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Physical Activity and Inflammatory Bowel Diseases: Evidence from Animal Models

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Abstract

Background:
Inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, are chronic inflammatory disorders of the gastrointestinal tract characterized by immune dysregulation, oxidative stress, and intestinal barrier dysfunction. Growing evidence suggests that physical activity exerts systemic anti-inflammatory and antioxidant effects; however, the mechanisms by which exercise influences intestinal inflammation remain incompletely understood. Animal models of experimental colitis provide a valuable platform for exploring these interactions.

Aim: The purpose of this review was to summarize and critically evaluate current preclinical evidence regarding the effects of physical activity on inflammatory bowel diseases, focusing on immunological, oxidative, and microbiota-related mechanisms in animal models.

Material and Methods: A narrative review of studies published in peer-reviewed journals up to September 2025 was conducted using PubMed, Scopus, and Web of Science databases. Search terms included combinations of "exercise", "physical activity", "colitis", "IBD", "DSS", "TNBS", and "animal models". Eligible studies involved rodent models of experimentally induced colitis with defined exercise interventions. Data on animal strain, colitis induction method, exercise type/intensity, and major biological outcomes were extracted and analyzed qualitatively.

Results: Moderate physical activity consistently reduced colonic inflammation, oxidative damage, and intestinal permeability across experimental models. Exercise downregulated pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) and upregulated anti-inflammatory mediators (IL-10). It enhanced antioxidant enzyme activity (SOD, catalase) via Nrf2 signaling and improved gut microbiota diversity. Conversely, high-intensity or forced exercise exacerbated mucosal injury, oxidative stress, and cytokine imbalance, demonstrating a dose-dependent effect.

Conclusions: Evidence from animal models indicates that regular, moderate exercise exerts protective effects in experimental colitis by modulating immune, oxidative, and microbial pathways. These findings support the concept of physical activity as a potential adjunctive strategy for IBD prevention and management, though further translational research is required to establish optimal exercise prescriptions for clinical application.

Key words: physical activity, exercise, inflammatory bowel disease, animal models, experimental colitis, oxidative stress, gut microbiota, inflammation

1. Introduction

Inflammatory bowel diseases (IBD), encompassing **Crohn's disease (CD)** and **ulcerative colitis (UC),** are chronic, relapsing inflammatory disorders of the gastrointestinal tract characterized by a dysregulated immune response, epithelial barrier dysfunction, and intestinal microbiota imbalance. The pathogenesis of IBD is multifactorial, involving genetic susceptibility, environmental triggers, microbial dysbiosis, and immune dysregulation (Mehta et al., 2017). Although substantial progress has been made in understanding the immunopathology of IBD, the precise mechanisms leading to chronic inflammation remain only partially elucidated.

The **global burden of IBD** has increased dramatically over recent decades, extending from Western Europe and North America to Asia, the Middle East, and South America (Ng et al., 2017). Recent epidemiological data indicate that the prevalence of IBD in industrialized nations now exceeds 0.5% of the population and continues to rise in

developing regions, marking IBD as a global health concern (Kaplan & Windsor, 2021). The chronic nature of these conditions significantly impairs patients' quality of life, physical performance, and mental well-being, while current therapeutic options—though increasingly effective—remain costly, may cause adverse effects, and often fail to achieve sustained remission (Kalafateli et al., 2013).

Given these challenges, **non-pharmacological interventions** have become an area of growing interest in IBD management. Among lifestyle factors, **physical activity (PA)** has been recognized for its broad systemic benefits, including metabolic regulation, immune modulation, stress reduction, and improvement in psychological health (Pedersen & Saltin, 2015; Walsh et al., 2020). In non-IBD populations, regular moderate exercise reduces systemic inflammation, alters cytokine profiles, and enhances antioxidant defenses (Gleeson et al., 2011). These systemic effects raise the possibility that physical activity could similarly modulate the intestinal inflammatory milieu characteristic of IBD.

Emerging clinical evidence suggests a potential protective association between **physical activity and IBD risk or severity**. Observational cohort studies indicate that individuals engaging in regular moderate to vigorous exercise may have a lower risk of developing Crohn's disease (Khalili et al., 2013), and that structured physical activity programs can improve fatigue, bone density, and quality of life in patients with established IBD (Khalili et al., 2013). However, due to variability in study design, patient characteristics, and exercise modalities, the underlying **mechanistic basis** of these associations remains poorly defined.

