

Evaluation of ciprofloxacin, prednisolone, and infliximab effects on liver functions in acetic acid-induced ulcerative colitis rat model

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ABSTRACT

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by recurring episodes of gastrointestinal inflammation and damage, affecting millions worldwide. Emerging evidence suggests a complex relationship between UC and liver dysfunction, with increased risk of hepatotoxicity and liver-related disorders.

Objectives: To investigate the effects of ciprofloxacin, prednisolone, and infliximab on liver function in an acetic acid-induced UC rat model.

Materials and methods: Fifty male Sprague-Dawley rats were divided into five groups of ten rats each: control, UC, ciprofloxacin, prednisolone, and infliximab group. UC was induced with 2 ml of 4% acetic acid solution transrectal. Liver function tests (AST, ALT, ALP), oxidative stress markers (MDA), protein synthesis (total protein, albumin), and bilirubin processing were evaluated, and histological examination of liver tissues was performed.

Results: The UC group showed significant increase in liver function enzymes (ALP, AST, ALT), oxidative stress markers (MDA) and significant decrease in total protein, albumin, total bilirubin and conjugated bilirubin level when compared with the control group. Respective treatment groups demonstrated improved liver enzyme levels, reduced oxidative stress, enhanced protein synthesis and bilirubin processing. Histological examination revealed improved liver architecture and reduced inflammation in treatment groups when compared with the UC group.

Conclusion: This study provides evidence that ciprofloxacin, prednisolone, and infliximab exert protective effects on liver function in acetic acid induced UC model. These findings suggest potential benefits of these therapies in mitigating liver damage associated with UC, highlighting the importance of considering liver health in UC management.

Introduction

Ulcerative colitis (UC) is a chronic and debilitating inflammatory bowel disease characterized by recurring episodes of gastrointestinal inflammation and damage.^{1,2} This condition affects millions worldwide, significantly impacting quality of life and morbidity. Emerging evidence suggests a complex relationship between UC and liver dysfunction, with studies indicating an increased risk of hepatotoxicity and liver-related disorders in UC patients.^{3,4}

The liver plays a critical role in metabolizing

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drugs and toxins, regulating immune responses, and maintaining overall health. However, its dysfunction can exacerbate the severity of UC, leading to adverse reactions and compromised therapeutic outcomes.⁵ The liver's role in UC is multifaceted, involving the metabolism of pro-inflammatory cytokines, detoxification of bacterial products, and regulation of immune cell function.⁶

Current treatments for UC, including ciprofloxacin, prednisolone, and infliximab, have shown promise in mitigating intestinal inflammation. Ciprofloxacin target pathogenic bacteria, while prednisolone reduce inflammation and immune activity.² Infliximab, particularly those targeting tumor necrosis factor- α (TNF- α), have revolutionized UC management by modulating immune responses.⁷

However, the impact of these treatments on liver function in the context of UC remains poorly understood. This knowledge gap is concerning, as ciprofloxacin and prednisolone are known to have hepatotoxic potential.⁸ Infliximab, while generally safe, may modulate liver immune responses in unpredictable ways, potentially affecting liver function. To address this critical knowledge gap, this study aims to investigate the effects of ciprofloxacin, prednisolone, and infliximab on liver function in a rat model of acetic acid-induced ulcerative colitis.

Materials and methods

Fifty adult male Sprague-Dawley rats seven weeks old (weight = 180-200g) obtained from Animal House of the Olabisi Onabanjo University, Sagamu Campus, Ogun State, Nigeria were housed in a standard environment conditions with 12 hours light/dark cycle and air filtration. Animals have free access to water and feed. Experimental protocols met the Guideline of Animal Experimentation approved by Olabisi Onabanjo University Teaching Hospital Human Research Ethics Committee (approval number: OOUTH/HREC/746/2023 AP). The animals were divided into five groups of ten rats each:

- Group A: Normal control group
- Group B: Ulcerative colitis group
- Group C: Ciproflaxin-treated group
- Group D: Prednisolone-treated group
- Group E: Infliximab-treated group

Induction of ulcerative colitis

The induction of ulcerative colitis was done according to the method described by Al-Rejaie et al.,⁹. After 24 hours fast, the rats were anesthetized using 1.75 mL ketamine (1 gm/mL) and 0.25 mL Xylazine (1 gm/mL) intra-peritoneal prior to ulcerative colitis induction. 2 mL of 4% acetic acid solution was administered transrectally using a (2.7 mm) soft pediatric catheter. Rats were held horizontally for 2 min to prevent acetic acid leakage. Control group rats undergo the same procedure using equal volume of

normal saline instead of acetic acid solution.

