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CLINICAL TRIAL REPORT

Fenofibrate as an Adjunct Therapy for Ulcerative Colitis: Targeting Inflammation via SIRT1, NLRP3, and AMPK Pathways: A Randomized Controlled Pilot Study

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Background: Ulcerative colitis (UC) is an idiopathic chronic inflammation of colonic and rectal mucosa. The peroxisome proliferator-activated receptor α (PPARα) has been identified as having protective effects in UC.

Aim: The study aimed to investigate the efficacy of fenofibrate, a PPARα agonist, in UC.

Methods: A total of 70 patients with mild to moderate UC were allocated randomly and assigned to two groups (n = 35 each) from Gastroenterology Department, Faculty of Medicine, Menoufia University. The mesalamine group received a placebo along with 1 g of mesalamine three times daily, while the fenofibrate group received 1 g of mesalamine three times and fenofibrate 160 mg once daily. The study duration was for six months. A gastroenterologist assessed patients by non-invasive Partial Mayo Score (PMS) and the Inflammatory Bowel Disease Questionnaire (IBDQ) to evaluate clinical response and remission. The serum levels of silent information regulator 1 (SIRT1), NOD-like receptor protein 3 (NLRP3), and adenosine monophosphate activated protein kinase (AMPK), as well as fecal calprotectin levels were examined to determine the biological effect of fenofibrate.

Results: After treatment, the fenofibrate group showed statistically significant reductions in PMS ($p = 0.044$) and improved digestive domain of IBDQ ($p = 0.023$). Additionally, there were significant decreases in serum NLRP3 ($p = 0.041$) and fecal calprotectin ($p = 0.035$), along with significant increases in SIRT1 ($p = 0.002$) and AMPK ($p = 0.0003$). The fenofibrate group also had higher response and remission rates compared to the mesalamine group.

Conclusion: Fenofibrate may be a promising adjunct for improving clinical outcomes, quality of life, and modulating inflammation in mild to moderate patients with UC.

Trial Registration Identifier: NCT05781698.

Keywords: Ulcerative colitis, Fenofibrate, Mesalamine, NLRP3/AMPK, PPARα

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Introduction

Worldwide, the incidence and prevalence of ulcerative colitis (UC) are increasing, leading to a significant medical and economic burden on society.[1] As a result, a primary focus for improving UC outcomes is the exploration of therapeutic targets and diagnostic biomarkers. Although the exact cause of UC remains unknown, current research indicates that UC is mainly driven by a combination of immune system dysfunction, genetic predisposition, epithelial barrier abnormalities, and environmental factors.[2] Among these factors, an impaired immune system is considered the most critical in the development and progression of UC.[3] Both adaptive and innate immune responses significantly influence gut inflammation.[4] When the tolerance mechanisms of the intestinal barrier are disrupted, chemokines are released, leading to the infiltration of local immune cells.

The intestinal mucus barrier is the main defense mechanism for intestinal epithelial cells against bacterial invasion at the host-bacterium interaction.[5] Studies on animals and data from patients have demonstrated a strong correlation between the severity of UC and a compromised mucus barrier.[6] The depletion of the mucus barrier is the sole independent risk factor that can reliably predict relapse in patients with UC, establishing it as the most significant predictor. Additionally, the regulation of inflammatory cytokine expression is linked to the nuclear transcription factor peroxisome proliferator-activated receptor gamma (PPARγ).[7] In pathological circumstances, it is also known to encourage mucus secretion to remove harmful microorganisms or poisons.[7] Significantly, it has been demonstrated that PPARγ influences the energy consumption of colonocytes and the intestinal microbiome's availability of oxygen, hence impacting the interactions between the host and microbiota.[7,8] Thus, it is possible that PPARγ, which serves as the mucus barrier's central coordinator, could be a good target for the creation of potent anti-UC drugs.[7] Till now in literature, there are no sufficient clinical trials regarding the effect of PPARγ agonist in UC. It has been noted that PPARγ agonist such as rosiglitazone improved disease activity and clinical response in patients with mild to moderate UC.[9] Only few experimental research and review articles highlighted the role of PPARγ agonist in inflammatory bowel diseases.[10,11] Silva et al, reported that a novel topical PPARγ agonist, AS0002, induces PPARγ activity in ulcerative colitis mucosa and prevents and reverses inflammation in induced colitis models.[12] There is an interplay between PPAR-γ and PPAR-α as transcription factors in the intertwining of several metabolic pathways and regulating lipid metabolism. Activation of PPAR-γ and PPAR-α rescues body mass and insulin resistance, induces beige adipocytes with thermogenic activity increased energy expenditure, reduces liver steatosis. PPAR-γ and PPAR-α synergism modulate the gut-adipose tissue axis and inflammation.[13] However, there are some distinct functions of each type. PPAR-α regulating fatty acid oxidation and energy homeostasis in the liver, while PPAR-γ is primarily involved in adipocyte differentiation, lipid storage, and insulin sensitivity in adipose tissue.[14] Upon activation of PPAR-α, it diminishes inflammatory signaling pathways involving AMPK,[15] toll-like receptor 4 (TLR4),[16] SIRT1,[17] and nuclear factor kappa-B (NF-κB).[18]

