

Efficacy of Empagliflozin in Patients with Mild-to-Moderate Ulcerative Colitis: A Randomized Controlled Pilot Study.

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Abstract

Ulcerative colitis (UC) is a relapsing-remitting inflammatory bowel disease characterized by chronic mucosal inflammation of the colon. Preclinical evidence suggests that sodium-glucose cotransporter 2 (SGLT2) inhibitors, such as empagliflozin, exert anti-inflammatory and antioxidant effects through activation of the adenosine monophosphate-activated protein kinase (AMPK) pathway. This randomized, double-blind, placebo-controlled pilot study aimed to evaluate the clinical efficacy, safety, and biomarker modulation of adjunctive empagliflozin in patients with mild-to-moderate UC. A total of 60 adult patients were allocated (1:1) to receive either standard background therapy plus placebo or standard therapy plus empagliflozin (25 mg orally once daily) for 6 months. The primary composite endpoints were improvements in disease activity (Montreal grade response and remission) and health-related quality of life (SF-36 score). Secondary endpoints included changes in serum tumor necrosis factor-alpha (TNF- α), C-reactive protein (CRP), AMPK, fecal calprotectin, number of daily stools, hemoglobin, and erythrocyte sedimentation rate (ESR). Following 6 months of intervention, empagliflozin treatment significantly reduced serum TNF- α , CRP, and fecal calprotectin levels compared to placebo ($P < 0.01$). Serum AMPK levels showed marked upregulation in the empagliflozin group ($P < 0.001$). Patients receiving empagliflozin demonstrated a significantly higher clinical response rate (93.3% vs. 66.6%, $P = 0.001$) and clinical remission rate (63.3% vs. 46.7%, $P = 0.001$) based on the Montreal classification. Significant improvements were also observed in SF-36 scores (68.6 vs. 58.2, $P = 0.008$), number of daily stools (2.3 vs. 4.8, $P < 0.001$), hemoglobin (12.8 vs. 11.1 g/dL, $P < 0.001$), and ESR (18.4 vs. 34.5 mm/1st hr, $P < 0.001$). Adverse events were minimal and comparable between the study arms. In conclusion, adjunctive empagliflozin therapy demonstrated significant clinical benefit, improved quality of life, and attenuated both systemic and mucosal inflammatory biomarkers in mild-to-moderate UC, likely mediated via AMPK pathway activation.

Clinical Trial Registration

Registered at ClinicalTrials.gov (Identifier NCT05610956).

1. Introduction

Inflammatory bowel disease (IBD) encompasses Crohn's disease (CD) and ulcerative colitis (UC), two distinct chronic entities characterized by intestinal inflammation (Cai et al. 2021). While CD can involve any segment of the gastrointestinal tract in a transmural fashion, UC is strictly confined to continuous mucosal inflammation of the colon (Carallo et al. 2026; Colombel et al. 2019). According to the Montreal classification, UC extent is categorized into ulcerative proctitis (E1), left-sided colitis (E2), and extensive colitis (E3), while clinical severity is categorized as S0 (clinical remission), S1 (mild), S2 (moderate), and S3 (severe) (Silverberg et al. 2005).

Oxidative stress and aberrant cytokine signaling—particularly driven by tumor necrosis factor-alpha (TNF- α)—play critical roles in driving chronic inflammation and epithelial barrier degradation in UC (El-Haggar et al. 2024; El-Rous et al. 2021). Current therapeutic regimens (aminosalicylates, corticosteroids,

immunomodulators, and biological agents) often carry risk of systemic side effects or secondary loss of response, creating a need for novel adjunctive modalities (Cai et al. 2021; El-Haggar et al. 2024; Grgić et al. 2022; Iannantuoni et al. 2019).

Beyond glucose homeostasis, sodium-glucose cotransporter 2 (SGLT2) inhibitors have demonstrated anti-inflammatory and tissue-protective effects (El-Rous et al. 2021; Iannantuoni et al. 2019; Morsy et al. 2021; Ruderman et al. 2013). Experimental models of colitis have revealed that SGLT2 inhibition suppresses nuclear factor kappa B (NF-κB) and NLRP3 inflammasome signaling via activation of adenosine monophosphate-activated protein kinase (AMPK) (El-Rous et al. 2021; Morsy et al. 2021). However, clinical evaluation of SGLT2 inhibitors in IBD remains limited (Carallo et al. 2026).

This randomized controlled pilot study was conducted to evaluate the clinical efficacy, safety, background treatment comparability, and biomarker modulation (TNF-α, CRP, fecal calprotectin, and AMPK) of adjunctive empagliflozin in patients with mild-to-moderate UC.

