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Fidaxomicin Ameliorates Dextran Sulfate Sodium-Induced Colitis in Type 2 Diabetes Mice Model

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Abstract

Patients with Inflammatory Bowel Disease (IBD) and Type 2 Diabetes Mellitus (T2DM) are very critical illness. Since both conditions are linked with dysbiosis, therefore it is possible that inappropriate antibiotic therapy in the T2DM condition would increase the risk of IBD. With these concerns in mind, there is a clear incentive to promote narrow-spectrum antibiotics when treating both diseases together. The current study evaluated the effect of fidaxomicin, a new class of macrocyclic antibiotics, as a therapeutic approach for IBD treatment in the T2DM mice model. To achieve this goal, we first established a High-Fat Diet (HFD) induced T2DM mice model with IBD. We observed that the induction of IBD in HFD-fed mice increased susceptibility to the inflammatory environment as compared to controls. IBD induction also shortened the colon length in HFD mice when compared to Normal-Fed Mice (NFD). The overall Disease Activity Index (DAI) score was also found to be significantly higher in the HFD + DSS group of mice. Fidaxomicin treatment significantly improved the symptoms of colitis in HFD mice. The treatment further attenuated pro-inflammatory cytokine production and other physiological parameters like blood glucose and cholesterol levels. In addition, histological examinations and histological scores showed that fidaxomicin prevented colon damage in acute DSS-induced colitis in HFD mice. Moreover, fidaxomicin reshaped the gut microbiome in HFD colitis mice by increasing the relative abundance of the Firmicutes and Lactobacillus sp. In conclusion, we observed that T2DM enhanced the IBD severity, that prevented by fidaxomicin.

Keywords: IBD (Inflammatory Bowel Disease); DSS (Dextran Sulfate Sodium); Gut microbiome; T2DM (Type 2 Diabetes Mellitus); HFD (High Fat Diet); NFD (Normal Feed Diet)

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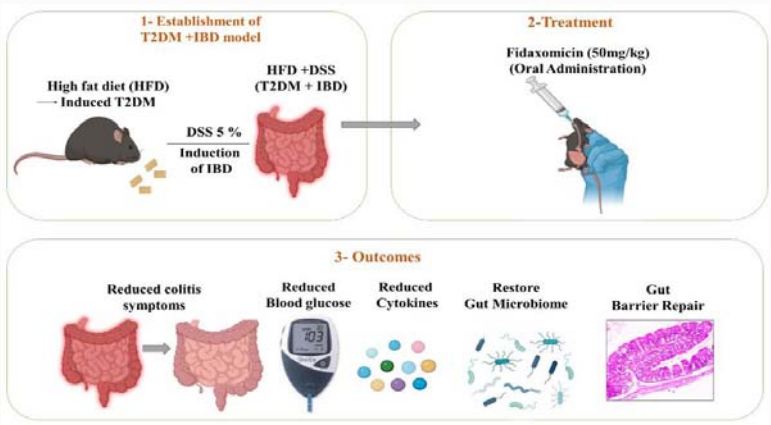

Graphical Abstract:

Introduction

Inflammatory Bowel Disease (IBD) is an autoimmune, severe inflammation disorder that affects the colon and other parts of the gastrointestinal tract [1-3]. There is a 10% to 15% increased risk of colorectal cancer in patients with IBD [4,5]. Ulcerative Colitis (UC) and Crohn's Disease (CD) are the two main clinical manifestations of IBD, which include a variety of intestinal diseases [6,7]. IBD's complexity is widely recognized, even though its exact cause is still unknown. IBD is caused by three basic factors: (1) a genetic susceptibility, (2) a dysregulated immune response, and [8]

a changed response to gut microbes [9,10]. Another independent risk factor for IBD is type 2 diabetes mellitus (T2DM), a common endocrine condition that may also affect the outcome of the disease [11,12]. However, it is still unclear how T2DM contributes to the development, preservation, and evaluation of IBD severity.

The microbiota of intestines, plays a crucial role in health and in the development of diseases such as IBD and T2DM [13]. The main mechanism, in healthy subjects, for controlling intestinal bacterial colonization is gastric acidity; however, the intestinal microenvironment can also be influenced by endoluminal temperature, competition between bacterial strains, peristalsis, and drugs that contain host defence peptides, like defensin [14]. The microbiota performs a variety of physiological tasks, including regulating intestinal lymphoid tissue, synthesizing chemicals beneficial for the tropism of colonic mucosa, inhibiting the growth of pathogenic microbes, and synthesizing amino acids. Furthermore, mucus appears to be crucial for preserving the integrity and protecting the intestinal mucosa [15,16]. Changes in the composition of the microbe are mainly driven by food and age, as well as genetic factors. There is growing evidence that dysbiosis promotes the synthesis of genotoxins and compounds linked to carcinogenesis and causes immune response dysregulation, which results in several types of diseases [17,18]. Since both IBD and T2DM are linked with dysbiosis, it could be possible that IBD risk may be higher in T2DM patients. The big question is how T2DM could alter the microbial signature, and what are complications lead to IBD.