Administration of ciprofloxacin, prednisolone and infliximab

100 mg of ciprofloxacin was dissolved in 2.5 mL of distilled water to give a solution of 40 mg/mL, 40 mg/kg of ciprofloxacin was administered every 72 hours for forty-two days orally,¹⁰. 10 mg of prednisolone was dissolved in 5 mL of distilled water to give a solution of 2 mg/mL, 2 mg/kg of prednisolone was administered every 72 hours for forty-two days orally,¹¹. Five mg/kg body weight of infliximab was administered bi-weekly for forty-two days intra-peritoneal.¹²

Determination of liver function test

Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) activities were carried out according to the method of Reitman and Frankel.¹³ For Serum Alanine aminotransferase (ALT) determination, diluted sample (0.01 mL) was mixed with phosphate buffer (100mM, pH 7.4), L-alanine (200mM) and the mixture was incubated for exactly 30 minutes at 37 °C. An aliquot (0.5 mL) of 2, 4 dinitrophenylhydrazine (2mM) was added to the reaction mixture and allowed to stand for exactly 20 minutes at 25 °C. NaOH (0.4 M, 5 mL) was then added, and the absorbance was read against reagent blank after 5 minutes at 546 nm. Reagent blank was prepared as described above by replacing sample with 0.1 mL of distilled water.

For determination of Aspartate Aminotransferase (AST) activity, 0.1 mL of diluted sample was mixed with phosphate buffer (100 mM, pH 7.4), L-asparatate (100 mM), and α -Oxoglutarate (2 mM) and the mixture was incubated for exactly 30 minutes at 37 °C. An aliquot of 2, 4 dinitrophenylhydrazine (2 mM, 0.5 mL) was then added to the reaction mixture and allowed to stand for exactly 20 minutes at 25 °C. Then, 0.5 mL of NaOH (0.4 M) was added and the absorbance was read against reagent blank after 5 minutes at 546 nm. Reagent blank was prepared as described above replacing sample with 0.1 mL of distilled water.

Alkaline phosphatase (ALP) activities were determined using 2.2 mL of 0.1 M carbonate buffer (pH 10.1), 0.1 mL of 0.1 M $\text{MgSO}_4 \cdot 7\text{H}_2\text{O}$, and 0.2 mL of the sample were mixed and incubated at 37 °C for 10 minutes. Thereafter, 0.5 mL of 19 mM of paranitrophenyl phosphate was added and again incubated at 37 °C for 10 minutes. NaOH (2.0 mL) was added and mixed, and read against blank at 400 nm.

Serum protein concentration was determined using the Biuret method.¹⁴ Serum albumin was determined by the method of Doumas et al.,¹⁵ based on the ability of bromocresol green (BCG), pH 4.2, to bind albumin which results in the formation of a complex that exhibits optical properties different from dye.

Following the method described by Tietz,¹⁶ serum total bilirubin and conjugated bilirubin was determined

based on the principle of bilirubin in the serum that is coupled with diazotized sulphanilic acid to form azobilirubin.

Determination of malondialdehyde activity (lipid peroxidation)

The MDA activity was measured by the double heating method.¹⁷ One ml of tissue homogenate was combined with 2 mL of TCA-TBA-HCL and mixed thoroughly. The solution was heated for 15 minutes in a boiling water bath. After cooling, the fluorescent precipitate was removed by centrifugation at 1000g for 10 mins. The absorbance of the sample was determined at 535 nm against a blank that contains all the reagents minus the sample. The malondialdehyde concentration of the sample was calculated using an extinction coefficient of $1.56 \times 10^{-5} \text{ M}^{-1} \text{ Cm}^{-1}$. Calculation of lipid peroxidation:

$$\text{MDA}(\text{nmol/ml}) = \text{OD} \sum \times \frac{V}{v}$$

OD = Absorbance (optical density) of sample

$\sum$ = Molar extinction coefficient

V = Total volume of the reacting sample

v = Volume of the sample

Histological analysis

The organs were carefully removed, and then the fat was removed. After weighing, they were fixed in 10% formal saline right away. The tissues were fixed, placed in progressively higher alcohol grades, and finally

cleansed in xylene. After embedding them in paraffin, 5µm serial slices were produced. Hematoxylin and eosin were used to stain the sections. The slides were observed under a light microscope for the histological changes and morphometrical examination.