A preserved fuel-sensing enzyme, adenosine monophosphate (AMP)-activated protein kinase (AMPK) is a crucial regulator of cellular metabolism. It increases the uptake of glucose and fatty acids and initiates the oxidation process to optimize cellular energy utilization.[19] Furthermore, it is thought that AMPK activation counteracts a variety of cellular abnormalities, including inflammatory processes, insulin resistance, and aberrant accumulation of fat.[20]

Due to the over-activation of caspase-1 and IL-18, multiprotein complexes known as inflammasomes are directly implicated in the onset of inflammation.[21,22] The inflammasome development process involves five potential pattern recognition receptor (PRR) candidates. Absent-in-melanoma 2 (AIM2), Leucine-rich repeat (LRR)-containing proteins (NLR) family (NLRP1, NLRP3), pyrin, nucleotide-binding oligomerization domain (NOD), and other known PRRs like NLRP2, NLRP6, NLRP7, and NLRP12 are among these members.[23] NLRP3 inflammasome recruitment and stimulation are implicated in a number of inflammatory diseases, including UC.[24] It is reported that there is crosstalk between AMPK, mTOR, and NLRP3 inflammasome signaling since AMPK stimulation reduces NLRP3 activity.[25]

Mesalamine is the first-line treatment for mild-to-moderate UC. To produce a therapeutic effect, it must be released locally at the level of the inflammatory mucosa.[26] Mesalamine, through a PPAR-gamma-dependent mechanism, inhibits inflammatory mediators and has anti-inflammatory and apoptotic effects.[27,28] El-Haggar et al, reported that mesalamine significantly reduced inflammatory markers such as IL-6, tumor necrosis factor alpha (TNF-α), decreased adhesion molecules, upregulated tight junction proteins and improved clinical response and remission in patients with mild and

moderate UC.[27] In cells, mesalamine phosphorylates AMPK and its corresponding substrate, acetyl-CoA carboxylase. The existence of inflammatory cytokines did not affect mesalamine-induced AMPK activation.[29]

Fibrates, which are specific pharmacological agonists of PPARα, are commonly prescribed for managing hypercholesterolemia and hypertriglyceridemia. In addition to their metabolic effects, fibrates have been reported to possess anti-inflammatory properties, including the suppression of pro-inflammatory cytokine production.[30] Fenofibrate, a widely used PPAR-α agonist, is effective in lowering triglyceride (TG) levels in clinical practice.[31] Numerous studies have demonstrated that fibrates exhibit anti-inflammatory effects both in vitro and across various disease models.[32,33] Treatment with fenofibrate in experimental colitis has been shown to reduce the expression of genes associated with inflammatory cytokines in the colon, delay the onset of colitis, and lower the colonic histopathology score.[32,34]

Considering these data, the study hypothesis was that Fenofibrate, as a PPARα agonist, will significantly improve clinical outcomes and reduce inflammation in patients with mild to moderate ulcerative colitis compared to mesalamine alone. Therefore, the current study aimed to assess the effects of fenofibrate as an adjunct therapy for patients with mild to moderate UC and to investigate its underlying mechanistic pathways through AMPK/NLRP3 and SIRT1.

Patients and Methods

Seventy patients who met the inclusion criteria were recruited from the internal medicine department of Menoufia University between March 2023 and April 2024. This study was approved by the Menoufia University Faculty of Medicine's Institutional Review Board (approval code 1–2023INT.13). The Helsinki Declaration and its 1964 revisions were followed in the study's design and methodology. The patients were made aware that they could leave the trial at any moment. The type of exposure and randomization were kept blinded from both patients and doctors.

Study Design

The safety and effectiveness of fenofibrate + mesalamine in the treatment of UC were assessed in this double-blind, randomized, controlled clinical study. Under the NCT05781698 registration number, the trial was registered at WWW.ClinicalTrials.gov in 2023.

As per the CONSORT flow diagram presented in Figure 1, a random allocation of the patients was made into two groups (n = 35 each). For the randomization phase, randomly permuted blocks were selected using a computer random number generator. Seventy patients (n = 70) who met the requirements for participation and gave written, informed consent were split into two groups at random.

Mesalamine group: For six months, patients in this group received 1 g mesalamine tablets t.i.d. (Pentasa® 500 mg, Multi Pharm, Egypt) plus placebo. This was considered as the control group.

Fenofibrate group: For six months, patients received 160 mg of fenofibrate tablets once daily (Lipanthyl® Supra 160 mg, Mina Pharm, Abbot Laboratories, Egypt) plus 1 g of mesalamine tablets (Pentasa® 500 mg, Multi Pharm, Egypt) t.i.d. This is considered as the fenofibrate group throughout the manuscript.

Inclusion Criteria

Patients between the age of eighteen and sixty, both male and female, were included in this study. Patients naïve or on mesalamine therapy. This clinical study included only patients who were diagnosed with mild to moderate UC according to partial mayo score (PMS) index.

Exclusion Criteria

Patients receiving systemic or rectal steroids, immunosuppressive medications, or having severe grade of UC were excluded. Renal or hepatic patients were not included. Individuals who had undergone a full or partial colectomy or had a history of colorectal cancer were also ineligible. Lastly, patients with musculoskeletal diseases, hyperlipidemic patients, pregnant, and breastfeeding women were excluded.