2. Patients and Methods

2.1. Ethical Considerations

The study protocol was approved by the Institutional Review Board of the Faculty of Medicine, Tanta University, Egypt (Approval No. 35744/9/22). All procedures complied with the ethical standards of the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from all participants prior to enrollment.

2.2. Study Design and Patient Selection

This single-center, randomized, double-blind, placebo-controlled parallel-group pilot study was conducted from January 2023 to December 2025 (ClinicalTrials.gov ID: NCT05610956). Eligible participants were adults aged 18 years or older with mild-to-moderate UC, confirmed via clinical presentation, endoscopic features, and histopathological evaluation.

2.3. Interventions and Background Standard Therapy

- **Control Group (Placebo):** Received standard UC background pharmacotherapy (5-aminosalicylic acid derivatives, oral corticosteroids, and/or immunosuppressants maintained at stable doses for at least 4 weeks prior to enrollment) plus matching placebo orally once daily for 6 months.
- **Intervention Group (Empagliflozin):** Received standard UC background pharmacotherapy plus empagliflozin (25 mg orally once daily; Empacoza, ZetaPharm, Egypt) for 6 months.

2.4. Biochemical and Clinical Evaluations

Venous blood and stool samples were collected at baseline and after 6 months of intervention. Serum levels of TNF-α, CRP, and AMPK, alongside fecal calprotectin, were measured using commercially

available ELISA kits. Routine laboratory markers (hemoglobin, ESR, renal, and liver function) were evaluated concurrently. Health-related quality of life was quantified using the validated SF-36 survey.

2.5. Statistical Analysis

Data were analyzed using IBM SPSS Statistics for Windows, Version 27.0. Continuous variables are expressed as mean $\pm$ SD or median (IQR). Between-group comparisons were performed using independent Student's t-test or Mann-Whitney U test. Categorical variables were compared using Pearson's Chi-square or Fisher's exact test. Statistical significance was set at two-tailed $P < 0.05$.

3. Results

3.1. Demographic, Clinical, and Background Therapy Characteristics

Baseline demographic parameters, disease extent, and background standard pharmacotherapy (5-ASA, oral corticosteroids, and immunosuppressants) showed no statistically significant differences between the placebo and empagliflozin cohorts ($P > 0.05$), confirming baseline comparability and avoiding confounding bias.

Table 1
Baseline demographic, clinical parameters, and background standard therapy distribution

Parameter	Placebo (n = 30)	Empagliflozin (n = 30)	P-value
Age (years), Mean $\pm$ SD	41.2 $\pm$ 9.4	42.8 $\pm$ 8.7	0.501
Gender (Male / Female)	16 / 14	15 / 15	0.795
Fasting Blood Glucose (mg/dL)	94.3 $\pm$ 10.2	92.8 $\pm$ 9.8	0.566
Disease Extent (E1 / E2 / E3)	8 / 14 / 8	7 / 15 / 8	0.952
Concomitant Standard Therapy, n (%)			
- 5-ASA Derivatives (Mesalamine)	28 (93.3%)	29 (96.7%)	0.554
- Oral Corticosteroids (Prednisolone)	12 (40.0%)	11 (36.7%)	0.787
- Immunosuppressants (Azathioprine)	8 (26.7%)	9 (30.0%)	0.774
Mean Prednisolone Dose (mg/day)	18.5 $\pm$ 5.2	19.1 $\pm$ 4.8	0.648

3.2. Disease Activity and Quality of Life

Post-treatment assessment demonstrated significant clinical improvement in the empagliflozin group compared to placebo ($\chi^2 = 10.82$, $P = 0.001$). The empagliflozin cohort achieved a clinical response rate of 93.3% and a remission rate of 63.3%, compared to 66.6% response and 46.7% remission in the placebo group. SF-36 quality of life scores also improved significantly ($P = 0.008$).

Table 2
Assessment of disease activity (Montreal severity) pre- and post-treatment

Outcome Measure	Timepoint	Placebo (n = 30)	Empagliflozin (n = 30)	Between-Group P-value
Montreal Severity Grade	Baseline			0.598
- Mild (S1)		18 (60.0%)	16 (53.3%)	
- Moderate (S2)		12 (40.0%)	14 (46.7%)	
Montreal Severity Grade	Post-6 Months			0.001*
- Remission (S0)		14 (46.7%)	19 (63.3%)	
- Mild (S1)		12 (40.0%)	9 (30.0%)	
- Moderate (S2)		4 (13.3%)	2 (6.7%)	

3.3. Biomarker Modulation and Hematological Parameters

Following 6 months of intervention, the empagliflozin group exhibited marked upregulation in serum AMPK expression ($P < 0.001$) alongside significant reductions in serum TNF- α , CRP, and fecal calprotectin compared to placebo ($P < 0.01$). Furthermore, daily stool frequency, hemoglobin concentrations, and ESR showed highly significant improvements in the empagliflozin arm relative to placebo ($P < 0.001$).

