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Original article

Arnica montana L. and exercise: a promising combination for managing a mouse model of ulcerative colitis

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Abstract

Objective: Ulcerative colitis (UC) is a lifelong condition that causes inflammation and ulcers inside the colon. We investigated the antioxidant and fibrinolytic effects of hydroalcoholic extract of *Arnica montana L.* flowers(Ar) in a mouse colitis model when combined with exercise.

Materials and methods: Animals were segregated into the following groups: Exercise (Ex), dextran sulfate sodium for induction of colitis (DSS), Ex+DSS, and Ar+Ex+DSS (n = 6 in each group). All groups, except the DSS group, underwent training with a forced swimming test 6 weeks before and during the experiment. Body weight and disease activity indicators (DAI) were assessed during colitis induction and treatment. Then, the colon tissue of sacrificed mice was examined for clinical symptoms and histological changes. Additionally, homogenized colon tissue was evaluated for oxidant and antioxidant markers.

Results: The Ar+Ex+DSS group exhibited improvements in DAI. Administration of Ar along with exercise also led to improvements in histological changes in colitis tissues. Furthermore, an increase in antioxidants and a decrease in oxidants were observed in the Ar+Ex+DSS group. Trichrome staining revealed a decrease in collagen content in the Ar+Ex+DSS group.

Conclusion: Although exercise has shown potential to improve colitis, the concomitant administration of Ar and exercise led to a more significant enhancement in clinical and histological symptoms, as well as oxidative stress markers. However, compared to the cohort receiving exercise alone, these improvements did not reach statistical significance.

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Introduction

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease impacting the mucous membrane of the colon, predominantly seen in individuals between the third and fourth decades of life, leading to disability (Høivik et al. 2013; Torres et al. 2012).

UC is often characterized by the presence of blood in the stool and diarrhea (Dignass et al. 2012). Symptoms may encompass urgency, incontinence, fatigue, heightened bowel movement frequency, discharge of mucus, defecations during the night, and abdominal discomfort (cramps), with abdominal pain being less prominent compared to Crohn's disease (CD) (Baumgart and Sandborn 2007). In severe cases, individuals may also experience fevers and weight loss. Management seeks to attain prompt alleviation of symptoms, restoration of mucosal integrity, and enhancement of a patient's quality of life. 5-Aminosalicylic acid drugs continue to be the initial choice for treating mild to moderate disease (Feagan et al. 2013). Should patients exhibit an inadequate response to these drugs, it may be essential to progress to immunosuppressive agents and biologics (e.g. anti-cytokines and anti-integrins) (Bressler et al. 2015).

Studies indicated that oxidative stress plays a pivotal role in the induction and progression of UC (Guan and Lan 2018). Also, inflammation responses and higher production of pro-inflammatory cytokines lead to an inflammatory cascade, causing chronic inflammation. Furthermore, inflammation in UC is known to cause an overproduction of Reactive Oxygen Species (ROS) which causes higher oxidative stress factors production and degrades the gastrointestinal tract mucosa, and some clinical symptoms such as abdominal pain and diarrhea (Muro et al. 2024). Thus, it seems that oxidative stress has a crucial role in the pathogenesis of inflammatory bowel diseases.

Physical activity (Exercise (Ex)) has the potential to influence the composition of the intestinal microbiome, thereby changing the operational dynamics of the gastrointestinal ecosystem. The act of exercising is linked to heightened biodiversity and advantageous metabolic processes; however, intense exercise training could potentially lead to an imbalance in the gut microbiota, fostering adverse metabolic consequences and inflammation (Mancin et al. 2021; Ticinesi et al. 2019). Regular, moderate physical activity has been shown to confer benefits on various tissues such as the heart, adipose tissue, muscle, and brain, while also decreasing the likelihood of developing metabolic and inflammatory disorders (Allen et al. 2018). Exercise plays a role in modulating inflammation and enhancing the anti-inflammatory response through mechanisms like visceral fat reduction, augmented release of anti-inflammatory cytokines from skeletal muscles, and decreased expression of Toll-like receptors in monocytes and macrophages (Gleeson et al. 2011). Although a decrease in systemic inflammation due to regular exercise has been observed in other chronic diseases, its impact on UC remains unproven (Baker et al. 2022).