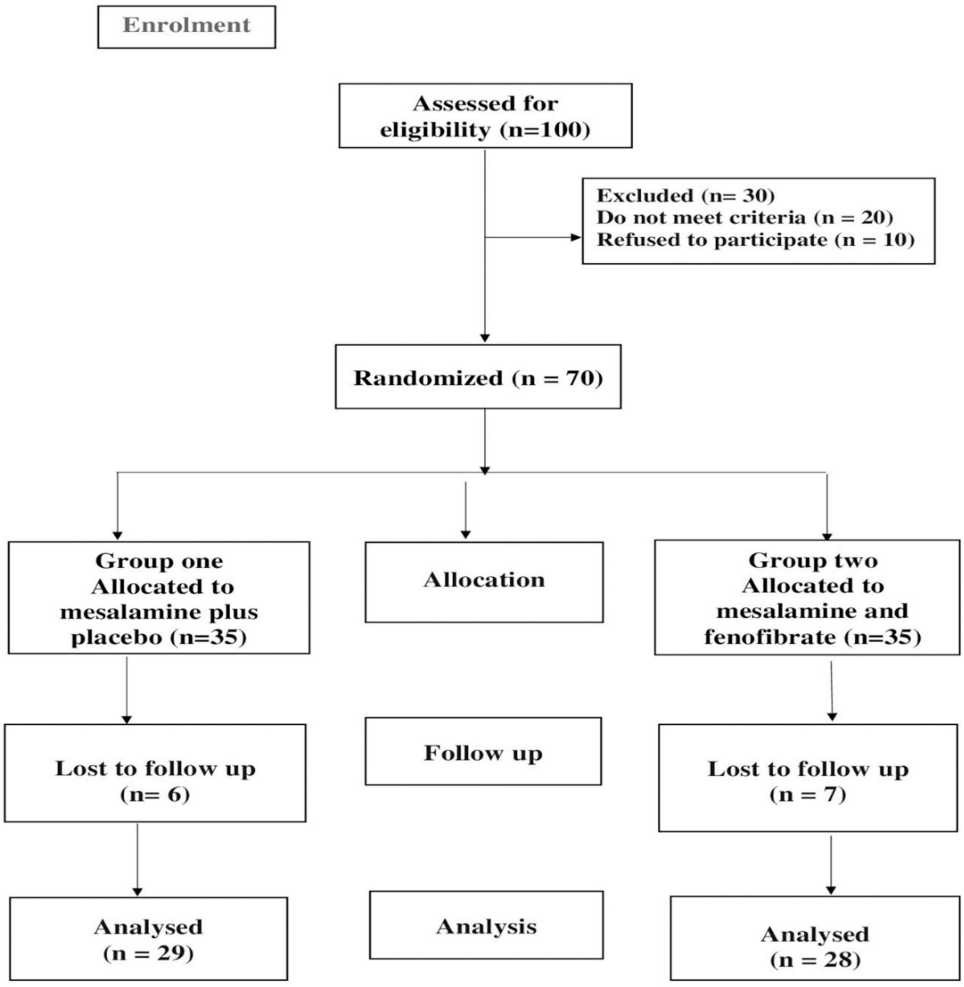

Figure 1 CONSORT diagram showing the flow of patients during the study.

Sample Size Calculations

There was no previous research to determine the actual effect size of fenofibrate treatment on change in PMS. This research was intended to be a pilot one and according to Teare et al,[35] who recommend a sample size of 35 in each group for small to medium effect size to minimize combined size. A sample size of 35 patients was randomized in each group, supposing α-error = 0.05 (2-tailed) and a power of 0.80, with a 20% dropout rate.

Study Protocol

In addition to eligibility checks, UC patients received thorough physical, mental, and psychological exams. Patients were randomized to receive either mesalamine tablets and a placebo or mesalamine tablets in addition to fenofibrate tablets (the fenofibrate group). The patients also received nutritional and lifestyle counseling.

The selected dose for mesalamine is 1 g t.i.d[36,37] and for fibrate is 160 mg[38] were defined based on previous studies. Placebo tablets were manufactured by Zeta Pharma Company and had the same look as fenofibrate tablets.

Study Outcomes

Primary Outcomes

The primary outcome of the study is the change in the PMS, which assesses clinical response and remission in patients with mild to moderate ulcerative colitis.

Secondary Outcomes

The secondary outcomes include changes in the Inflammatory Bowel Disease Questionnaire (IBDQ-32) scores, serum levels of NOD-like receptor protein 3 (NLRP3), Sirtuin 1 (SIRT1), and adenosine monophosphate-activated protein kinase (AMPK), as well as fecal calprotectin levels, which collectively evaluate the biological effects of fenofibrate treatment.

Follow-Up

To follow up with patients, monthly meetings and weekly phone conversations were used. In order to rule out any organic dysfunction, complete blood counts, lipid profile, liver and kidney function tests, and a thorough medical history were investigated for all patients at their initial visit. Serum levels of NLRP3, SIRT1, and AMPK and fecal calprotectin were also measured at the start and after 6 months of initiating the treatment intervention.

