg, CDAI, UCDAI).[58,59]

Future Directions

The current research faces challenges such as "model human differences", "lack of standardization in protocols", and "insufficient depth of mechanisms". Among them, methodological heterogeneity in the study of gut microbiota is one of the key factors leading to inconsistent results and affecting the extrapolation of conclusions. Future research should focus on:

Standardization of the plan: It is not only necessary to establish matching guidelines for "model subtypes inflammation stages exercise parameters" but also to promote methodological standardization at the level of gut microbiota analysis. It is recommended to provide detailed reports on key information such as sequencing platforms, primer sequences, bioinformatics processes, and reference databases for future original research, and encourage the disclosure of raw data in public repositories (such as NCBI SRA) where feasible to enhance comparability and reproducibility of results.

Multi omics mechanism analysis: Integrating metagenomics (rather than just 16S rRNA sequencing), metabolomics, transcriptomics, and other multi omics technologies can more accurately analyze the changes in microbial functional potential (such as SCFAs synthesis pathways) under exercise intervention, rather than just changes in microbial structure, thus more reliably elucidating the core interaction pathways of the "exercise microbiota immune barrier" axis.

Clinical translational studies: When designing human trials, strong confounding effects of diet, medication, etc. on the microbiota should be fully considered and controlled as much as possible, and functional indicators of the microbiota that are highly correlated with clinical outcomes (such as fecal SCFAs concentration) should be used as one of the key biomarkers.

Conclusion

The pathological characteristics of IBD animal models (subtype, inflammatory stage, microbiota composition) are the core determinants of exercise intervention efficacy. Tailored matching of exercise regimens (voluntary, moderate intensity, ≥12 weeks for chronic models) can alleviate inflammation through multi-target mechanisms: including modulating gut microbiota (increasing beneficial bacteria and SCFA production), balancing inflammatory cytokines (inhibiting NF-κB/STAT3 pathways), enhancing the intestinal barrier (upregulating tight junction proteins), and remodeling immune homeostasis (promoting Treg differentiation and M2 polarization). Emerging models (eg, hMBM, organoids) significantly enhance translational value. Future efforts should focus on "protocol standardization, multi-omics mechanistic validation, and clinical trials" to advance exercise as a key non-pharmacological intervention in the comprehensive management of IBD, providing patients with safe and effective therapeutic options.

Data Sharing Statement

No new data were created. Data sharing is not applicable (systematic review of published studies).

Acknowledgments

The authors thank the research teams at Pingxiang University School of Physical Education and Pingxiang Hospital of Traditional Chinese Medicine for technical support, and the anonymous reviewers for constructive comments.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

There is no funding to report.

Disclosure

The authors declare no competing financial interests or personal relationships that could have influenced the work.