Antibiotics are the most effective tools for controlling infections in IBD [19,20]. Clinical trials have assessed a variety of antibiotics for the treatment of IBD, including ciprofloxacin, metronidazole, the combination of both, rifaximin, and anti-tuberculous regimens [21,22]. However, inappropriate and prolonged antibiotic treatment could create antibiotic resistance, a major problem worldwide. The usage of antibiotics may also play a significant role in the development of dysbiosis [23]. In IBD, the data supporting the effectiveness of antibiotics is less clear, while using them has occasionally been demonstrated to cause remission. Promoting unique narrow-spectrum antibiotics that specifically target harmful microorganisms while ignoring the larger native microbiota is clearly motivated by these concerns [24].

Recently, fidaxomicin, a relatively novel macrocylic antibiotic, has been used to treat dysbiosis due to C. difficile with modest effectiveness [25,26]. It is a fermented product obtained from *Actinomyces dactylosporangium aurantiacum* subspecies *hamdenesis*. Previously, an in-vivo study showed that fidaxomicin maintains microbiota diversity when compared to vancomicin [27].

In this study, we investigated the severity of IBD using a T2DM mouse model. In order to induce colitis in T2D mice, we fed them a high-fat diet and then measured the resulting disease activity. We also analyzed the gut microbial signatures associated with T2DM that could enhance colitis severity. In addition, we assessed the therapeutic potential of fidaxomicin for the treatment of IBD in the T2DM mouse model [28].

Materials and Methods

Material

DSS (molecular weight, MW 40 kDa) was obtained from MP Biomedicals, Soho, OH, USA. High Fat Diet (60% kcal fat) from M.P. Biomedical Pvt. Ltd., Mumbai, India; cat. no. D12492). Bioassay Technology Laboratory ELISA kits, (IL-6, Cat no. E0049Mo), (TNF-α, Cat no. E0117Mo), (IL1β, Cat no. E0192Mo. DNA extraction kit for stool (Qiagen, Germany, Lot no. 175028918). Using Roche 454 FLX+ technology, sequencing was carried out at Medgenome in Bengaluru, India. Alpha diversity was examined using QIIME (Shannon, Simpson).

Animal model

Male C57BL/6 mice, weight 20-25 grams and 8 weeks old, were acquired from CSIR-IIIM animal facility. Mice were kept in conventional conditions (12/12 light-dark cycle, humidity at 50 ± 15%, temperature at 22 ± 2°C) at the CSIR-IIIM, Jammu. The animal study was approved by the Institutional Animal Ethical Committee of CSIR-IIIM, Jammu, India, under approval No- IAEC-284/80/2/2023.

Methods

DSS- Induced colitis model in C57BL/6 Mice: Thirty mice were randomly selected (body weight: 20g - 25g) and divided into two groups of 15 animals per group. They were fed with a Normal Feed Diet (NFD, 13% kcal from fat) and High-Fat Diet (HFD, 60% kcal from fat) for 16 weeks. Weekly measurements of blood glucose, body weight, and food consumption were made as previously mentioned [29]. The mice were further separated into 6 groups after 16 weeks: the control group (NFD), HFD group, NFD + DSS group, HFD+DSS group, NFD+DSS+ Fidaxomicin, and HFD+DSS+ Fidaxomicin.

Each group consisted of five animals per cage, and the experiment continued for 10 days following 3 days of adaptation. The two groups (NFD + DSS and HFD + DSS) were given 5% (w/v) DSS dissolved in deionized water for the first 5 days, whereas the NFD and HFD groups were maintained without DSS administration.

Following DSS-induced colitis, the following groups received daily treatment for five days: gavage water (NFD group), gavage water (HFD group), NFD + DSS group, HFD + DSS group, gavage 50 mg/kg (BW) fidaxomicin (NFD + DSS group), and gavage 50 mg/kg (BW) fidaxomicin (HFD+DSS group). On day 10, following blood sample collection, all animals were euthanized according to institutional ethical guidelines, and the colon was harvested for histological evaluation.

Evaluation of colitis symptoms: Following a prior study, weight loss percentage, stool consistency, and blood in stool were all scored to determine the Disease Activity Index (DAI) score. In order to evaluate the impact of antibiotics on the severity of IBD in T2DM mice, the determination of colon length was performed as described earlier [16].

Histopathological study: After completion of the study, animals were dissected, and the colon was taken, stored in a 10% formalin solution, and subsequently dehydrated using various ethanol grades for histopathological examination. After being preserved with paraffin wax, the tissue samples were cut into 10-µm slices, stained with Hematoxylin and Eosin (H&E) dye, and examined at 10x and 40x magnification using a light microscope (Magnus Mx21i). Clinical and histological changes in colon tissues were assessed before calculating the epithelial loss score.

Cytokine analysis: The ELISA (Enzyme-Linked Immunosorbent Assay) method is based on the principle of determing the antigen-antibody interaction, and the enzyme activity linked to antibody. The serum samples were collected from mice and analysed to quantify the levels of cytokines (TNF-α, IL-6, IL-1β) by using (Bioassay

Technology Laboratory) kits protocol [55].