Evaluation of Colitis

The activity of the disease was determined using the PMS measure. The PMS index is one non-invasive diagnostic tool for assessing the severity of UC. Three subcategories contribute to the composite sub score: rectal bleeding, stool frequency, and general physician assessment. The overall result is in the range of 0 to 9.[39] PMS findings were recorded before beginning treatment and at the end of the study. Clinical response was defined as either an absolute rectal bleeding sub score of 0 or 1, or a drop in the rectal bleeding sub score of ≥1 point, and a decrease in PMS of ≥2 points and ≥30% from baseline. A PMS of less than 2 and no single sub score of more than 1 were considered clinical remission.[40]

Assessment of Health-Related Quality of Life (HRQoL)

In randomized clinical trials for ulcerative colitis, the most commonly used tool for measuring disease-specific quality of life is the 32-item Inflammatory Bowel Disease Questionnaire (IBDQ-32). Bowel and systemic symptoms, as well as emotional and social function, are the four categories of functioning and well-being that the IBDQ-32 measures.[41] There is evidence to support the IBDQ-32's responsiveness, construct validity, reliability, and content validity, according to reviews of its measurement qualities.[42,43] The sum of the 32 items can also be used to determine the overall score (score range: 0–224). Better HRQoL is indicated by higher domain and total scores.

Furthermore, patients were continuously observed for the appearance of unusual symptoms or unfavorable outcomes related to the medication.

Sample Collection

Before the experiment commenced and six months after the intervention, ten milliliters of venous blood were drawn from the antecubital vein. The sample was centrifuged for 10 minutes at 4500 g (Hettich Zentrifugen EBA 20) after the blood was progressively transferred into test tubes and allowed to coagulate. To measure the amounts of certain cytokines, the serum was frozen at −80°C. Weighed and dissolved in saline, the stool samples were vortexed. For the analysis of calprotectin, cleared supernatants were utilized.

Biochemical Analysis

Adhering to the manufacturer's instructions, commercially available enzyme-linked immunosorbent assay (ELISA) kits were used to measure the serum levels of NLRP-3 (catalog no. 201–12-5748), AMPK (catalog no. 201–12-0747), calprotectin (201–12-5461) and SIRT1 (catalogue no. 201–12-2558). Sunredio, Shanghai, China, supplied the kits.

Statistical Analysis

The statistical analysis was conducted using Prism version 9 from GraphPad software, Inc., San Diego, California, USA. Using the Shapiro–Wilk method, the normal distribution of a continuous variable was examined. The Wilcoxon test was used to assess significant differences within the group before and after therapy. To determine statistical differences between groups before and after therapy, the Mann–Whitney test and the unpaired Student's *t*-test were used. While the

mean ± SD was utilized to convey quantitative data, the interquartile range, median, and numbers were utilized to represent qualitative features. The Spear man correlation test was applied to find the correlation between the parameters. The Chi-square test, Fisher exact test, across groups, and the McNamar test within groups were used for categorical data.

Results

Clinical and Demographic Characteristics

Regarding the demographic baseline data, there were no statistically significant differences between the control and fenofibrate groups in terms of age (p = 0.238), sex (p = 0.230), weight (p = 0.083), height (p = 0.185), alanine aminotransferase (ALT) levels (p = 0.390), aspartate aminotransferase (AST) levels (p = 0.630), serum creatinine (SrCr) levels (p = 0.897), body mass index (BMI) (p = 0.768), smoking (p = 0.525), and disease duration (p = 0.692) as shown in Table 1.

After two months of the trial, six patients from the control group withdrew due to a transition to immunosuppressive therapy, while seven patients from the fenofibrate group withdrew due to non-compliance. Ultimately, fifty-seven patients completed the study, and statistical analysis was conducted based on intention-to-treat analysis (ITT) for the PMS and IBDQ-32 score using the baseline-observation-carried-forward (BOCF) approach to handle missing data from early treatment discontinuation. For the analysis of biological markers, a protocol analysis was used to assess the treatment's biological and causative effects.

Effect of Study Medications on Partial Mayo Score Index

The Mann–Whitney test indicated no statistically significant differences in the baseline PMS index values between the two groups ($p > 0.05$). In the control group, the Wilcoxon test revealed a significant reduction in the median PMS index from baseline (5 vs 2, $p < 0.0001$) (Table 2). Similarly, in the fenofibrate group, the Wilcoxon test showed a significant

Table 1 Clinical and Demographic Data in the Two Study Groups

parameter	Group (1) Control group (n=35)	Group (2) Fenofibrate group (n=35)	*P*-value
Age (year)	40.37 ± 11.7	43.37 ± 10.2	0.238
Sex			0.230
M	18 (51.4%)	20 (57.1%)	
F	17 (48.6%)	15 (42.8%	
Height (m^2)	1.71 ± 0.08	1.74 ± 0.09	0.185
Weight (kg)	67.06 ± 5.77	69.71 ± 6.85	0.083
BMI (kg/m^2)	22.80 ± 1.38	22.91 ±1.75	0.768
ALT (U/L)	26.57 ± 4.87	27.57 ± 4.816	0.390
AST (U/L)	31.26 ± 5.01	30.71 ± 4.37	0.630
SrCr (mg/dl)	0.95 ± 0.13	0.96 ± 0.11	0.897
Smoking	7 (20%)	5 (14.2%)	0.525
Disease duration (year)	1.3 (0.8–2.3)	1.6 (0.8–2.7)	0.692
Mild UC	16 (45.7%)	20 (57.1%)	0.338
Moderate UC	19 (54.3%)	15 (42.9%)	0.338

Note: Data are expressed as mean ±SD, numbers, median, and interquartile range.
Abbrevations: M, Male; F, Female; BMI, Body mass index; ALT, Alanine amino-transferase; AST, Aspartate amino-transferase; SrCr, Serum creatinine, Significance at ($p < 0.05$).