References

1. Seyedian SS, Nokhostin F, Malamir MD. A review of the diagnosis, prevention, and treatment methods of inflammatory bowel disease. *J Med Life*. 2019;12(2):113–122. doi:10.25122/jml-2018-0075
2. Stephanie C, Fiona C, Eric IB, et al. Past and future burden of inflammatory bowel diseases based on modeling of population-based data. *J Hepatol*. 2019;156(5):1345–1353.
3. Chen M, Shen N, Du Q. Research progress of intestinal flora in rheumatic immune diseases. *Chin J Gen Pract*. 2019;18(3):279–282. In Chinese.
4. Wenxi J, Jiali W, Shefeng Z, et al. The role of short chain fatty acids in irritable bowel syndrome. *J Neurogastroenterol Motil*. 2022;28(4):540–548. doi:10.5056/jnm22093
5. Abhinav K, Aditya K, Ikuo I, et al. Animal models of the immunology and pathogenesis of human babesiosis. *Trends Parasitol*. 2023;39(1):38–52. doi:10.1016/j.pt.2022.11.003
6. ShuTing W, XinXin W, WenBo X, et al. An update on animal models of liver fibrosis. *Front Med*. 2023;10:1–15.
7. Raffaele S, Giuseppina MR, Claudio P, et al. An orally administered butyrate-releasing derivative reduces neutrophil recruitment and inflammation in dextran sulphate sodium-induced murine colitis. *Br J Pharmacol*. 2017;174(11):1484–1496. doi:10.1111/bph.13637
8. Zhengguo Z, Lin D, Anna J, et al. Glucocorticoids promote the onset of acute experimental colitis and cancer by upregulating mTOR signaling in intestinal epithelial cells. *Cancers*. 2020;12(4):1–18.
9. Chunpeng L, Jianmin L, Qiaorui Z, et al. Effects of physical exercise on the microbiota in irritable bowel syndrome. *Nutrients*. 2024;16(16):1–23.
10. Abhijit D, Nirmalya C, Rajat KD. Metabolic pathway engineering: perspectives and applications. *Comput Methods Programs Biomed*. 2020;192:105436. doi:10.1016/j.cmpb.2020.105436
11. Ilse DJ. Animal models to study mucormycosis. *J Fungi*. 2019;5(2):1–12.
12. Chen L, Xu Z, Zhang C, et al. Establishment of acute ulcerative colitis model induced by acetic acid in dog. *China Animal Husbandry Veterinary Med*. 2018;45(5):1395–1400.
13. Nana YDA, David BB, Matthew B, et al. Enhancing microbiome research through genome-scale metabolic modeling. *mSystems*. 2021;6(6):1–15.
14. Robert R, Bret HG, Lauren GK, et al. Precision exercise medicine: understanding exercise response variability. *Br J Sports Med*. 2019;53 (18):1141–1153. doi:10.1136/bjsports-2018-100328
15. Jae-Young K, Chang-Hyeon A, Jae-Young K, et al. Experimental animal model systems for understanding salivary secretory disorders. *Int J Mol Sci*. 2020;21(23):8423. doi:10.3390/ijms21228423
16. Zegarra Ruiz DF, Dasom VK, Kendra N, et al. Microbiota manipulation to increase macrophage IL-10 improves colitis and limits colitis-associated colorectal cancer. *Gut Microbes*. 2022;14(1):1–23. doi:10.1080/19490976.2022.2119054
17. Lei Z, Coco C, Fei T, et al. Innate lymphoid cells support regulatory T cells in the intestine through interleukin-2. *Nature*. 2019;568(7752):405–409. doi:10.1038/s41586-019-1082-x
18. Lucy JM, Jacob MA, Thomas WB, et al. Exercise and the gut microbiome: a review of the evidence, potential mechanisms, and implications for human health. *Exerc Sport Sci Rev*. 2019;47(2):75–85. doi:10.1249/JES.0000000000000183