Arnica montana L. (Ar), belonging to the Asteraceae family, is a perennial herbaceous plant indigenous to the elevated regions of central Europe and extensively farmed across various geographical locations. Recognized for its medicinal properties, Ar has been historically employed for diverse therapeutic purposes including contusion, bruise, hematoma, edema, and rheumatism (Phytotherapy 2003; Wichtl 2004). Ar displays noteworthy properties including anti-inflammatory, antibacterial, antifungal, antioxidant, and immunomodulatory effects (Kriplani et al. 2017). So, we hypothesized that regular moderate physical activity combined with Ar supplementation will have a protective effect on colitis caused by Dextran sulfate sodium (DSS), potentially reducing inflammation and improving symptoms in

animals with UC. This study aims to observe the protective effect of Ar along with exercise in the treatment of colitis caused by DSS.

Materials and Methods

DSS with a molecular weight of 40 kDa and a purity of 98% was acquired from Sigma-Aldrich in St. Louis, MO. Essential reagents for assessing oxidative stress, such as Malondialdehyde (MDA), Superoxide Dismutase (SOD), Thiol, and Catalase (CAT), were sourced from Kushan Zitazama Co. in Tehran, Iran. Ketamine 10% was obtained from Medistar in Ascheberg, Germany, and Xylazine 2% was procured from Riemser in Greifswald, Germany.

Extract preparation

The hydroalcoholic extract was obtained by combining 100 g of Ar flower with 1800 ml of 70% ethanol (composed of 540 ml distilled water and 1260 ml ethanol) and subjecting the mixture to maceration for 72 hr with periodic agitation. Subsequently, the extract was filtered, and the solvent was eliminated using a rotary evaporator (Hamounpeima et al. 2020).

Animal ethics statement

Male C57BL6 mice (weighing 22-24 g) were procured from the local animal center. They were housed under standard conditions. All procedures involving the animals were approved and conducted by the Guidelines for the Use of Local Laboratory Animals (Approval ID: IR.MUMS.AEC.1402.125).

Experimental design

Animals were separated into 4 groups (n=6) in a randomized manner as follows: Group 1: control group (Ex), received only drinking water (DW) along with Ex training. Group 2: The DSS group received only DSS (1.5 g dissolved in 100 ml of DW) (Mostafapour et al. 2024), Group 3: EX + DSS received DSS in DW along with Ex training, and Group 4: Ex+ Ar received DSS in DW and Ar (100 mg/kg/day, oral gavage) along with Ex training (Kawakami et al. 2011a; Oliveira et al. 2021; Toma et al. 2024). The study protocol is visually presented in Figure 1A. The exercise program spanned six weeks, after which the DSS-receiving groups (groups 2, 3, and 4) were subjected to DSS dissolved in distilled water (DW) daily (2.5% (w/v)) for one week, whereas Group 1 served as vehicle control and consumed DW throughout the study period. Ex was maintained consistently across groups 1,3, and 4 throughout the experiment, while group 2 had a sedentary lifestyle. In the group treated with Ar, 100 mg/kg/day was given to mice by gavage for 7 consecutive days.

During the investigation, the disease activity indicator (DAI) was assessed daily after DSS administration, with the highest scores recorded (Table 1). DAI scoring was performed according to the criteria described by (Yaghoubi et al. 2021). DAI scores were monitored throughout the study period. At the study's end, animals were weighed and euthanizedusing CO_2 inhalation; spleens were collected for imaging and weighing, and colon samples were processed per standard protocols (Mostafapour et al. 2024).

Table 1. Disease activity index (DAI) was scored during the experiment

Disease activity index				
Score	**Rectal bleeding**	**Stool consistency**	**Rectal prolapse**	**Lose weight**
0	None	Normal	None	<5%
1	Red	Soft	Sign of prolapse	5-10%
2	Dark red	Very soft	Clear prolapse	10-15%
3	Gross bleeding	Diarrhea	Extensive prolapse	>15%

Forced swimming test (FST)

This study conducted the Forced Swim Test (FST) as previously described (Can et al. 2012). In a glass container (120 cm long, 80 cm deep) with water at 34–37°C. Rodents adapted for one week before undergoing training sessions of 15-20 min, five days a week, for six weeks. All groups except the DSS group received FST training before and during the experiment.

Histopathological assessment

Colon tissues were preserved in 10% neutralized formalin, embedded in paraffin, and sectioned into 5 µm slices on polylysine-coated slides. After deparaffinization, sections were stained with hematoxylin and eosin (H&E) for histological scoring (Table 2). Mason trichrome staining assessed collagen content, and fibrosis was analyzed using Image J software (Mostafapour et al. 2024).

Table 2. Scoring of colon tissue damage according to histopathological criteria

Score	0	1	2	3	4
Inflammation	None	Mild	Moderate	Severe	
Mucosal damage	None	Mucus layer	Submucosa	Muscular and serosa	
Crypt loss	None	1/3	2/3	100% + intact epithelium	100% with epithelium lose
Pathological change range	None	1-25%	26-50%	51-75%	76-100%

Oxidant and anti-oxidant indicators

To assess the levels of oxidative stress indicators, the concentrations of MDA, total thiol, SOD, and CAT were quantified in colon tissues following established protocols (Hashemzehi et al. 2020).