Table 2 Effect of Study Medications on Clinical Outcomes

Character	Group (1) Control group (n=35)			Group 2 Fenofibrate group (n=35)			*P* value
	Before treatment	After treatment	*P* value	Before treatment	After treatment	*P* value	After treatment
Partial Mayo score (PMS)	5 (4–6)	2 (1–3)	<0.0001*	5 (3–5)	1.25 (0–3)	<0.0001*	0.044**
Diarrhea	29/35 (85.71%)	20/35 (62.85%)	0.042#	32/35 (88.88%)	11/35 (37.14%)	<0.0001#	0.03##
Rectal bleeding	31/35 (88.57%)	19/35 (57.14%)	0.006#	28/35 (80%)	10/35 (31.42%)	<0.0001#	0.029##

Note: Data was presented as numbers, percentage, median and interquartile range, Control group, UC patients treated with mesalamine alone, Fenofibrate group, UC patients treated with mesalamine plus fenofibrate, (*) level of significance within the same group using Wilcoxon test. (**) level of significance between groups using Mann Whitney test. (#) level of significance within group using McNamar test. (##) level of significance between groups using Chi-square test. Significance at ($p < 0.05$).

decrease in the median PMS index (5 vs 1.25, $p < 0.0001$) (Table 2). The Mann–Whitney test also demonstrated statistically significant changes in the PMS index ($p = 0.044$) (Table 2).

According to the McNemar test, the number of patients experiencing diarrhea (29 vs 20, $p = 0.042$) and bleeding (31 vs 19, $p = 0.006$) significantly decreased in the control group after treatment compared to baseline. In the fenofibrate group, there was a statistically significant reduction in the number of patients with diarrhea (32 before treatment vs 11 after treatment, $p < 0.0001$) and bleeding (28 before treatment vs 10 after treatment, $p < 0.0001$), as determined by the McNemar test.

The Chi-square test revealed significant differences in the incidence of diarrhea ($p = 0.03$) and bleeding ($p = 0.029$) between the two groups. The response rate for PMS in the control group was 68.57% (n = 24/35), while the remission rate was 31.42% (n = 11/35). In the fenofibrate group, the response rate for PMS was 74.28% (n = 26/35), and the remission rate was 42.85% (n = 15/35).

Effect of Study Medication on IBDQ

The baseline values of the two groups did not differ significantly, according to the Mann Whitney test ($p > 0.05$).

After treatment, when comparing the control and fenofibrate group's median to their baseline, the Wilcoxon test revealed a significant increase in IBDQ and its subscale ($p < 0.05$). The Mann Whitney test demonstrated no statistically significant changes in IBDQ total score ($p > 0.05$) apart from a statistically significant difference in digestive domain ($p = 0.023$). (Table 3)

Table 3 Effect of Study Medications on IBDQ Subscale

Character	Group (1) Control group (n=35)			Group 2 Fenofibrate group (n=35)			##*P* value
	Before treatment	After treatment	#*P* value	Before treatment	After treatment	#*P* value	After treatment
Social domain	12 (9–18)	19 (11–23)	0.001	15 (11–21)	20 (13–25)	0.0002	0.335
Systemic domain	17 (11–21)	19 (17–22)	0.003	18 (12 −22)	20 (17–23)	0.002	0.583
Digestive domain	32 (26–35)	51 (36–59)	<0.0001	34 (25–37)	56 (47–63)	<0.0001	0.023
Emotional domain	28 (19–42)	36 (23–52)	0.005	31 (16–46)	36 (24–52)	0.002	0.719
Total IBDQ score	96 (79–106)	125 (105–144)	<0.0001	100 (79–114)	129 (124–149)	<0.0001	0.325

Note: Data was presented as median and interquartile range, Control group, UC patients treated with mesalamine alone, Fenofibrate group, UC patients treated with mesalamine plus fenofibrate, (#) level of significance within group using Wilcoxon test. (##) level of significance between groups using Mann Whitney test, (IBDQ), inflammatory bowel disease questionnaire, Significance at ($p < 0.05$).

Table 4 Comparison of Serum and Fecal Biomarkers in the Two Study Groups

Character	Group (1) Control group (n=29)			Group (2) Fenofibrate group (n=28)			### p value
	Before treatment	After treatment	# p value	Before treatment	After treatment	# p value	After treatment
SIRT1 (pg/mL)	20.1 (11.95–24.50)	23.87 (20.25–25.45)	0.012	19.27 (8.15–27.73)	28.04 (23.82–33.7)	0.009	0.002
NLRP-3 (pg/mL)	294 (257.5–316.5)	280.4 ± 21.09	0.047	305 (277–328.5)	140 (107.5–295)	<0.0001	0.041
AMPK (ng/mL)	104 (99–111.7)	141 (125–152.5)	0.006	107 (101.3–112.6)	159 (146–177.5)	<0.0001	0.0003
Calprotectin (ng/mL)	28.56 (23.94–30.8)	16.80 (14.35–28.3)	0.003	29.55 (24.08–33.04)	12.85 (9.6–27.28)	<0.0001	0.035

Note: Data are expressed as mean ±SD, Significance at ($p < 0.05$). Silent information regulator 1 (SIRT1), adenosine monophosphate activated protein kinase (AMPK), nucleotide-binding domain, leucine-rich–containing family, pyrin domain–containing-3 (NLRP-3), (#) within group comparison, (###) between group comparison.