19. Ranit K, Tariq AN, Kailin RM, et al. A RORγt+ cell instructs gut microbiota-specific Tregcell differentiation. *Nature*. 2022;610(7933):737–743. doi:10.1038/s41586-022-05089-y
20. John AH. Microbiota and muscle highway — two way traffic. *Nat Rev Endocrinol*. 2020;16(2):71–72. doi:10.1038/s41574-019-0291-6
21. Daniel BG, Ramnik JX. Pathway paradigms revealed from the genetics of inflammatory bowel disease. *Gut*. 2020;578(7796):527–539.
22. Peng W, Xiaodong C. Development and application of in vitro biomimetic intestinal models. *Sci China Life Sci*. 2022;74(4):1–18. In Chinese.
23. Cassie MM, Brenda MD, Matthew WH, et al. Does exercise alter gut microbial composition? A systematic review. *Med Sci Sports Exerc*. 2019;51 (1):160–167. doi:10.1249/MSS.0000000000001760
24. Bryant HK, Nicholas AK, Christina MS, et al. Exercise and intestinal permeability: another form of exercise-induced hormesis? *Am J Physiol Gastrointest Liver Physiol*. 2020;319(4):G512–G518. doi:10.1152/ajpgi.00232.2020
25. Laura W, Paul DC, Orla O, et al. The potential impact of probiotics on the gut microbiome of athletes. *Nutrients*. 2019;11(10):1–18.
26. Yuli Q, Leilei Y, Fengwei T, et al. In vitro models to study human gut-microbiota interactions: applications, advances, and limitations. *Microbiol Res*. 2023;270:1–15.
27. David JD, Juneyoung L, Louise DM, et al. Examining the role of the microbiota-gut-brain axis in stroke. *Stroke*. 2019;50(8):2270–2277. doi:10.1161/STROKEAHA.119.025140
28. Lavelle A, Sokol H. Gut microbiota-derived metabolites as key actors in inflammatory bowel disease. *Nat Rev Gastroenterol Hepatol*. 2020;17 (4):223–237.
29. Aguilar-Rojas A, Olivo-Marin J-C, Guillen N. Human intestinal models to study interactions between intestine and microbes. *Open Biol*. 2020;10 (10). doi:10.1098/rsob.200199
30. Jiang Y, Wu D, Feng-yu W. Changes in the skeletal muscle morphology and supercompensation after different intensities of training under aerobic energy supply[J. *Chin J Tissue Eng Res*. 2018;22(24):3811–3817.
31. Mark AT, Chiara R. How regulatory T cells are primed to aid tolerance of gut bacteria. *Nature*. 2022;610(7933):638–640. doi:10.1038/d41586-022-03368-2
32. Marta D, Malgorzata G, Aleksandra G, et al. Selected techniques for physiotherapy in dogs. *Animals*. 2022;12(12):1–15.
33. Mariangela T, Carlo B, Jose Angel G, et al. The effect of acute moderate-intensity exercise on the serum and fecal metabolomes and the gut microbiota of cross-country endurance athletes. *Gastrointest Endosc*. 2021;11(1):1–12.
34. Kevin PL, Shannon AK, Katherine JB, et al. Production of an interleukin-10 blocking antibody by genetically engineered macrophages increases cancer cell death in human gastrointestinal tumor slice cultures. *Cancer Gene Ther*. 2023;30(9):1227–1233. doi:10.1038/s41417-023-00632-z
35. Rong F, Ruiyan N, Fangye Z, et al. Exercise alleviated intestinal damage and microbial disturbances in mice exposed to fluoride. *Chemosphere*. 2022;288:132658.