Microbiome analysis: To find out the specific microbiome signature associated with fidaxomicin treatment in DSS- induced colitis in the T2DM mice, we performed microbiome analysis. The microbiome signatures were further correlated with disease severity. Further microbiome signatures were also correlated between the fidaxomicin-treated and untreated groups. In the experiment, mice were sacrificed, and fecal samples were collected from the gut (ideally the cecum or ileum) in order to perform microbiome analysis, the fecal DNA was extracted through, Stool DNA extraction kit (Qiagen).

Bacterial DNA was amplified further using universal bacterial primers that have sample-specific barcode sequences flanking the V3 and V4 sections of the 16S rRNA gene. Sequencing was performed at Med genome, using Roche 454 FLX+ technology. Using USEARCH (v7.0.1090), tags were grouped into Operational Taxonomic Units (OTUs) at 97% similarity after singletons and chimeras were eliminated. The RDP database, used to conduct a taxonomy-based analysis on a representative sequence of every OTU. R. Cluster analysis was used to build a heatmap. QIIME was used to investigate alpha diversity (Shannon, Simpson).

Statistical analysis: The mean ± SD was used to display the data. Using GraphPad Prism (Software Version 8.0), one-way ANOVA in different groups and t-tests for paired samples were used to evaluate the statistical significance of differences. At (*<p 0.05 statistically significant, **<p 0.01, Highly statistically significant and ***<p 0.001Very highly statistically significant).

Results

Fidaxomicin attenuates T2DM-associated colitis severity in mouse model

To examine the effect of T2DM on the severity of colitis, we fed C57BL/6 mice a High-Fat Diet (HFD) for 16 weeks before subjecting them to the DSS-induced colitis paradigm. As expected, Mice given the HFD increased their body weight more quickly than those given the NFD (Figure 1A). Additionally, over the duration of experiment, HFD mice blood glucose levels gradually and noticeably increased compared to NFD mice (Figure 1B). Consuming 5% DSS with distilled water induced the colitis after 5 days of HFD T2DM mice model (Figure 1C). To evaluate the effect of fidaxomicin on colitis, mice were orally administered 50 mg/kg every day, followed by DSS administration for 5 days. The untreated group showed a significant weight drop after DSS distribution, while the fidaxomicin treatment group did not appear to lose any weight until the 12th day (Figure 1C). Fidaxomicin lowers the blood glucose level in the treated group (HFD+DSS+Fidaxo) of mice when compared to the group (HFD+DSS) (Figure 1D). Similar observation was also found in NFD group, where fidaxomicin significantly lowers the blood glucose level in the treated group (NFD+DSS+Fidaxo) when compared to vehicle control group (NFD+DSS). The main sign of colon cancer and inflammatory severity is the reduction in colon length. The colon length in our experiment was not significantly affected by HFD in comparison to the NFD group. However, DSS treatment shortened the colon length in HFD mice when compared to HFD mice without DSS (Figure 2A and Figure 2B). Colon length was significantly shorter in HFD-fed mice than in NFD animals, according to a semi-quantitative assessment of the colons of DSS-treated mice, which also showed symptoms of bleeding and no discernible fecal pellet production. Fidaxomicin treatment further improves the colon length in both NFD and HFD group respectively (Figure 2A and Figure 2B). The Disease Activity Index (DAI) score was used to assess the severity of colitis (Figure 2C). Treatment with fidaxomicin may improve weight loss and blood in stools. Compared to the untreated group, the DAI score of the fidaxomicin-treated group was significantly lower. The HFD+DSS+Fidaxo group's DAI score was considerably lower ($p<0.05$) than that of the HFD+DSS group (Figure-2C).

Fidaxomicin attenuates alleviated colon histological damage inT2DM associated colitis mouse model

This study examines the effects of fidaxomicin as a treatment for diet-induced colitis using histological sections of mouse colon tissues stained with Hematoxylin and Eosin (H&E) to evaluate intestinal shape and inflammation under various treatment conditions. The histological examination revealed that NFD and HFD groups displayed normal colonic histology with continuous, intact mucosa and formed tubular glands, lined by goblet cells (Figure 3A, 3B). However, a focal area of crypt loss and epithelial disruption was observed in HFD (Figure 3C, 3D). The (NFD+DSS and HFD+DSS) groups exhibited diffuse crypt loss and disruption of epithelium,