Statistical analysis

Statistical procedures involved in the study comprised the application of one-way ANOVA and LSD post hoc tests. The presentation of data is in the form of mean ± SEM, where disparities with a p value < 0.05 were regarded as statistically significant.

Results

The impact of physical activity and *Arnica montana* L. in alleviating the clinical manifestations linked to UC in a murine model

Daily monitoring revealed a significant increase in body weight during Ex and Ar treatment (Figure 1B), based on daily weight monitoring. Also, the Ar+Ex+DSS group significantly reduced DAI compared with the DSS group ($p<0.001$) (Figure 1C), and also improved the highest DAI in the Ar+Ex+DSS group ($p<0.001$) (Figure 1D).

Effects of exercise and *Arnica montana* L. on colon and spleen

The Ex (Ar) group appears to protect against DSS-induced colon inflammation, as indicated by reduced colon weight loss (Figure 2C), shortening, and increased spleen weight (Figure 2D and F). These findings suggest anti-inflammatory and immunomodulatory effects, with a lower colon weight-to-length ratio and decreased spleen weight-to-body weight ratio compared to the DSS group ($p<0.05$ and $p<0.001$, respectively) (Figure 2).

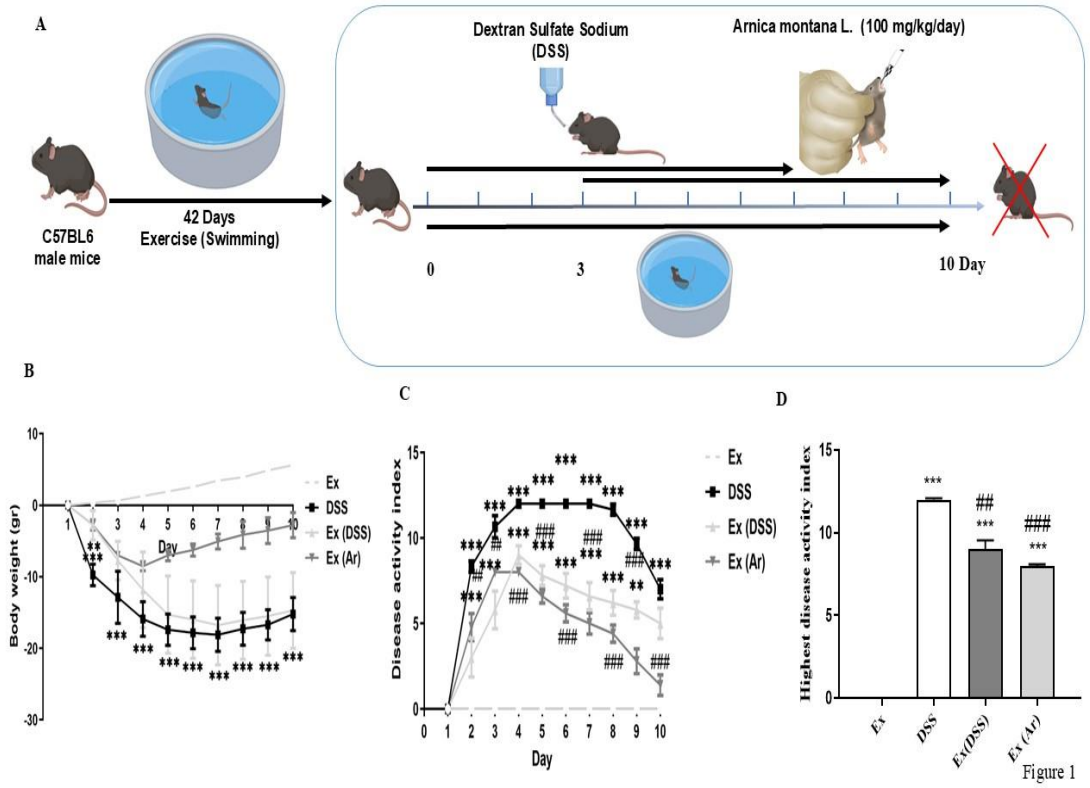

Figure 1. Efficacy of Exercise + *Arnica montana* L. on colitis clinical symptoms. The schematic presentation of the study (A). Daily changes in Body weight during colitis (B). The effects of Ex+Ar on daily disease activity index (DAI) (B) and highest DAI (C). * p<0.05, ** p<0.01 and *** p<0.001 vs. Exercise group. # p<0.05, ## p<0.01 and ### p<0.001 vs. DSS group. Data is presented as Mean ± SEM. Abbreviation: Exercise: Ex; *Arnica montana* L. : Ar; Dextran sulfate sodium: DSS