Table 3
Serum and fecal inflammatory biomarkers pre- and post-treatment (Between-Group Analysis)

Biomarker	Group	Baseline	Post-6 Months	Between-Group P-value
TNF-α (pg/mL)	Placebo	34.2 $\pm$ 6.1	30.1 $\pm$ 5.4	0.008*
	Empagliflozin	35.1 $\pm$ 5.8	21.4 $\pm$ 4.2	
AMPK (ng/mL)	Placebo	1.82 $\pm$ 0.31	1.89 $\pm$ 0.28	< 0.001*
	Empagliflozin	1.79 $\pm$ 0.35	3.45 $\pm$ 0.42	
CRP (mg/L)	Placebo	13.1 $\pm$ 3.4	11.8 $\pm$ 2.9	< 0.001*
	Empagliflozin	12.8 $\pm$ 3.1	5.2 $\pm$ 1.6	
Fecal Calprotectin (μg/g)	Placebo	285.4 $\pm$ 32.1	242.1 $\pm$ 28.5	< 0.001*
	Empagliflozin	291.0 $\pm$ 30.5	124.6 $\pm$ 21.3	

Table 4
Clinical symptom and hematological disease activity parameters

Parameter	Group	Baseline	Post-6 Months	Between-Group P-value
Number of daily stool	Placebo	5.2 ± 1.1	4.8 ± 0.9	< 0.001*
	Empagliflozin	5.4 ± 1.0	2.3 ± 0.6	
Hemoglobin (g/dL)	Placebo	10.8 ± 1.2	11.1 ± 1.1	< 0.001*
	Empagliflozin	10.6 ± 1.3	12.8 ± 0.9	
ESR (mm/1st hr)	Placebo	38.2 ± 6.4	34.5 ± 5.8	< 0.001*
	Empagliflozin	39.1 ± 6.1	18.4 ± 4.2	

3.4. Safety and Adverse Event Profile

Adverse events were minimal and showed no significant differences between the two study arms ($P > 0.05$). Minor genitourinary infections were successfully managed with standard antimicrobial therapy without requiring study drug discontinuation.

Table 5
Summary of drug-related adverse events

Adverse Event	Placebo (n = 30)	Empagliflozin (n = 30)	P-value
Urinary tract infection	1 (3.3%)	3 (10.0%)	0.612
Genital mycotic infection	0 (0.0%)	2 (6.7%)	0.492
Gastrointestinal discomfort	2 (6.7%)	2 (6.7%)	1.000
Dizziness / Hypoglycemia	0 (0.0%)	0 (0.0%)	—

4. Discussion

Intestinal mucosal dysfunction and persistent inflammation in UC stem from complex interactions between pathogenic inflammatory cytokines and impaired cellular metabolic pathways (Cai et al. 2021; Carallo et al. 2026; Colombel et al. 2019; El-Haggag et al. 2024; El-Rous et al. 2021). Conventional therapeutic options may be limited by tolerability issues, systemic toxicities, or secondary loss of response, highlighting the need for novel adjunctive options (Cai et al. 2021; Carallo et al. 2026; Grgić et al. 2022; Iannantuoni et al. 2019).

Our findings indicate that adjunctive empagliflozin (25 mg daily for 6 months) led to significant clinical improvements, reduced daily stool frequency, enhanced disease remission rates, and improved health-related quality of life (Carallo et al. 2026; Vieujean et al. 2025). These clinical improvements were accompanied by significant decreases in systemic and mucosal inflammatory markers, including serum TNF- α , CRP, ESR, and fecal calprotectin (Carallo et al. 2026; El-Rous et al. 2021; Iannantuoni et al. 2019;

Morsy et al. 2021; Kristensen et al. 2015; Grgić et al. 2022). Fecal calprotectin serves as a reliable non-invasive biomarker for evaluating intestinal mucosal inflammation and predicting mucosal healing (Kristensen et al. 2015; Grgić et al. 2022).