Statistical analysis

All the values are expressed as mean±standard error of mean (SEM). Analysis of data was done using Graph Pad Prism version 5 for Windows. Differences between groups were analyzed by one-way ANOVA followed by Bonferroni *post-hoc* test. Differences were considered significant at $p < 0.05$.

Results

Results of liver function enzymes presented in figure 1 showed a significant increase in AST, ALT, and ALP in the ulcerative colitis group B (114.00 ± 10.39 , 75.66 ± 10.26 , and 79.00 ± 9.50 , respectively) when compared with the control group A (79.33 ± 5.20 , 39.00 ± 1.52 , and 38.66 ± 14.43). Elevated AST, ALT and ALP levels indicate liver damage or dysfunction, hepatocellular damage or necrosis, and cholestasis or bone disorders respectively. Treatment group C, D, E showed a significant decrease in AST (88.00 ± 2.64 , 84.00 ± 3.05 , and 72.66 ± 5.33), ALT (32.00 ± 1.00 , 29.33 ± 9.66 , and 37.00 ± 1.00), ALP (40.66 ± 1.20 , 33.33 ± 2.02 , 39.33 ± 6.88) when compared with group B respectively. No significant difference was observed within the respective treatment group.

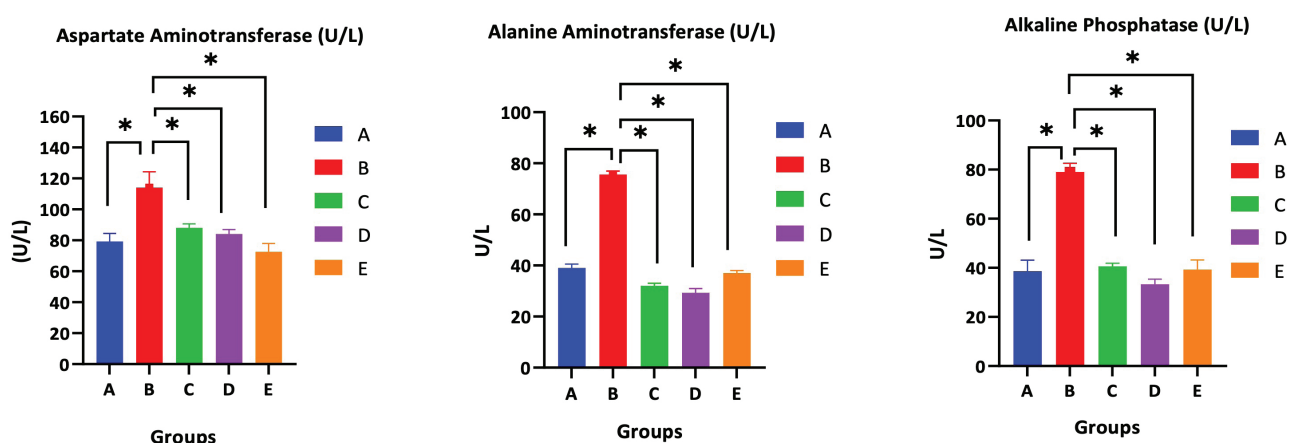


Figure 1. The effect of ciprofloxacin, prednisolone and infliximab on liver function enzymes in acetic acid induced ulcerative colitis rat model. A-E: experimental groups, * $p < 0.05$.