36. Claire B, Keith ET, Fiona SLB. Microbial genomic island discovery, visualization and analysis. *Brief Bioinform*. 2018;20(5):1685–1698.
37. Wenqian Y, Yuqian L, Guang Y, et al. Moderate-intensity physical exercise affects the exercise performance and gut microbiota of mice. *Front Cell Infect Microbiol*. 2021;11:1–15.
38. Ana MA, Claire EB. Exercise in the context of substance use treatment: key issues and future directions. *Curr Opin Psychol*. 2019;30:103–108. doi:10.1016/j.copsyc.2019.04.001
39. Joris L, Joke De P, Timia Van S, et al. The effect of aerobic exercise on the number of migraine days, duration and pain intensity in migraine: a systematic literature review and meta-analysis. *J Headache Pain*. 2019;20(1):1–15. doi:10.1186/s10194-018-0948-x
40. Zhenrun JZ, Christopher JL, Cody GC, et al. Translating microbiome research from and to the clinic. *Annu Rev Microbiol*. 2022;76(1):435–460. doi:10.1146/annurev-micro-041020-022206
41. Allen JM, Mailing LJ, Cohrs J, et al. Exercise training-induced modification of the gut microbiota persists after microbiota colonization and attenuates the response to chemically-induced colitis in gnotobiotic mice. *Gut Microbes*. 2018;9(2):115–130. doi:10.1080/19490976.2017.1372077
42. Patrick I, Andreas P, Falk-Bach L. Drug metabolism in animal models and humans: translational aspects and chances for individual therapy. *Acta Physiol*. 2021;233(4):1–18.
43. Kate MS, Raylene AR. Unlocking a novel determinant of athletic performance: the role of the gut microbiota, short-chain fatty acids, and "biotics" in exercise. *J Sport Health Sci*. 2023;12(1):36–44. doi:10.1016/j.jshs.2022.09.002
44. Shi-Jun Y, Juan L, Ai-Ting W, et al. Berberine alleviates insulin resistance by reducing peripheral branched-chain amino acids. *Am J Physiol Endocrinol Metab*. 2019;316(1):E73–E85. doi:10.1152/ajpendo.00256.2018
45. Elena B, Alessandra Carcereri de P, Sofia M. Redox regulation of STAT1 and STAT3 signaling. *Int J Mol Sci*. 2020;21(19):1–23.
46. Ling L, Soochi K, Matthew TB, et al. Exercise reprograms the inflammatory landscape of multiple stem cell compartments during mammalian aging. *Cell Stem Cell*. 2023;30(5):689. doi:10.1016/j.stem.2023.03.016
47. Lucio Della G, Roberto C. Exercise tolls the bell for key mediators of low-grade inflammation in dysmetabolic conditions. *Cytokine Growth Factor Rev*. 2021;62:83–93. doi:10.1016/j.cytogfr.2021.09.003
48. Yuntian G, Joshua CD, Zhen Y. Exercise-induced mitophagy in skeletal muscle and heart. *Exerc Sport Sci Rev*. 2019;47(4):189–198.
49. Yan L, Yao W, Yueqiong N, et al. Gut microbiome fermentation determines the efficacy of exercise for diabetes prevention. *Cell Metab*. 2019;31 (1):77–91.e5. doi:10.1016/j.cmet.2019.11.001
50. Michael DD, Isao S, Shuichi K, et al. Tissue factor facilitates wound healing in human airway epithelial cells. *Chest*. 2019;155(3):534–539. doi:10.1016/j.chest.2018.10.007
51. Xu Z, Davis AE, Zaira A, et al. Exercise counters the age-related accumulation of senescent cells. *Exerc Sport Sci Rev*. 2022;50(4):213–221. doi:10.1249/JES.0000000000000302
52. Davide B, Qi X, Briana CP, et al. CHMP2A regulates tumor sensitivity to natural killer cell-mediated cytotoxicity. *Nat Commun*. 2022;13(1):1–15. doi:10.1038/s41467-021-27699-2
53. Gwenny MF, Gail AH, Sage EF, et al. 2019 gut microbiota for health world summit. *J Hepatol*. 2020;158(1):28–31.
54. Federica A, Ettore D, Antonio B, Valentina R, Diego C, Fabio B Physical exercise and synaptic protection in human and pre-clinical models of multiple sclerosis. *Neural Regener Res*. 2024;19(8):1768–1771.
55. Hirak S, Eunmi L, L SL, et al. Deciphering Normal and Cancer Stem Cell Niches by Spatial Transcriptomics: Opportunities and Challenges[J]. *Genes Devel*. 2025;39(1–2):64–85.
56. Keir DA, Pogliaghi S, Murias JM. The respiratory compensation point and the deoxygenation break point are valid surrogates for critical power and maximum lactate steady state. *Med Sci Sports Exercise*. 2018;50(11):2379–2382. doi:10.1249/MSS.0000000000001698
57. Nicolo A, Marcora SM, Sacchetti M. Last word on viewpoint: time to reconsider how ventilation is regulated above the respiratory compensation point during incremental exercise. *J Appl Physiol*. 2020;128(5):1447–1449. doi:10.1152/japplphysiol.00814.2019
58. Lucius K. Nutritional and botanical approaches for inflammatory bowel disease. *Alternative Complementary Ther*. 2021;27(3):141–151. doi:10.1089/act.2021.29331.klu
59. David JD, Jasenka Z, Matam V, et al. Prospects for leveraging the microbiota as medicine for hypertension. *Hypertension*. 2024;81(5):951–963. doi:10.1161/HYPERTENSIONAHA.124.21721