At the cellular level, AMPK acts as a central metabolic regulator that dampens inflammation by inhibiting NF- κ B transactivation and suppressing NLRP3 inflammasome assembly (El-Rous et al. 2021; Morsy et al. 2021; Ruderman et al. 2013; Park et al. 2019). In our trial, adjunctive empagliflozin treatment led to significant upregulation of serum AMPK levels, which negatively correlated with clinical disease severity, confirming that the tissue-protective effects are mediated via AMPK pathway activation (El-Rous et al. 2021; Morsy et al. 2021; Carallo et al. 2026; Ruderman et al. 2013; Park et al. 2019).

5. Conclusion

Adjunctive empagliflozin therapy demonstrated clinical benefit, improved health-related quality of life, and attenuated mucosal and systemic inflammatory markers in patients with mild-to-moderate UC, mediated via upregulation of AMPK signaling pathways.

Declarations

Ethical Approval and Consent to Participate

Approved by the Research Ethics Committee, Faculty of Medicine, Tanta University, Egypt (Approval No. 35744/9/22). Written informed consent was obtained from all individual participants.

Competing Interests

The authors declare no conflict of interest.

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Author Contribution

Younna Hamdy Eldeeb: Conceptualization, Investigation, Methodology, Data Analysis, and Writing – Original Draft. Sahar M. El-Haggag, Sahar K. Hegazy: Supervision, Methodology, Manuscript Review & Editing. Mohamed El-Sayed Sarhan: Patient Recruitment, Clinical Assessment, Supervision, and Manuscript Review.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study

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Figures

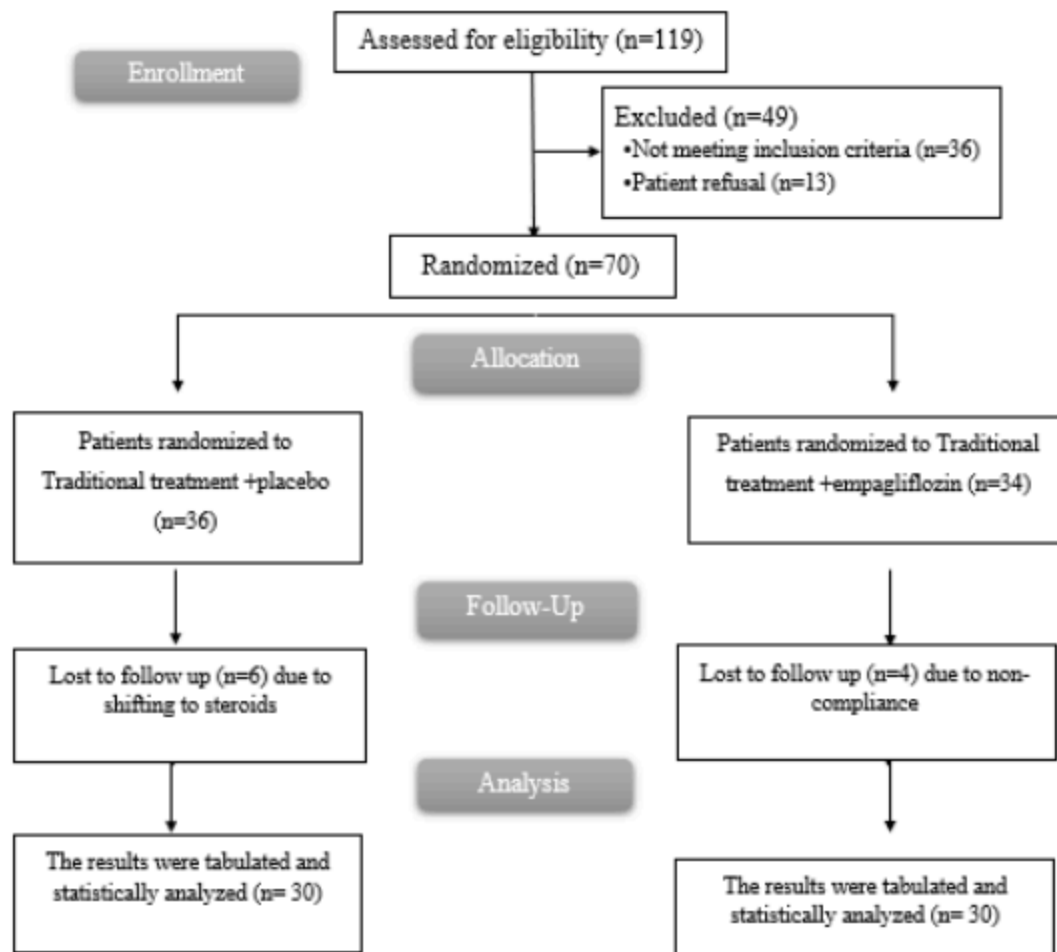


Figure 1

CONSORT diagram showing the flow of participants during the study