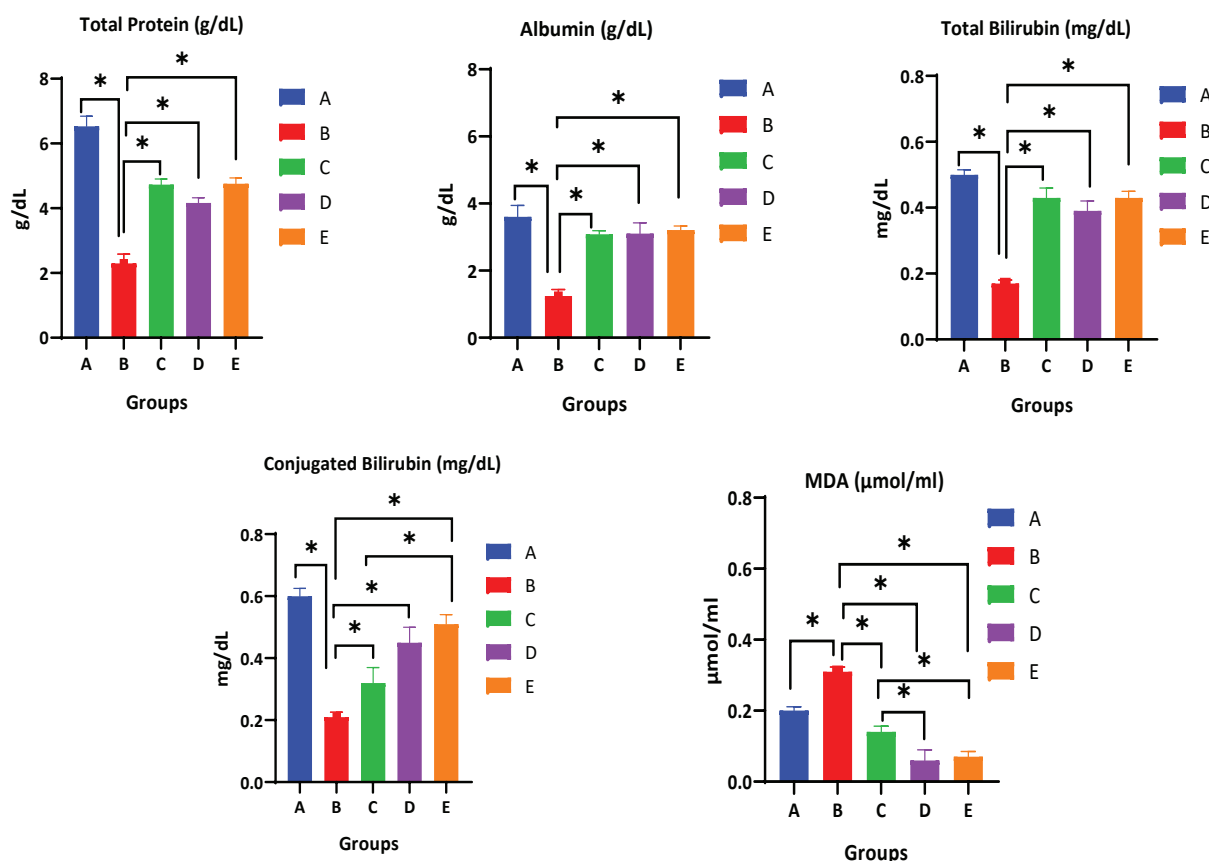
Results of some liver function markers and marker of oxidative stress presented in figure 2 showed a significant decrease in Total Protein, Albumin, Total Bilirubin, Conjugated Bilirubin in group B (2.30 ± 1.28 , 1.24 ± 0.99 , 0.17 ± 0.10 , 0.21 ± 0.16) when compared with group A (6.53 ± 0.31 , 3.60 ± 0.34 , 0.50 ± 0.15 , 0.60 ± 0.25 , respectively). The decrease in total protein and albumin may be attributed to inflammation-induced suppression

of protein synthesis, malabsorption of amino acids due to intestinal inflammation, and increased catabolism of proteins due to systemic inflammation while total bilirubin and conjugated bilirubin decrease may be attributed to reduced hepatic uptake and conjugation of bilirubin due to inflammation and impaired bile duct function and bile flow. Also, there was a significant increase in liver MDA in group B (0.31 ± 0.13) when

compared with group A (0.20 ± 0.11) which indicates lipid peroxidation and cellular damage.

Treated group C, D, E showed a significant increase in TP (4.73 ± 0.75 , 4.16 ± 1.16 , 4.76 ± 0.78), ALB (3.08 ± 0.11 , 3.10 ± 0.32 , 3.21 ± 0.12), TB (0.43 ± 0.06 , 0.39 ± 0.03 , 0.43 ± 0.02), CB (0.32 ± 0.05 , 0.45 ± 0.05 , 0.51 ± 0.03) and significant

decrease in MDA (0.14 ± 0.16 , 0.06 ± 0.03 , 0.07 ± 0.05) when compared with group B respectively. However, there was a significant decrease in conjugated bilirubin in group C compared to group E. More so, a significant increase was observed in liver MDA in group C compared to group D and E respectively.



shows the effect of antibiotics, anti-inflammatory agent and monoclonal agent on some liver function markers and marker of oxidative stress in acetic acid induced ulcerative colitis rat model.