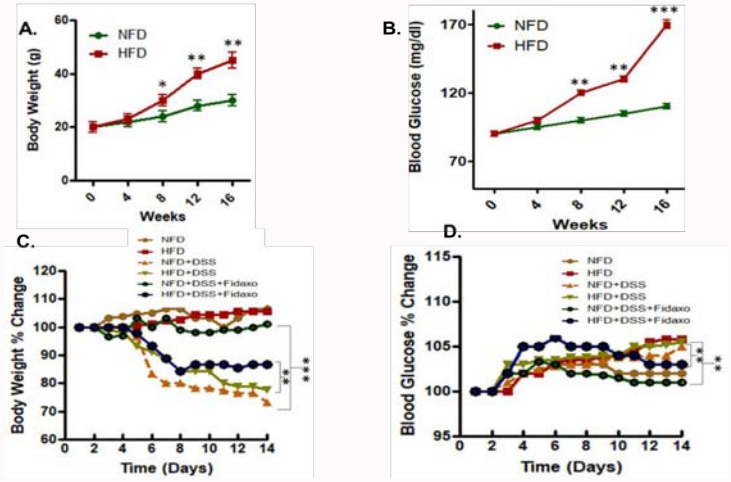

Figure 1: (A). The weight of mice fed a High-Fat Diet (HFD) compared to a Normal-Fat Diet (NFD) is shown. **(B)** The NFD and HFD groups' blood glucose levels. **(C)** Changes in body weight after 5% DSS administration in mice groups. **(D)** Changes in blood glucose levels after 5% DSS administration in mice groups. (*<p 0.05 statistically significant, **<p=0.01, Highly statistically significant and ***<p=0.001 very highly statistically significant).

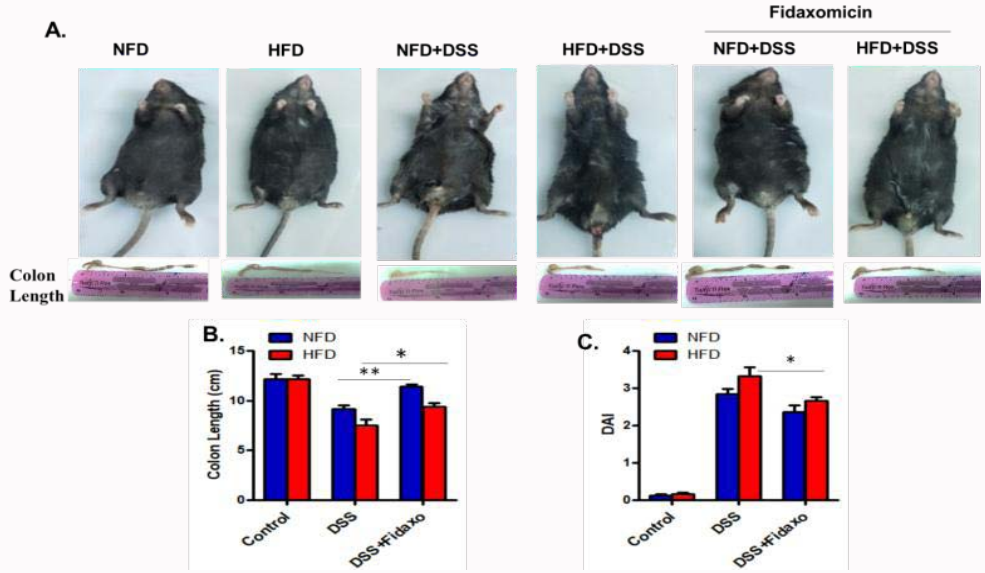

Figure 2: (A). Colon length measurements of mice treated with Fidaxomicin, DSS-induced colitis, and Control (NFD + HFD). **(B)** Colon length (cm) in the DSS + Fidaxomicin, DSS, and Control groups. **(C)** The Disease Activity Index (DAI) for the Control, DSS, and DSS + Fidaxomicin groups shows the severity of the disease and the response to treatment. (*<p 0.05 statistically significant, **<p 0.01 Highly statistically significant).