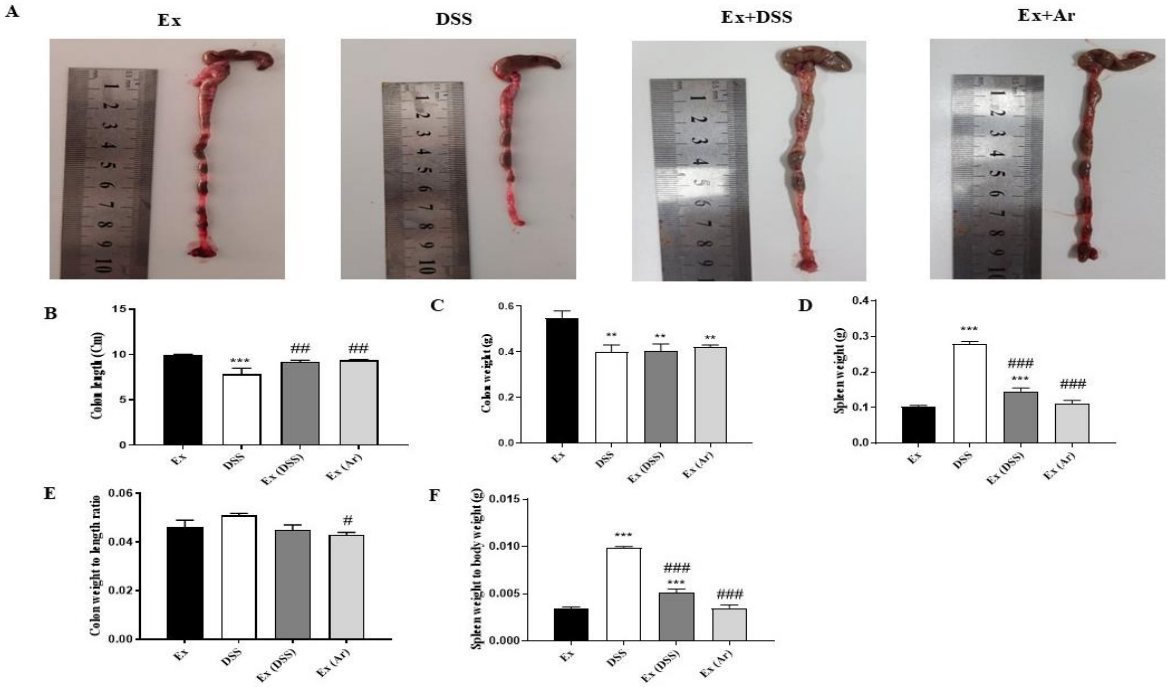

Figure 2. Colon and spleen changes in DSS-induced colitis were improved by the administration of Exercise + *Arnica montana* L. The effect of Ex and Ar on colon and spleen macroscopic image (A), (B) Colon length, (C) Colon weight, (D) Spleen weight, (E) Colon weight to length ratio, (F) Spleen weight to body weight. * p<0.05, ** p<0.01 and *** p<0.001 vs. Exercise group. # p<0.05, ## p<0.01 and ### p<0.001 vs. DSS group. Data is presented as Mean ± SEM. Abbreviation: Exercise: Ex; *Arnica montana* L. : Ar; Dextran sulfate sodium: DSS

Histopathological changes

Ar and Ex administration markedly reduced inflammatory cell infiltration and inflammation severity in DSS-induced damage (Figure 3 A and B). Key findings include decreased mucosal damage, crypt loss, and pathological changes in the Ar+Ex+DSS group compared to the DSS group ($p<0.001$), along with a significantly lower histological score (Figure 3 A-F).

Fibrosis evaluation

Fibrosis was evaluated by Masson's trichrome (MT) staining and quantification of collagen content. The results showed more collagen content in the DSS group, in which Ar, along with Ex, decreased collagen content in trichrome staining ($p<0.001$) (Figure 4A-B).

Measurement of oxidant/antioxidant markers

SOD levels significantly decreased in the DSS group compared to the Ex group ($p<0.001$), with a similar decrease in Ex+DSS. The treated group showed a significant increase in SOD ($p<0.001$). Catalase activity also decreased in the DSS versus Ex group ($p<0.001$), with a similar trend in Ex+DSS. Ar+Ex+DSS had a significant increase in MDA compared to DSS ($p<0.001$). Total thiol levels decreased in DSS versus Ex ($p<0.001$) but increased in Ex(DSS) and Ar+Ex+DSS groups ($p<0.05$ and $p<0.001$ respectively). MDA increased in DSS and Ex(DSS) compared to Ex ($p<0.001$) but decreased significantly in Ar+Ex+DSS versus DSS ($p<0.001$) (Figure 5).