Table 5 Comparison of Drug-Related Adverse Effects Between the Groups

Side effect	Group (1) Control group (n=35)	Group (2) Fenofibrate group (n=35)	P value
Nausea	7 (20%)	6 (17.14%)	0.758
Fatigue	7 (20%)	8 (22.85%)	0.770
Muscle pain	3 (8.57%)	5 (14.28%)	0.709
Heartburn	6 (17.14%)	7 (20%)	0.758
Skin rash	7 (20%)	6 (17.14%)	0.758

Note: Data were presented as numbers and percentages. Significance at ($p < 0.05$) using chi-square test or fisher exact test as appropriate.

Analysis of Serum and Fecal Biomarkers

No significant changes in baseline values between the two study groups using Mann Whitney test ($P > 0.05$). After treatment, fenofibrate group showed a statistically significant reduction in the level of NLRP3 ($p = 0.041$), calprotectin ($p = 0.035$) and a statistically significant increase SIRT1 ($p = 0.002$), and AMPK ($p = 0.0003$) when compared to the control group. Additionally, after therapy, levels of NLRP3 and calprotectin in both groups decreased statistically from their baseline values. On the other hand, Table 4 demonstrates a statistically significant rise in SIRT1, and AMPK serum levels following therapy in both groups when compared to baseline values.

Analysis of Drug's Related Adverse Effects

Table 5 demonstrated that the following side effects did not significantly differ between the two groups: nausea ($p = 0.758$), heartburn ($p = 0.758$), muscle pain ($p = 0.709$), skin rash ($p = 0.758$), and fatigue ($p = 0.770$).

Correlation Analysis Between the Studied Biomarkers

There was a significant indirect correlation between SIRT1 and PMS (r = - 0.3, $p = 0.004$), AMPK and PMS (r = - 0.415, $p < 0.0001$), and digestive domain and PMS (r = - 0.637, $p < 0.0001$). There was a significant direct correlation between SIRT1 and AMPK (r = 0.247, $p = 0.013$), and PMS and calprotectin (r = 0.284, $p = 0.003$).

Discussion

This clinical trial explores the effects of fenofibrate in patients with ulcerative colitis, adding valuable insights to the emerging evidence surrounding its therapeutic potential in this condition. Our findings indicate that adding fenofibrate to mesalamine significantly decreased the PMS and enhanced the digestive domains of the IBDQ-32. Additionally, the

fenofibrate group demonstrated a significantly higher response and remission rate compared to the control group. Moreover, the inclusion of fenofibrate led to a significant reduction in NLRP3 and fecal calprotectin levels, while also increasing the levels of SIRT1 and AMPK.

The anti-inflammatory properties of fenofibrate, both directly and indirectly, may explain the positive outcomes observed in this study. In inflammatory environments, lipid metabolism is often disrupted, but fenofibrate can help mitigate inflammation and restore normal metabolic processes. It enhances the expression of high-density lipoprotein (HDL) while reducing low-density lipoprotein (LDL) levels.[44] By decreasing cholesterol accumulation, fenofibrate alleviates inflammation and slows the progression of various inflammatory diseases.[45–47] Furthermore, fenofibrate may increase very-long-chain sphingolipids, contributing to its anti-inflammatory effects.[48] These findings highlight the indirect anti-inflammatory actions of fenofibrate. Additionally, fenofibrate directly reduces inflammation primarily by activating PPAR-α, which plays a crucial role in lipid metabolism and inflammatory processes, independent of its cholesterol-lowering effects. Upon activation of PPAR-α, fenofibrate diminishes inflammatory signaling pathways involving AMPK,[15] toll-like receptor 4 (TLR4),[16] SIRT1,[17] and nuclear factor kappa-B (NF-κB).[18] Moreover, fenofibrate directly inhibits the expression of genes associated with inflammation.[30] Moreover, fenofibrate was previously used in managing primary sclerosing cholangitis (PSC), a condition that is closely related to IBD.[49] Primary sclerosing cholangitis (PSC) is a chronic, progressive cholestatic disease characterized by inflammation and fibrosis of the biliary tree resulting in multifocal strictures.[49] Fifty to 80% of individuals with PSC have or subsequently develop colonic IBD.[50] What has become increasingly clear, however, is that IBD occurring in the setting of PSC is a distinct entity from IBD alone.[51] This is supported by genetic findings and by numerous clinical studies that endorse a unique IBD phenotype in individuals with concomitant PSC, characterized by extensive colitis and an increased risk of colorectal cancer.[52]