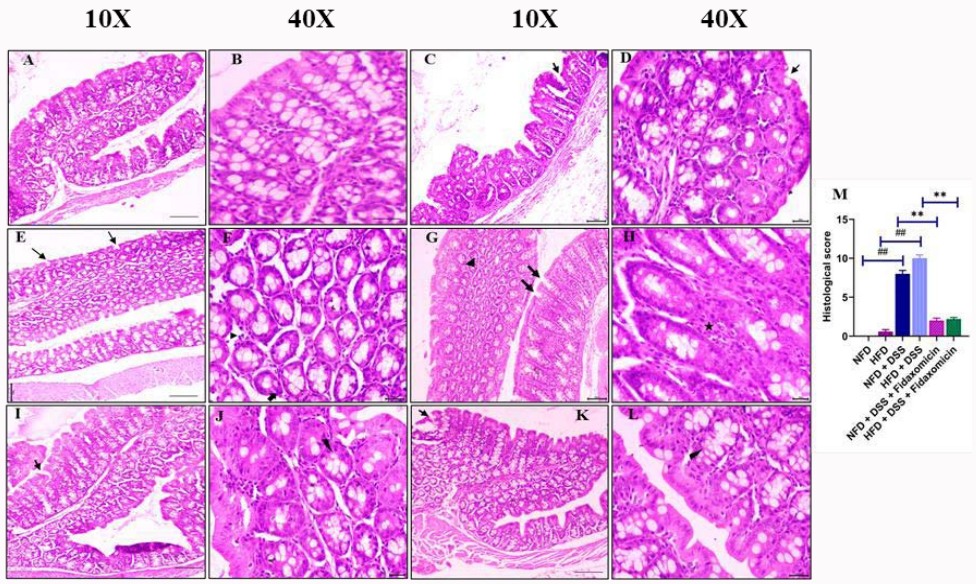

Figure 3: Represent that Haematoxylin and Eosin (H&E)–stained sections of mouse colon showing histological changes under different dietary and treatment conditions. The NFD and HFD groups exhibited normal colonic architecture with intact mucosa, well-formed tubular glands, and goblet cells, although focal crypt loss and epithelial disruption were observed in the HFD group (A-D). DSS-treated groups (NFD+DSS and HFD+DSS) showed marked colonic injury characterized by diffuse crypt loss, epithelial disruption, goblet cell depletion, intraluminal cellular debris, mononuclear cell infiltration, and architectural distortion, indicative of colitis (E-H). Fidaxomicin treatment (NFD+DSS+Fidaxo and HFD+DSS+Fidaxo) markedly improved histoarchitecture, with restoration of epithelial integrity and goblet cells and minimal distortion (I-L). Histological scores were significantly increased in DSS-treated groups compared with respective controls, while fidaxomicin significantly reduced colitis severity (**p<0.01), demonstrating its protective effect against DSS-induced colitis (M).

multifocal areas of depletion of goblet cells, presence of intraluminal cellular debris, multifocal areas of infiltration of mononuclear cells, and a moderate degree of distortion in architecture indicative of colon inflammation (Figure 3E-3H). Compared to DSS-induced colitis groups, fidaxomicin-treated groups (NFD+DSS+Fidaxo and HFD+DSS+Fidaxo) displayed normal histoarchitecture with minimal distortion of epithelium and restoration of goblet cells (Figure 3 I-L). The histological score of DSS-induced colitis groups (NFD+DSS and HFD+DSS) were significantly high compared to the control groups (NFD and HFD), respectively. The fidaxomicin-treated groups (NFD+DSS+Fidaxo and HFD+DSS+Fidaxo) showed a statistically significant decrease in the histological score compared to (NFD+DSS and HFD+DSS) groups, indicating the protective effect of fidaxomicin on DSS-induced colitis (Figure 3M). The colon sections (10 µm) were stained with Hematoxylin and Eosin (H&E) and viewed at 10x and 40x objectives of the light microscope (Magnus, Mx21i). Farther the histological parameters were scored on a scale of 0 - 4 to grade the severity of the colitis induced by DSS.

Table 1: Represent that, the score of all histological features was used to reflect the colon sections' histological score.

Scores	NFD	HFD	NFD+DSS	HFD + DSS	NFD + DSS + Fidaxomicin	HFD + DSS + Fidaxomicin
Edema	0	0	0	0	0	0
Crypt Damage	0	1	3	3	1	1
Architecture disorders	0	1	3	3	1	2
Leucocyte Infiltration	0	0	2	2	0	0
Inflammation	0	0	2	3	0	0

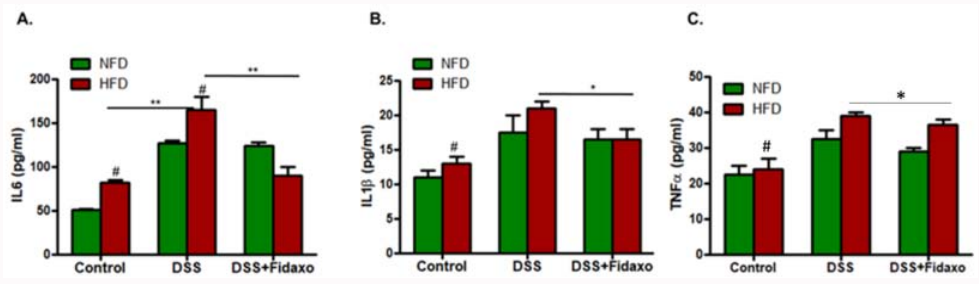

Figure 4: (A) IL-6 levels (pg/ml) were significantly higher in the DSS-treated group than in the controls, whereas fidaxomicin treatment (DSS+Fidaxo) significantly lowered IL-6 levels. **(B)** IL-1β levels (pg/ml) were higher in the DSS-treated group than in the controls; fidaxomicin treatment attenuated this increase; and **(C)** TNF-α levels (pg/ml) were significant higher in the DSS+Fidaxo group and the DSS+Fidaxo group showed a lower reduction, indicating improved inflammatory status. (*<p=0.05 statistically significant, **<p=0.01Highly statistically significant).

The scorings are as follows, edema: 0 - absent, 1 - focal, 2 - zonal, 3 - diffuse, 4 - extensive; crypt damage: 0 - none, 1 - focal, 2 - multifocal, 3 - diffuse, 4 - extensive; architecture damage: 0 - normal, 1 - focal/minimal, 2 - zonal/mild, 3 - diffuse/moderate, 4 - extensive/severe; Inflammatory cell infiltration: 0 - None, 1 - focal, 2 - multifocal/zonal, 3 - diffuse/severe and Inflammation: 0 - none, 1 - minimal, 2 - mild, 3 - moderate, 4 - severe. The histological score of colon sections was represented as the sum of scores of all histological parameters. The data were analyzed by Mann-Whitney test using GraphPad Prism 8.0 and represented as mean ± SE at p value (<0.01) (Table. 1).