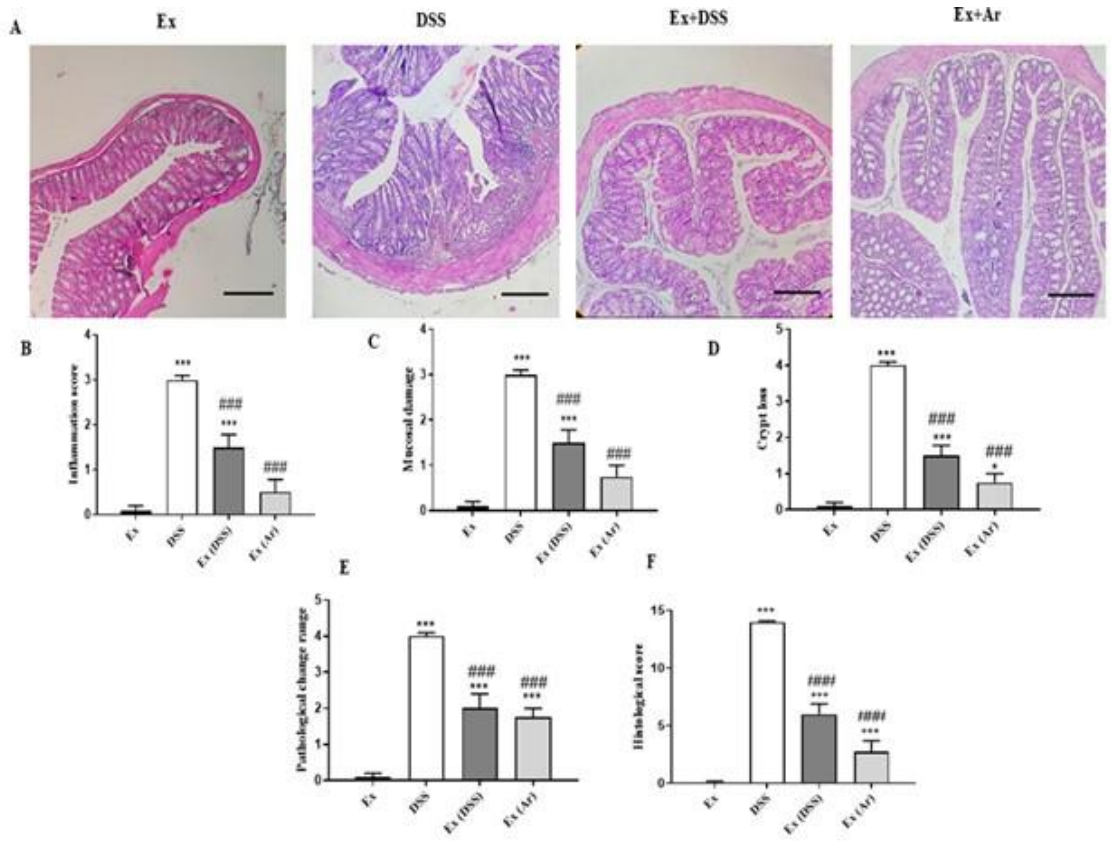

Figure 3. DSS-induced colon tissue inflammation was reduced by Exercise + *Arnica montana* L. administration. (A) Colon histological sections are shown after hematoxylin and eosin (H&E) staining of colitis tissues, indicating its inhibitory effect on the histological damage caused by DSS administration. (B) Quantifying the effect of Ex + Ar on the inflammation score, (C) mucosal damage, (D) crypt loss, (E) Pathological change range, and (F) histological score in DSS-induced colitis mice. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ vs. Exercise group. $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$ and $^{\#\#\#}$ $p<0.001$ vs. DSS group. Data were presented as Mean ± SEM. Abbreviation: Exercise: Ex; *Arnica montana* L. : Ar; Dextran sulfate sodium: DSS