The fenofibrate group demonstrated a significant reduction in the PMS and a notable decrease in diarrhea and bleeding scores compared to both baseline measurements and the control group. While both groups exhibited significant reductions in the IBDQ relative to their baseline values, no significant differences were observed between them, except in the digestive domains. It is well established that UC adversely affects health-related quality of life (HRQL) and imposes a considerable economic burden.[53] Hoivik et al found that HRQL was lower in UC patients compared to the general Norwegian population,[53] which aligns with our findings of a significant reduction in IBDQ scores among UC patients. Another study indicated that fenofibrate significantly lowered inflammatory biomarkers and alleviated inflammation, apoptosis, and histopathological damage in animal models of colitis.[32] Previous research has also shown that mesalamine positively impacts HRQL, with significant differences from baseline values.[54] Fenofibrate improved HRQL by reducing abdominal pain, bleeding, and diarrhea through its anti-inflammatory effects in UC patients. Furthermore, our results are consistent with prior studies on the use of anti-inflammatory medications as adjunct therapies for IBDs, which demonstrated that atorvastatin and metformin have a colo-protective effect and enhance the efficacy of mesalamine.[27,55,56] Atorvastatin markedly reduced the severity of colitis, as evidenced by diminished rectal bleeding, shorter colon length, less histological damage, and improved survival rates. Treatment with atorvastatin also significantly lowers systemic TNF-α levels and Th17 cytokine levels. Additionally, atorvastatin therapy shifts the Th1 T-cell response towards a Th2 (IL-4, IL-10) response.[55] These findings may elucidate the beneficial effects of fenofibrate in decreasing the PMS index, reducing bleeding scores, and improving digestive domains.

In control group, our study revealed that there was a significant decrease in serum NLRP3 and a significant increase in AMPK, and SIRT1. Given that mesalamine is the mainstay and widely utilized in the treatment of mild to moderate UC, it is highly likely that these observations are the result of mesalamine. Mesalamine possesses anti-inflammatory and apoptotic properties and suppresses inflammatory mediators via a PPAR-γ-dependent manner.[57] Mesalamine activates phosphorylation of AMPK and its substrate acetyl-CoA carboxylase in cellular process.[29] AMPK was activated by mesalamine even in the absence of inflammatory mediators such as lipopolysaccharide and tumor necrosis factor alpha (TNF-α). The stimulation of AMPK dampens TNF-α-dependent NF-κB stimulation, which is occurred by mesalamine.[29]

The current study demonstrated a significant increase in SIRT1 serum level in fenofibrate group after treatment when compared to its baseline and control group. These observations were matched with previous studies.[58–60] By upregulating SIRT1, this finding may demonstrate the therapeutic benefit of fenofibrate in UC patients. SIRT1's numerous advantageous roles in inflammation and metabolism have been shown in multiple diseases, including IBD.[61] It has been established that

SIRT1 modifications play a critical role in regulating persistent inflammation.[62] Research shown that SIRT1 can affect the UC model's tissue homeostasis and intestinal inflammation modulation.[63,64] Since SIRT1 expression is down-regulated, pro-inflammatory cytokines involved in UC pathogenesis have higher quantities; therefore, activating SIRT1 resulted in a considerable reduction in IBD symptoms.[65] A new study's findings demonstrate that curcumin and resveratrol therapy protects the colitis model by boosting SIRT1 expression and suppressing pro-inflammatory mediators.[66] Fenofibrate activates PPARα, which in turn upregulates SIRT1. Research conducted on mammals has demonstrated that PPARα and SIRT1 collaborate to alleviate inflammation and dysregulation of metabolism.[67,68] Wang et al additionally revealed that PPARα inhibited the expression of markers associated with inflammation by deacetylating NF-κB via a process mediated by SIRT1.[69] In mild to moderate UC patients in our investigation, fenofibrate raised the level of SIRT1, indicating that fenofibrate's anti-inflammatory benefits might also be attributable to the upregulation of SIRT1 cascade stimulation. Fenofibrate inhibited endothelial cells with TNF-α, upregulating SIRT1 expression and inhibiting CD40 expression; however, GW6471, an antagonist of PPARα, reversed these effects.[70] Moreover, the impact of fenofibrate on CD40 expression in endothelial cells may be mitigated by SIRT1 inhibitors such as sirtinol/nicotinamide (NAM) or SIRT1 knockdown. Furthermore, fenofibrate reduced the production of acetylated-NF-κB p65 (Ac-NF-κB p65) in endothelial cells activated with TNF-α, an effect that was eliminated by SIRT1 silencing. Additionally, GW501516, a PPARβ/δ agonist, was shown in another study to greatly boost SIRT1 protein synthesis and decrease interleukin (IL)-8 secretion in human keratinocytes.[71] These findings advocate that certain drug, such as fenofibrate, may control cellular inflammation via SIRT1.

The current study revealed that, there was a significant increase in serum level of AMPK and a significant decrease NLRP3 in the fenofibrate group in comparison with its baseline and the control group. These promising results were in line with previous studies in the same field.[60,72,73] The mTOR/NLRP3 inflammasome cascade is one of the main downstream mechanisms that AMPK regulates. As previously noted, the decreased phosphorylation of AMPK may cause an increase in mTOR and NLRP3.[25] In order to suppress it, AMPK phosphorylates two locations in mTORC1, raptor, the mTOR binding partner, and the tuberous sclerosis protein 2 (TSC2) tumor suppressor. In multiple colitis models, AMPK activity was reduced, which increased mTOR activity and activated the production of the NLRP3 inflammasome. This may be explained by mTOR's documented function in controlling the NLRP3 inflammasome's activation and assembly through ROS-induced NLRP3 expression.[74] One possible explanation for the mTOR-mediated induction of the NLRP3 inflammasome could be the increase of glycolysis, a crucial metabolic process involved in the inflammasome's activation.[75] In diabetic mouse endothelial progenitor cells (EPCs), fenofibrate decreased the level of expression of caspase-1, NLRP3, and thioredoxin-interacting protein (TXNIP), which in turn altered the function of the NLRP3 inflammasome.[76] It has been noted that fenofibrate suppressed NLRP3 inflammasome activity and mitigated high glucose-induced EPC malfunction in vitro.[76] Fenofibrate exerts its activity on NLRP3 by indirectly inhibiting NF-κB activation.[77] Fenofibrate suppresses the release of inflammatory mediators in human THP-1 macrophages via down-regulating NF-κB Transcription through the activation of PPAR-α.[78] Al-Rasheed et al have shown that fenofibrate has a reno-protective effects which are mediated through the reduction of endothelial dysfunction and the regulation of the mRNA expression of AMPK, which in turn activates liver kinase B1 (LKB1), a downstream kinase of AMPK.[79] The sustained stimulation of AMPK and vascular endothelial growth factor (VEGF) mRNA expression was potently enhanced by fenofibrate.[80] Metformin, an AMPK activator, has proven its efficacy in UC.[81] Similarly, fenofibrate may have a protective role in UC by activating AMPK by stimulating PPARα.