To better elucidate these mechanisms, researchers increasingly turn to **preclinical animal models** of IBD, such as those induced by **dextran sulfate sodium (DSS)** or **2,4,6-trinitrobenzene sulfonic acid (TNBS)**. These models reproduce key histopathological and immunological features of human colitis, enabling precise control over exercise parameters and experimental conditions (Gadaleta et al., 2017). Studies using such models have demonstrated that **moderate voluntary exercise** may attenuate colonic inflammation, decrease oxidative stress, and favorably alter gut microbiota composition (Bilski et al., 2016; Allen et al., 2018). Conversely, excessive or forced high-intensity exercise may exacerbate inflammation and mucosal damage, suggesting a **dose-dependent effect** of physical activity on intestinal homeostasis (Cook et al., 2013).

Understanding how physical activity interacts with intestinal inflammation at the molecular and systemic levels is crucial for developing evidence-based exercise recommendations for IBD patients. **Animal studies provide a vital mechanistic foundation** for this purpose, allowing for detailed assessment of cytokine signaling, redox pathways, epithelial integrity, and microbial ecology in response to exercise.

Therefore, the objective of this review is to **summarize and critically evaluate current evidence from animal model research** on the impact of physical activity on inflammatory bowel diseases, with a focus on the modulation of immune responses, oxidative stress, and gut microbiota. This synthesis aims to provide a translational perspective linking experimental findings to potential therapeutic applications in human IBD management.

2. Research materials and methods

2.1. Study Design

This paper is a **narrative review** summarizing and critically analyzing preclinical studies evaluating the effects of physical activity on experimental models of inflammatory bowel diseases (IBD). The review methodology followed established frameworks for narrative synthesis, ensuring transparency and rigor in search, selection, and

data analysis (Green et al., 2006; Ferrari, 2015; Popay et al., 2006). Although not a systematic review, it adopted structured procedures to enhance reproducibility and minimize bias.

2.2. Search Strategy

A comprehensive literature search was conducted in **PubMed, Scopus**, and **Web of Science** databases up to **September 2025.** The search combined the following keywords and Boolean operators:

("physical activity" OR "exercise" OR "training") AND ("inflammatory bowel disease" OR "IBD" OR "colitis" OR "Crohn's disease" OR "ulcerative colitis") AND ("animal model" OR "rodent" OR "experimental colitis" OR "DSS" OR "TNBS").

Additional records were identified through manual screening of reference lists from relevant reviews and original research papers. Only **peer-reviewed** articles published in **English** were included. No time restrictions were applied to ensure coverage of both foundational and recent research.

Studies were included if they met all the following criteria:

1. Conducted in **animal models** (mice or rats) of experimentally induced colitis.
2. Employed a **defined physical activity or exercise intervention**, such as voluntary wheel running, forced treadmill training, or swimming protocols.
3. Reported at least one **biological, histological, or microbiological outcome** related to intestinal inflammation, immune markers, oxidative stress, or gut microbiota.
4. Included a **control group** (sedentary or untrained animals).

Studies were **excluded** if they:

- Involved non-colitis gastrointestinal models (e.g., irritable bowel syndrome, intestinal ischemia).
- Were purely in vitro or cell culture experiments without in vivo validation.
- Lacked original quantitative data (reviews, commentaries, conference abstracts).

2.3. AI

Artificial intelligence tools were used solely for linguistic enhancement and consistency checking of English grammar and formatting, under full human supervision. No AI was employed for data analysis or interpretation.

3. Results and Discussion

3.1. Overview of Included Studies

A growing body of preclinical research has investigated the effects of physical activity on experimental models of inflammatory bowel disease (IBD). Most studies have employed rodent models, particularly mice (C57BL/6, BALB/c) and rats (Wistar, Sprague–Dawley), in which colitis is chemically induced using agents such as dextran

sulfate sodium (DSS) or 2,4,6-trinitrobenzene sulfonic acid (TNBS). These models reproduce key histopathological and immunological features of human ulcerative colitis and Crohn's disease and are widely used to examine the impact of exercise on intestinal inflammation, oxidative stress, and gut microbiota composition. (Chassaing et al., 2014).