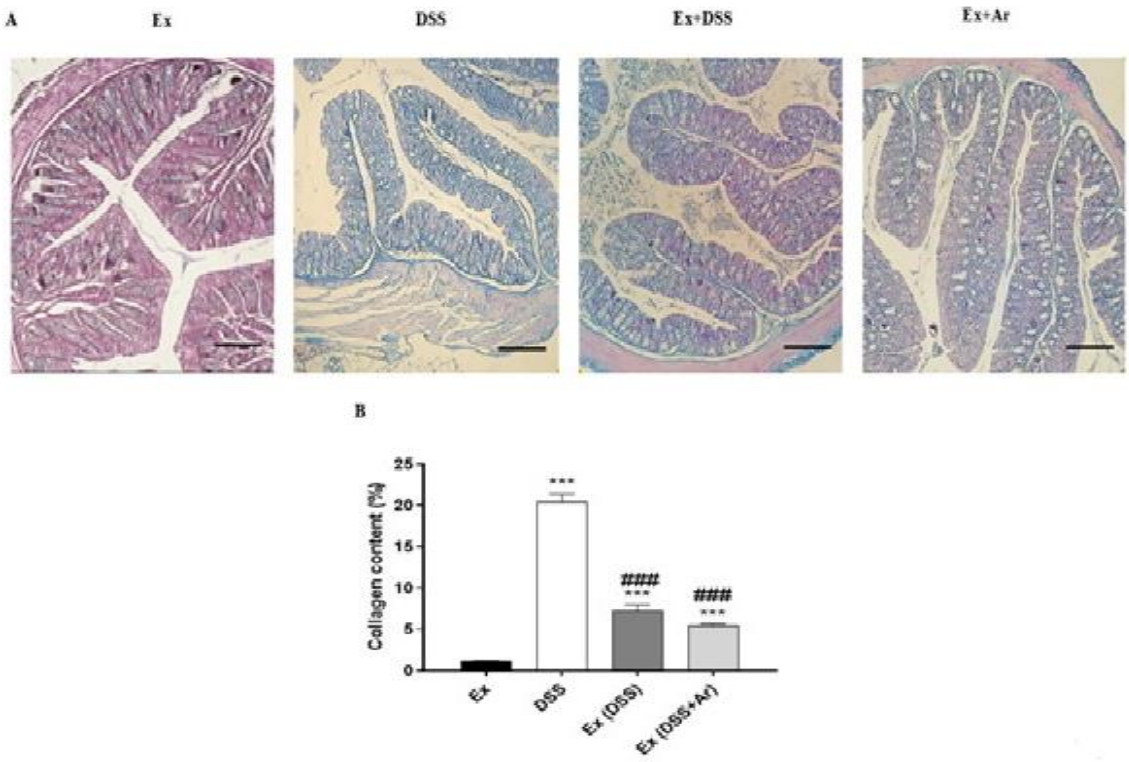

Figure 4. Exercise improved collagen content as well as DSS-induced fibrosis in colon tissues. (A) Collagen content was detected using Masson's trichrome staining. Administration of Ex + Ar significantly reduced collagen fibers. (B) The percent of collagen content is measured using Image J software. * $p<0.05$, ** $p<0.01$ and *** $p<0.001$ vs. Exercise group. $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$ and $^{\#\#\#}$ $p<0.001$ vs. DSS group. Data were presented as Mean ± SEM. Abbreviation: Exercise: Ex; *Arnica montana* L. : Ar; Dextran sulfate sodium: DSS