Polymorphonuclear neutrophils migrate from the circulation to the intestinal mucosa when there is active intestinal inflammation. Any disruption of the mucosal architecture brought on by the inflammatory process causes neutrophils to leak into the lumen, where they release calprotectin, which is then excreted in stool.[82] There is a good correlation between the severity of UC and the amount of calprotectin present in the stools.[83] The current study demonstrated that fenofibrate in combination with mesalamine significantly reduced calprotectin when compared to mesalamine alone which was in line with previous report.[84] Grip and Olof demonstrated that there was a significant correlation between calprotectin level and the inflammatory chemokines in Crohn's disease (CD) patients.[84] Additionally, they demonstrated that lipid lowering drugs, statins, taken at high doses lowers clinical disease activity and plasma levels of C-reactive protein (CRP) in CD patients. The amount of fecal calprotectin in a patient's stool indicates mucosal healing in UC patients and corresponds with endoscopic and histologic inflammation.[85] Treatment of IL-10 deficient mice with

fenofibrate delayed the onset of colitis, decreased the colonic histopathology score, and decreased colonic expression of genes encoding the inflammatory cytokines interferon-γ and IL-17.[32] Also, the mean number of lymphocytes was decreased by more than 75% in colonic sections of fenofibrate-treated as compared with control IL-10 deficient mice.[32]

In contrast to our findings, the acute colitis model demonstrated a significant increase in the expression of inflammatory markers which was not reduced by fenofibrate. Fenofibrate did enhance the synthesis of sphingomyelins, decreased their hydrolysis, upregulated receptor interacting protein kinase 3 (RIPK3)-dependent necrosis, and increased mitochondrial fatty acid β-oxidation, all of which may be associated with the worsening of colitis.[86] These differing results may be attributed to variations in metabolic pathways between humans and rats, as well as the use of low doses of fenofibrate. Therefore, further research is necessary to clarify these discrepancies.

Given that each drug is metabolized by a separate isoenzyme, it is remarkable that there were no pharmacokinetic interactions between mesalamine and fenofibrate recorded. Additionally, there were no reported clinically important adverse effects and no notable variations in the clinical parameters of the patients, such as their age, gender, liver function, or renal function. The therapeutic advantages of the combined treatment are therefore most likely attributable to fenofibrate by altering the signaling pathways for AMP/NLRP3 and SIRT1.

Our study has a number of strength points such as being the first randomized and double blinded pilot clinical study to investigate the adjunctive role of fenofibrate as added on therapy to the standard treatment in patients with mild to moderate UC. Furthermore, we assessed the role of fenofibrate on UC by two different ways; clinically through PMS and IBDQ-32, mechanistically, through measuring different mediators such as AMPK, SIRT1, NLRP3, and fecal calprotectin.

The present study had a number of limitations, including its short duration, its small sample size, and its use of specific fenofibrate dosages, despite its optimistic results. Furthermore, Creatine kinase (CK) should be monitored before and after treatment. Therefore, future trials may include placebo and a fenofibrate-only group to assess the fenofibrate and placebo impact on UC severity. Also, colonoscopy and histopathological scores were not performed in our study. Our study included only mild to moderate cases of UC. Also, this study was applied only to Egyptian patients, and it's well known that IBDs are abundant in western countries where fast foods and bad habits are mainly responsible for the prevalence of this diseases among western populations.

Conclusion

This trial showed that fenofibrate combination therapy with mesalamine significantly improved digestive domains, reduced inflammatory markers, and upregulated SIRT1 and AMPK. Fenofibrate combination therapy with mesalamine is safe and tolerable choice for further investigation of treatment of patients with mild to moderate UC.

Additional multicentre, long-term trials are required to evaluate these effects. Also, different doses of fenofibrate and all severity grades may be considered in other clinical studies. Placebo only group and fibrate only group may be used in future studies to assess the fenofibrate and placebo effect on UC.

Institutional Review Board Statement

Institutional Review Board of Menoufia University's Faculty of Medicine amended the study protocol and approved it after reviewing it for all ethical and academic issues.

Credit Author Statement

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.

Data Sharing Statement

Due to privacy and ethical concerns, data is only available upon request to the corresponding author.

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Informed Consent Statement

All the study's participants provided their informed consent.

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Disclosure

The authors have no conflicts of interest.

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