LEGEND: A= Group A, B= Group B, C= Group C, D= Group D, E= Group E * = statistically significant at $p \leq 0.05$

Figure 2. The effect of ciprofloxacin, prednisolone and infliximab on some liver function markers and marker of oxidative stress in acetic acid induced ulcerative colitis rat model. A-E: experimental groups, * $p \leq 0.05$.

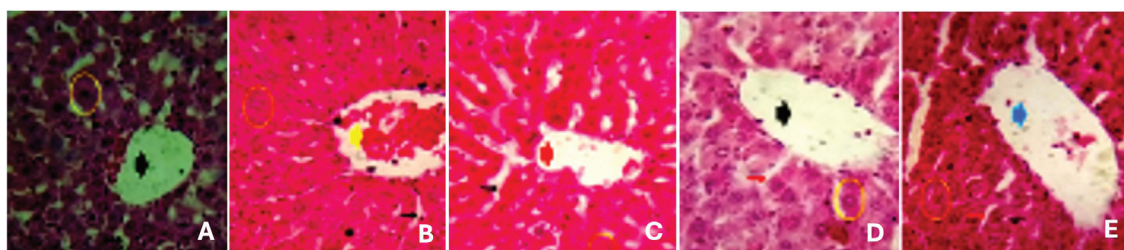


Figure 3. Photomicrograph of hepatic tissue showing the effect of ciprofloxacin, prednisolone and infliximab in acetic acid induced ulcerative colitis rat model. (H&E Staining, x400 magnification).

A: well differentiated and organized hepatocytes (yellow circle), sinusoids with Kupfer cells (black thin arrow) and clear central vein (black thick arrow),

B: congested central vein (yellow thick arrow), loss of hepatocytes (yellow circle) and constricted sinusoids (black thin arrow),

C: Normal sinusoids (black thin arrow), clear central vein (red thick arrow) and slight loss of hepatocytes (yellow circle),

D: clear central vein (black thick arrow), constricted sinusoids (red thin arrow) and hepatocytes (yellow circle),

E: clear irregular central vein (blue thick arrow), hepatocytes (yellow circle) and constricted sinusoids (red thin arrow).

Discussion

Aspartate transaminase (AST), a liver enzyme that catalyzes the conversion of aspartate and α -ketoglutarate to oxaloacetate and glutamate.^{18,19} Elevated AST levels indicate liver damage or dysfunction.²⁰ Alanine Aminotransferase (ALT), a cytosolic enzyme primarily found in hepatocytes, catalyzing the conversion of alanine and α -ketoglutarate to pyruvate and glutamate.^{18,19} Elevated ALT levels indicate hepatocellular damage or necrosis.²⁰ Alkaline Phosphatase (ALP), a membrane-bound enzyme, plays a crucial role in bile duct function and bone mineralization.²¹ Elevated ALP levels indicate cholestasis or bone disorders.²²

In this study, AST, ALT, and ALP level (Figure 1) significantly increased in the ulcerative colitis group compared to the control group, suggesting liver impairment, bile duct dysfunction or inflammation. Previous study showed that this elevation may be attributed to the systemic inflammation and oxidative stress associated with ulcerative colitis,²³ release of pro-inflammatory cytokines, such as TNF- α and IL-6, which induce hepatocellular damage.²⁴ Additionally, the acetic acid-induced colitis model triggers oxidative stress, leading to liver damage.²⁵

Treatment with ciprofloxacin, prednisolone, and infliximab significantly decreased AST, ALT, and ALP levels compared to the ulcerative colitis group. Based on previous findings, ciprofloxacin which is an antibiotic may likely reduce bacterial translocation and subsequent liver damage,²⁶ prednisolone may decrease inflammation and oxidative stress²⁷ and infliximab target TNF- α to reduce inflammation and improved liver function.²⁸

Malondialdehyde (MDA) levels (Figure 2), a marker of oxidative stress, significantly increased in the ulcerative colitis group compared to the control group. Previous study has showed that increase MDA indicates lipid peroxidation and cellular damage.²⁹ prednisolone and infliximab treatment groups showed significant decreased MDA levels compared with UC group and ciprofloxacin treated group, suggesting reduced oxidative stress. The reduction in MDA levels may be attributed to the antioxidant properties of prednisolone, infliximab targeting TNF- α also mitigate oxidative stress by reducing inflammation according to Rutgeerts *et al.*²⁸