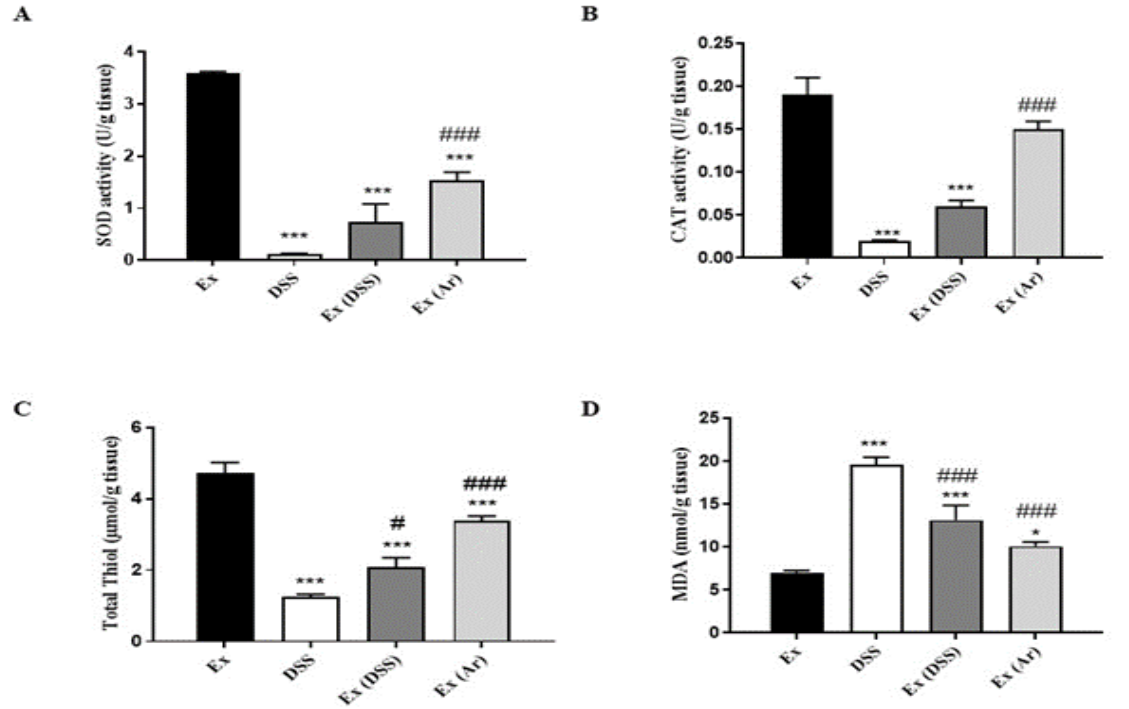

Figure 5. Exercise + *Arnica montana* L. could balance the oxidant/antioxidant in colitis mice. Changes in oxidative stress biomarkers, including (A) superoxide dismutase (SOD) activity, (B) catalase (CAT) activity, (C) total thiol content, and (D) malondialdehyde (MDA) levels.* $p<0.05$, ** $p<0.01$ and *** $p<0.001$ vs. Exercise group. $^{\#}$ $p<0.05$, $^{\#\#}$ $p<0.01$ and $^{\#\#\#}$ $p<0.001$ vs. DSS group. Data is presented as Mean ± SEM. Abbreviation: Exercise: Ex; *Arnica montana* L.: Ar; Dextran sulfate sodium: DSS

Discussion

The present study demonstrated that both exercise and *A. montana* L. significantly alleviated the clinical and histological features of DSS-induced UC (ulcerative colitis)in mice, with the combination of Ex and Ar showing the greatest protective effects. The interventions improved body weight, decreased the DAI, reduced colon shortening and spleen enlargement, ameliorated histological injury, attenuated fibrosis, and restored oxidative/antioxidative balance. These findings highlight the therapeutic potential of integrating physical activity and herbal agents in the management of UC.

In the DSS group, animals displayed marked weight loss, bloody stool, rectal prolapse, and stool inconsistency, which translated into an elevated DAI. Both Ex and Ar treatment improved these parameters, with the combination group achieving the most profound reduction. These findings are consistent with those reported by Jones et al. (Jones et al. 2015), who showed that moderate treadmill exercise reduced DAI and improved clinical status in colitis mice. Similarly, Raman et al. (Raman et al. 2022) reported that physical activity improves gastrointestinal symptoms in patients with IBD. Our results expand this evidence by demonstrating that Ar, either alone or in combination with Ex, provides additional benefits on clinical outcomes.

Colon shortening and splenomegaly are well-established indicators of colitis severity (Bertilla and Rupachandra 2025). In our study, DSS caused significant colon shortening and spleen enlargement, while Arnica and exercise, particularly in combination, improved these parameters. Comparable results were reported by Cho et al. (Cho et al. 2020) who demonstrated that regular exercise prevented colon shortening and attenuated immune-related splenomegaly in colitis models. These findings support the notion that both interventions exert anti-inflammatory and immunomodulatory effects.

Histological analyses confirmed that Ar and exercise reduced leukocyte infiltration, mucosal damage, and crypt loss, leading to significantly lower histological scores. These results are in line with (Verre et al 2024), who demonstrated the anti-inflammatory activity of Ar extracts *in vitro*, and (Macêdo et al 2004) who showed reduced cytokine expression and tissue inflammation in a UVB-induced mouse model. Importantly, our findings extend this evidence to the gastrointestinal tract, where Ar combined with Ex exhibited superior protective effects compared with either intervention alone.

Our results also revealed that DSS-induced colitis increased collagen accumulation and fibrosis in colon tissue, as detected by Masson's trichrome staining, whereas Ar and Ex markedly reduced these fibrotic changes. Chronic inflammation and dysregulated wound repair are known to drive excessive extracellular matrix (ECM) accumulation and intestinal fibrosis in UC (Derkacz et al. 2021; Kirov et al. 2019; Mortensen et al. 2019). The reduction in collagen content in our treated groups may be attributed to modulation of TGF-β(Transforming growth factor-beta) signaling, a central mediator of fibrosis (Wu et al. 2020). Previous studies have demonstrated similar anti-fibrotic effects of natural agents, such as curcumin (Robijns et al. 2022; Zhang et al. 2016) and resveratrol (Shi et al. 2017). Our study is the first, to our knowledge, to show anti-fibrotic effects of Ar in a colitis model, particularly when combined with Ex.