Fidaxomicin decreased the levels of inflammatory cytokines in the T2DM-associated colitis mouse model

An ELISA was used to evaluate the protection conferred by fidaxomicin against colitis through modulation of inflammatory cytokines (Figure 4). Pro-inflammatory cytokine levels were significantly greater in the HFD-treated animals than in the NFD group ($p<0.05$). After the DSS administration, we observed that the level of IL-6 and IL-1β was significantly increased compared to control group ($p<0.01$). Interestingly, fidaxomicin significantly reduced the IL-6 and IL-1β in HFD+DSS group, suggesting that fidaxomicin decreased the levels of inflammatory cytokines in the T2DM-associated colitis mice model (Figure 4A,4B). Although fidaxomicin also reduced the level of TNF-α, the data was not significant (Figure 4 C).

Modulates the gut microbiota in the T2DM-associated colitis mice model

The high-throughput Illumina MiniSeq was used to sequence the microbiomes of the animals in each group (feces). The 16S rRNA9V4 gene's sequencing produced 5,46,676 reads, or 31,849 reads on average per sample. Moreover, according to quality control protocols, 1.2% of readings were eliminated from all samples as a result of quality filtering. The most common bacteria identified at the phylum level include *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Patescibacteria* (Figure 5A). In the composition of gut bacteria from a Normal Feed Diet (NFD), Firmicutes are the dominant group, while Bacteroidetes are found in minimal numbers. A High-Fat Diet (HFD) causes *Bacteroidetes* and *Proteobacteria*, which are typically associated with dysbiosis, to grow and *Firmicutes* to decline. *Proteobacteria* are more common in both NFD+DSS and HFD+DSS, suggesting a greater microbial imbalance. In the groups HFD+DSS+Fidaxo and NFD+DSS+Fidaxo, the balance of *Proteobacteria* decreases while *Firmicutes* begin to increase again. The most commonly identified bacteria at the genus level include *Lactobacillus*, *Prevotellaceae*, *Lachnospiraceae*, Uncultured Bacterium, *Lachnoclostridium* NK4A136, Bacteroides, *Lachnoclostridium*, uncultured variants, *Rikenellaceae*, and *Ruminococcaceae* (Figure 5B). There are substantial amounts of *Lachnospiraceae* and *Ruminococcaceae* in the NFD Balanced families. A reduction in beneficial *Lachnospiraceae/Ruminococcaceae* and an increase in *Enterococcaceae* and *Staphylococcaceae* (associated with dysbiosis) were observed with HFD. An escalating imbalance, marked by the predominance of pathogenic families, was observed in NFD+DSS/HFD+DSS. By reducing harmful families and enhancing beneficial ones, the NFD+DSS+Fidaxo and HFD+DSS+Fidaxo groups reverse this trend. The most prevalent bacteria identified at the species level are shown in (Figure 5C). In the NFD group, there was a higher count of *Lactobacillus* and a lower presence of other bacteria, whereas the HFD group shows a decrease in *Lactobacillus* and an increase in Enterococcus and *Staphylococcus* bacteria. Pathogenic families like *Staphylococcus* thrive when there is a more pronounced imbalance between NFD+DSS and HFD+DSS. The groups NFD+DSS+Fidaxo and HFD+DSS+Fidaxo succeed in restoring *Lactobacillus* and other beneficial genera while reducing. The analysis of alpha diversity showed a significant disruption in the microbiome due to diet and DSS treatments. Mice on the Normal-Feed Diet (NFD) exhibited the highest levels of richness and evenness, indicating a stable gut microbiome. The NFD combined with DSS demonstrated only a slight decrease in diversity. On the other hand, mice on a High-Fat Diet (HFD) showed diminished alpha diversity, suggesting diet-induced dysbiosis. The most significant reduction in microbial richness occurred in the group receiving both HFD and