Exercise interventions varied substantially across studies, including **voluntary wheel running, treadmill running (low-to-moderate intensity)**, and **forced swimming protocols**. Duration ranged from **2 to 8 weeks**, and most interventions were performed either **before** (preventive paradigm) or **during** colitis induction (therapeutic paradigm). Overall, moderate-intensity voluntary or treadmill exercise tended to **reduce the severity of colitis**, while exhaustive or high-intensity exercise often **exacerbated mucosal injury** and inflammatory markers.

3.2. Modulation of Immune and Inflammatory Pathways

Multiple studies demonstrated that **moderate physical activity** exerts **anti-inflammatory effects** in experimental colitis. Bilski et al. (2015) showed that **voluntary wheel running** in TNBS-treated rats significantly decreased colonic damage and lowered the expression of pro-inflammatory cytokines such as **TNF-α, IL-1β, and IL-6**, while upregulating **IL-10**, a key anti-inflammatory mediator.

Similarly, Cook et al. (2013) reported that **moderate treadmill exercise** in DSS-induced colitis in mice reduced neutrophil infiltration and decreased myeloperoxidase (MPO) activity — a marker of acute inflammation. The anti-inflammatory effects of exercise were associated with suppression of the **NF-κB** signaling pathway and increased activation of **PPAR-γ,** known for its immunoregulatory role in the colon (Zhang et al., 2025).

In contrast, **high-intensity or exhaustive exercise** was found to aggravate inflammation. Bilski et al. (2019) demonstrated that forced treadmill running at 85% VO_2max during DSS-induced colitis elevated colonic levels of TNF-α and reactive oxygen species (ROS), exacerbating mucosal injury. These findings support the concept of a **"U-shaped" response,** in which moderate exercise is protective, whereas excessive intensity triggers stress-related pro-inflammatory responses (Dziewiecka et al., 2022).

Overall, data indicate that **controlled, moderate-intensity exercise** may downregulate key inflammatory mediators (e.g., TNF-α, IL-1β, IL-6) while promoting the release of **anti-inflammatory cytokines** (e.g., IL-10, IL-4) and regulatory immune cells, thereby restoring immune homeostasis in the gut.

3.3. Oxidative Stress and Antioxidant Defense

Oxidative stress is a critical component of intestinal inflammation, contributing to epithelial injury and barrier dysfunction. Several studies have shown that **exercise modulates oxidative and antioxidant pathways** in the colon.

In a TNBS rat model, Bilski et al. (2019) observed that prior moderate treadmill training enhanced the activity of antioxidant enzymes such as **superoxide dismutase (SOD)** and **catalase**, while reducing lipid peroxidation markers (MDA) and nitric oxide overproduction.

Mechanistically, these effects may be mediated through activation of **Nrf2-dependent antioxidant signaling**, which enhances transcription of protective enzymes like **HO-1** and **GPx** (Vargas-Mendoza et al., 2019). Furthermore, moderate exercise increased **colonic cNOS activity** while suppressing **iNOS expression**, suggesting improved nitric oxide balance (Szalai et al., 2014; Bilski et al., 2015).

However, forced high-intensity protocols induced opposite effects — increasing oxidative stress markers, mitochondrial dysfunction, and epithelial apoptosis (Takami et al., 2024). These data reinforce that **exercise intensity and adaptation time** are key determinants of whether oxidative pathways contribute to protection or injury in colitis.

3.4. Gut Microbiota and Instestinal Barrier Integrity

The gut microbiota plays a pivotal role in regulating immune and metabolic homeostasis. Recent evidence indicates that **physical activity can modify microbial composition and enhance barrier function** in colitis models.

Estaki et al. (2020) demonstrated that voluntary wheel running in mice enhanced gut microbial diversity and increased the relative abundance of short-chain fatty acid (SCFA)-producing bacteria, contributing to improved intestinal homeostasis.

In contrast, exhaustive exercise induced **microbiota dysbiosis**, decreased beneficial commensals, and increased *Proteobacteria*, a phylum linked to gut inflammation (Koutouratsas et al., 2021). Collectively, these findings suggest that moderate exercise promotes eubiosis and strengthens epithelial barrier integrity, while excessive training disrupts microbial homeostasis and may potentiate inflammation.