UC pathology involves increased oxidative stress due to the overproduction of ROS which contributes to mucosal damage and chronic inflammation (Wan et al. 2022). In our study, DSS elevated MDA levels and decreased antioxidant defenses (SOD, catalase, and total thiol), while Ar and Ex restored this imbalance. These results are consistent with (Kolahi et al 2023), who reported that exercise enhanced antioxidant enzyme activity in colitis models. Likewise, (Gaspar et al 2014)

showed that Ar exerts antioxidant and anti-inflammatory effects by inhibiting NF-κB signaling and reducing cytokines such as TNF-α(Tumor necrosis factor-alpha) and IL-6(Interleukin-6). Our findings provide *in vivo* confirmation that Ar improves oxidative stress parameters in colitis, and that its combination with Ex provides additive benefits.

While exercise has been repeatedly reported to confer beneficial effects in IBD(Inflammatory bowel disease) (Baker et al. 2022; Bilski et al. 2014; Bilski et al. 2016) . Ar has shown anti-inflammatory effects in other inflammatory models (Lass et al. 2008; Macêdo et al. 2004; Röhrl et al. 2023) . To date, no study has examined their combination in experimental colitis. Our results reveal for the first time that Ar and exercise act synergistically to attenuate clinical symptoms, histological injury, oxidative stress, and fibrosis. This integrative strategy, therefore, represents a novel therapeutic approach for UC management.

The authors acknowledge several limitations in the present study. First, in adherence to the 3Rs principles (Replacement, Reduction, and Refinement) in animal research, we intentionally limited the number of experimental groups to the minimum required to answer our primary research question. Consequently, certain control groups, or "Ar-only without exercise" group, were not included. The independent anti-inflammatory effects of Ar in colitis have been previously documented (Kawakami et al. 2011b), and the baseline physiological effects of exercise in healthy mice are well-established in the literature (Estaki et al. 2020). Therefore, the absence of an Ar-only group limits our ability to fully distinguish the independent effects of Ar from its synergistic interaction with exercise.

Second, the lack of direct measurement of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β, or molecular mediators like NF-κB and TGF-β, restricts our mechanistic understanding of the observed protective effects. Future studies should evaluate these pathways to confirm the molecular mechanisms underlying the beneficial effects of Ar and exercise in UC.

Third, the DSS-induced colitis model, despite its wide acceptance, primarily recapitulates acute epithelial injury-driven inflammation and may not fully reflect the chronic, relapsing nature of human ulcerative colitis. Thus, the generalizability of our findings to human patients requires cautious interpretation.

Finally, the absence of a standard drug control group (e.g. sulfasalazine or mesalamine) limits direct comparison of the therapeutic efficacy of our intervention with current clinical treatments. Future studies should include such comparisons to better position these findings within the translational pipeline.

In this study, we observed that the combination of Ar and exercise significantly improved disease activity, histological alterations, oxidative stress imbalance, and fibrosis in DSS-induced colitis in mice. These findings indicate that Ar, when combined with regular Ex, provides additional protective benefits against colitis compared with Ex alone. This integrative strategy represents a promising novel therapeutic approach for the management of ulcerative colitis. However, further studies with expanded experimental designs, including cytokine profiling and molecular pathway analyses, are warranted to confirm and refine these conclusions.

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Conflicts of interest

The authors had no competing interests.

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Ethical Considerations

All procedures involving the animals were approved and conducted by the Guidelines for the Use of Local Laboratory Animals.

Code of Ethics

IR.MUMS.AEC.1402.125

Authors' Contributions

Conceptualization, M.K. and F.A.; Methodology, M.K., M.S., F.A., M.A., S.E.N., K.K., M.E., A.K., H.N., S.M., A.A. and E.E.; Validation, M.K., F.A., M.S., M.A., S.E.N. and K.K.; Formal analysis, M.A., S.E.N., K.K. and M.E.; Investigation, F.A., M.A., S.E.N., M.E., A.K., H.N., S.M., A.A., E.E., K.K. and M.S.; Resources, M.K., F.A. and K.K.; Data curation, M.A., S.E.N. and E.E.; Writing—original draft preparation, M.A. and S.E.N.; Writing—review and editing, M.K., F.A., M.A., S.E.N., K.K., M.E., A.K., H.N., S.M., A.A. and E.E.; Visualization, M.S., S.E.N. and M.A.; Supervision, M.K.; Project administration, M.K. and F.A. All authors have read and agreed to the published version of the manuscript.

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