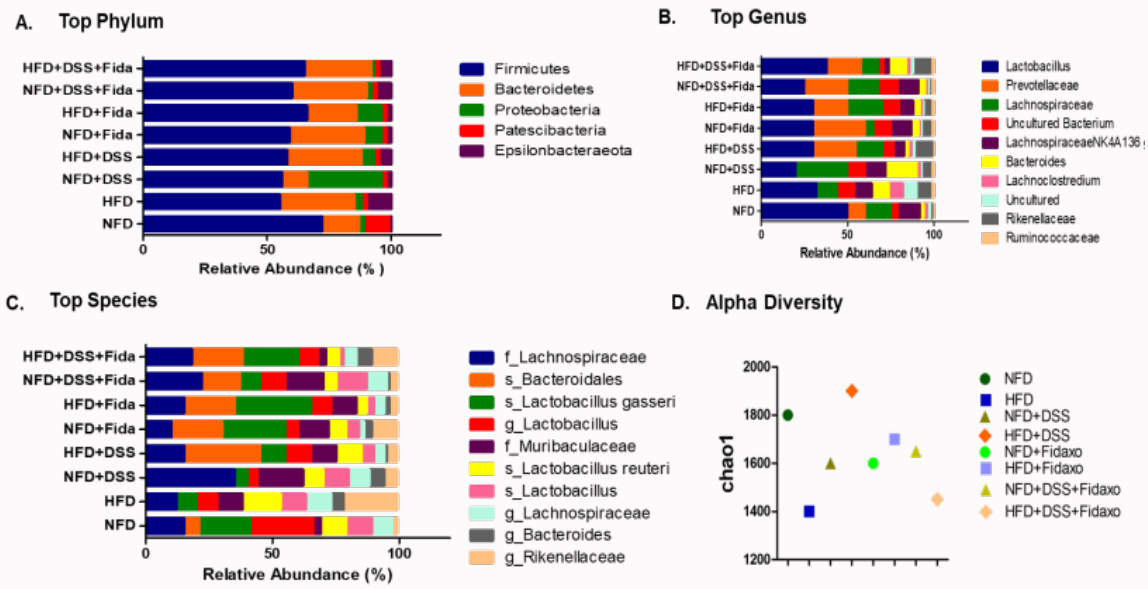

Figure 5: (A). Relative abundances of bacterial phyla level. **(B)** Relative abundances of bacterial genus level among five mice groups. **(C)** Relative abundances of bacterial Species class among five mice groups. **(D)** Alpha diversity indices for gut microbes measure microbial variety in a sample.

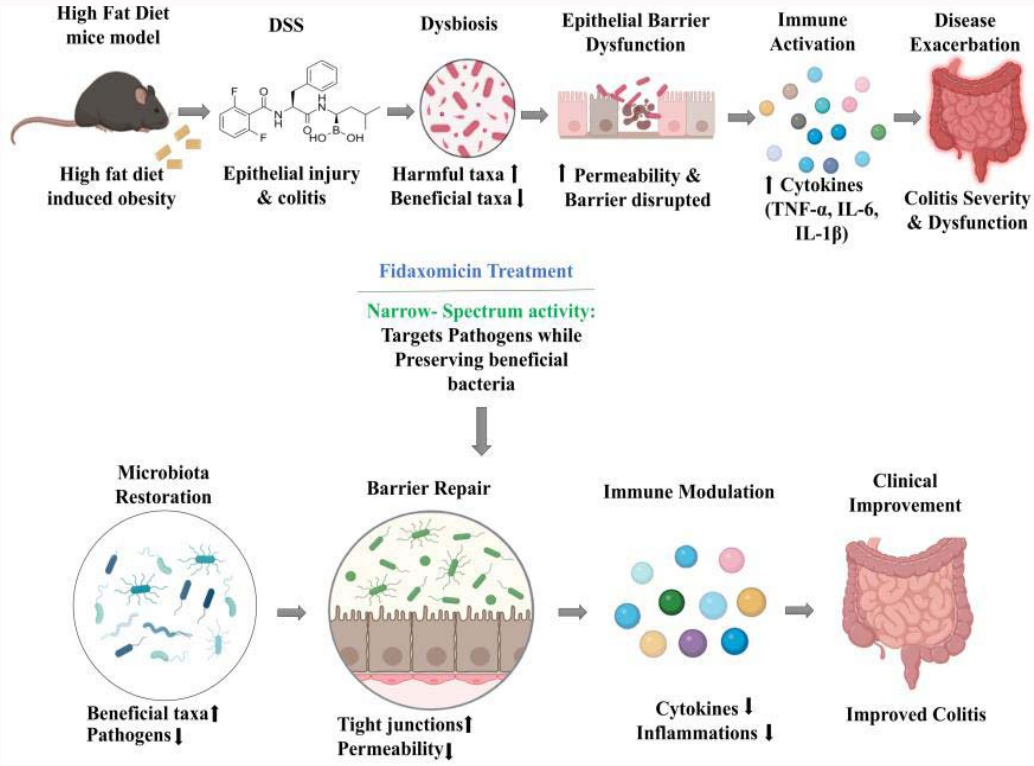

Figure 6: High-Fat Diet (HFD) induces gut dysbiosis, epithelial barrier disruption, and altered metabolite profiles leading to intestinal dysfunction, while treatment with Fidaxomicin selectively targets pathogenic bacteria to restore microbial balance, improve barrier integrity, normalize metabolites, and promote intestinal health.

DSS, where inflammation combined with a high-fat diet severely affected community structure. In summary, the combination of HFD and DSS resulted in the most intense dysbiosis (Figure 5D).