Total protein and albumin are essential proteins synthesized by the liver, playing critical roles in maintaining blood volume, transporting hormones, vitamins, and minerals, and regulating fluid balance.¹⁶ Decreased levels of total protein and albumin (Figure 2) in the ulcerative colitis group compared to the control group. These decrease according to previous studies may be attributed to inflammation-induced suppression of protein synthesis, malabsorption of amino acids due to intestinal inflammation, and increased catabolism of proteins due to systemic inflammation.^{30,31} Treatment

with ciprofloxacin, prednisolone, and infliximab significantly increased total protein and albumin levels compared to the ulcerative colitis group. This may be due to reduced inflammation and oxidative stress,²⁷ improved intestinal absorption of amino acids,²⁶ enhanced protein synthesis and reduced catabolism.²⁸

Total bilirubin and conjugated bilirubin are breakdown products of heme, primarily processed by the liver.³² Decreased levels in the ulcerative colitis group (Figure 2). The decrease may be attributed to reduced hepatic uptake and conjugation of bilirubin due to inflammation and impaired bile duct function and bile flow.²² Treatment groups showed increased total bilirubin and conjugated bilirubin levels, suggesting improved liver function and bilirubin processing. This may be due to reduced inflammation and oxidative stress, enhanced hepatic uptake and conjugation of bilirubin,²⁸ and improved bile duct function and bile flow.

Histological examination of liver tissues (Figure 3) revealed significant alterations in the ulcerative colitis group compared to the control group. The control group exhibited well-differentiated and organized hepatocytes, patent sinusoids with intact Kupffer cells, and a clear central vein, indicative of normal liver architecture. In contrast, the ulcerative colitis group showed a congested central vein indicating increased blood pressure and inflammation, loss of hepatocytes suggesting hepatocellular damage or apoptosis, constricted sinusoid indicating reduced blood flow and increased oxidative stress. These changes are consistent with liver dysfunction in inflammatory bowel disease (IBD).^{24,33} The systemic inflammation and oxidative stress associated with ulcerative colitis likely contribute to liver damage.

Ciprofloxacin treatment groups demonstrated improved histological features such as a normal sinusoid indicating restored blood flow and reduced inflammation, clear central vein suggesting improved blood pressure and reduced congestion, and a slight loss of hepatocytes which indicates partial recovery of hepatocellular damage. Ciprofloxacin likely reduced bacterial translocation and subsequent liver damage, leading to improved histological features.³⁴

Prednisolone treated group showed a clear central vein indicating reduced inflammation and improved blood pressure, constricted sinusoid which may indicate persistent oxidative stress, hepatocytes indicating preserved liver cell architecture. Prednisolone reduced inflammation and oxidative stress, preserving hepatocellular structure and function.²⁷

Infliximab treatment group showed a clear irregular central vein which suggests improved blood pressure and reduced congestion, hepatocytes indicating preserved liver cell architecture, constricted sinusoid which may indicate persistent oxidative stress.²⁵ Infliximab targeting TNF- α reduced systemic inflammation and oxidative stress, leading to improved liver histology.²⁸

Conclusion

The results of this study demonstrate that treatment with ciprofloxacin, prednisolone, and infliximab regulate liver enzyme levels, reduced oxidative stress, and improve protein synthesis and bilirubin processing. Histological examination revealed improved liver architecture, reduced inflammation, and oxidative stress in treatment groups. These findings suggest that these treatments particularly infliximab may be beneficial in reducing bacterial translocation, decreasing inflammation and oxidative stress, enhancing protein synthesis, and improving bilirubin processing.

Ethical approval

The National Research Council's guidelines for the care and use of laboratory animals were followed in all animal studies and methodology. Ethical approval was obtained from Olabisi Onabanjo University Teaching Hospital Human Research Ethics Committee (OOUTH-HREC), with the number OOUTH/HREC/746/2023AP.

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Conflict of interest

The authors declare no conflict of interest.

CRedit authorship contribution statement

Oyesola OA and **Adejo AR**: conceptualization and method; **Adejo AR**, **Olayemi OE**, **Ojo-Adebayo EO**, and **George ET**: data collection and analysis; **Adejo AR**, **Olayemi OE**, **Ojo-Adebayo EO**, and **George ET**: interpretation of results; **Oyesola OA**: supervision, writing: original draft. All authors contributed to writing and revising the manuscript.

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