3.5. Timing and Type of Exercise

Evidence also highlights the **importance of exercise timing** relative to disease onset. Studies where exercise was performed **before colitis induction** (preventive paradigm) consistently showed stronger anti-inflammatory and antioxidant effects than those initiated during active inflammation (Bilski et al., 2019). This suggests that **exercise preconditioning** may prime the immune system and mucosal defenses, enhancing resilience to inflammatory insults.

Moreover, in preclinical mouse models, the exercise modality plays a role: voluntary running tends to produce more beneficial outcomes compared with forced treadmill running, likely due to differences in stress response and glucocorticoid levels. (Cook et al., 2013). The combination of **moderate intensity, voluntary engagement, and chronic duration** appears to yield the most favorable results.

3.5. Translational Implications

The results from animal studies provide strong **mechanistic support** for the beneficial role of physical activity in modulating intestinal inflammation. The anti-inflammatory, antioxidant, and microbiota-stabilizing effects observed in rodents align with emerging clinical findings in human IBD patients. However, translational challenges remain, including interspecies differences in immune responses, exercise tolerance, and microbiota composition.

Future research should aim to define **dose–response relationships**, explore **sex-specific differences,** and employ **chronic colitis models** that better reflect human disease. Integrative approaches combining molecular, microbiological, and behavioral endpoints may further clarify how physical activity could be harnessed as a **complementary therapeutic strategy** in IBD management.

4. Conclusions

The collective evidence from animal studies strongly supports the hypothesis that **moderate physical activity** exerts protective effects in experimental models of inflammatory bowel disease (IBD). Consistent findings across various rodent models demonstrate that **voluntary or moderate-intensity exercise** attenuates colonic inflammation, decreases oxidative stress, and improves epithelial barrier function (Bilski et al., 2015; Cook et al., 2013). These beneficial effects are mediated through multiple interrelated mechanisms, including the **downregulation of pro-inflammatory cytokines** (e.g., TNF-α, IL-1β, IL-6), **activation of antioxidant pathways** (e.g., Nrf2, HO-1), and **enhancement of gut microbiota diversity and short-chain fatty acid production** (Cho et al., 2020; Ruan et al., 2020).

Conversely, **forced or high-intensity exercise** has been shown to exacerbate mucosal injury and inflammatory responses, likely due to excessive oxidative stress and activation of hypothalamic–pituitary–adrenal (HPA) axis pathways (Cook et al., 2013). This "U-shaped" relationship between exercise intensity and inflammatory response underscores the importance of appropriate **dose, duration, and modality** in the design of exercise interventions.

Mechanistically, beneficial adaptations to moderate exercise include **suppression of NF-κB activation,** stimulation of **PPAR-γ** and **Nrf2** signaling, restoration of nitric oxide synthase balance, and upregulation of anti-inflammatory cytokines such as **IL-10** (Allen et al., 2018; Bilski et al., 2019). These cellular and molecular pathways contribute to maintaining intestinal homeostasis and limiting oxidative and inflammatory damage during colitis.

From a translational perspective, preclinical data provide a solid foundation for developing **evidence-based exercise recommendations** in IBD management. Nevertheless, direct extrapolation to human disease remains challenging due to interspecies differences in immune regulation, gut microbiota composition, and stress physiology (Ruan et al., 2020). Future research should focus on:

1. **Standardizing experimental exercise paradigms** to improve reproducibility and comparability across studies.
2. Employing **chronic and genetically modified animal models** that better simulate human IBD pathophysiology.
3. Integrating **multi-omics approaches** (transcriptomics, metabolomics, microbiomics) to clarify molecular interactions between exercise, inflammation, and microbiota.
4. Conducting **translational and clinical studies** to determine the optimal exercise type, intensity, and timing for improving disease outcomes and patient well-being.

In conclusion, preclinical evidence suggests that **regular, moderate physical activity** represents a safe and promising adjunctive strategy to mitigate intestinal inflammation and enhance gut health. The integration of animal and clinical findings will be essential to define the optimal therapeutic framework for incorporating exercise into comprehensive IBD management.

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Supplementary Materials

None.

Author Contributions

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Conflicts of Interest

The authors declare no conflict of interest.

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