Discussion

Obesity is a major contributor to the development of Chronic illnesses, including diabetes, hypertension, and cardiovascular disease [30,31]. The consumption of an HFD has been shown to induce inflammation in the intestines and allow microbial end products in mice [32,33]. An HFD exacerbates the severity of colitis in experimental mouse models [34] and promotes the initiation of colon cancer [35]. Antibiotic therapy in patients with IBD and comorbid T2D may disrupt the gut microbiota, exacerbate dysbiosis, and influence both intestinal inflammation and metabolic regulation, underscoring the need for cautious use and personalized management strategies [36,37]. Broad-spectrum antibiotics disrupt a wide range

of commensal bacteria, leading to reduced microbial diversity, impairment of colonization resistance, and increased risk of disease flares, whereas narrow-spectrum agents target specific pathogens with less collateral damage to beneficial taxa. Evidence suggests that the incidence of IBD flares inclined toward broad-spectrum antibiotics as compared to narrow-spectrum antibiotics, supporting the concept that targeted therapies may have a relatively smaller impact on disease exacerbation. Furthermore, pathogen-selective or narrow-spectrum antibiotics have been shown in animal studies to preserve microbiome composition and abundance better than broad-spectrum regimens, thereby minimizing dysbiosis and its downstream effects on inflammation and metabolic homeostasis [38,39]. In continuation of efforts to minimize broad-spectrum antibiotic induced dysbiosis and its negative effects on gut microbiota and host immunity, we utilized fidaxomicin, a narrow-spectrum antibiotic, as an intervention in IBD with T2DM mice model. Although fidaxomicin is primarily approved for *C. difficile* infection and has not been extensively studied in IBD beyond this indication, retrospective cohort studies demonstrate that it is effective and safe for treating *C. difficile* infection in patients with Crohn's Disease (CD) or Ulcerative Colitis (UC) and may influence short-term IBD outcomes without substantial adverse events [40]. Our research demonstrates that the HFD-fed mice's recovery from colitis symptoms was sped up by fidaxomicin treatment, as evidenced by reduced body weight loss and a lower fecal blood score during the recovery phase. Supporting our findings, Rifaximin decreased the severity of colitis in DSS-induced colitis mice by lowering body weight loss, fecal blood score, and subsequent DAI score [41-43]. DSS induces damage to the mucosa and underlying tissue in the mouse gut, mimicking the inflammatory reaction observed in human Ulcerative Colitis (UC) [44,45]. Colitis is defined by the activation and absorption of immune cells, such as neutrophils and monocytes, a mechanism controlled by cell adhesion molecules, cytokines, and chemokines [46,47]. In the current investigation, fidaxomicin decreased the elevated blood levels of IL-1β, TNF-α, and IL-6 that were caused by DSS induction in mice given a high-fat diet. Smiler to our finding, rifaximin reduced serum TNF α and IL 6 levels in LPS induced inflammation models in mice, supporting its systemic cytokine modulating activity [48].

While HFD feeding increased body weight, blood glucose levels, disease activity index, and reduced colon length, these changes were not statistically significant compared with normal-fat diet controls, as shown in a previous study [49,50]. Notably, microbiota analysis revealed that HFD and DSS induced pronounced dysbiosis, characterized by increased *Bacteroidetes* and *Proteobacteria* and reduced *Firmicutes* abundance, whereas fidaxomicin partially restored microbial homeostasis by increasing beneficial taxa such as *Lactobacillus*, *Ruminococcaceae*, *Lachnospiraceae*, and *Ruminococcaceae* [51-53]. while suppressing pathogenic *Enterococcus* and *Staphylococcus*, accompanied by improved alpha diversity. Collectively, these data indicate that fidaxomicin provides dual therapeutic benefits by alleviating colonic inflammation and re-establishing gut microbial balance in a T2D-associated IBD model, highlighting its promise as a microbiota-sparing strategy for managing the complex interplay between metabolic dysfunction and intestinal inflammation [54,55].

Conclusion

The current study, revealed that narrow-spectrum macrocyclic antibiotic fidaxomicin has major therapeutic benefits for the treatment of (IBD) with Type 2 Diabetes Mellitus (T2DM). T2DM animals fed a High-Fat Diet (HFD) were prone to DSS-induced colitis, which was marked by a higher disease activity index, a shorter colon, and worsened inflammatory reactions. Fidaxomicin treatment notably alleviated these clinical symptoms by lowering pro-inflammatory cytokine levels, managing metabolic factors such as blood glucose and cholesterol levels, and restoring colon histology. Furthermore, fidaxomicin successfully altered the composition of the gut microbes, particularly by expanding the relative abundance of beneficial *Lactobacillus species* and *Firmicutes*, thereby reversing the dysbiosis brought on by DSS and HFD (Figure 6). These results confirm that fidaxomicin has potential as a dual-acting treatment approach for individuals with comorbid T2D and IBD by indicating that it not only reduces colonic inflammation but also restores gut microbial balance. Fidaxomicin offers a microbiome-preserving strategy that may get around the drawbacks of broad-spectrum antibiotics by specifically targeting harmful bacterial populations without upsetting beneficial microbes. Overall, the study established fidaxomicin as a promising option for the treatment of metabolic inflammation-associated colitis and emphasizes the critical role of microbiota-targeted therapy in enhancing intestinal and metabolic health.

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