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Role of liraglutide and probiotics in managing chronic kidney disease induced in rats

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Abstract

Background and objective: Chronic kidney disease (CKD) is an incurable disorder involving widespread inflammation and gut dysbiosis, which facilitates disease progression via the gut-kidney axis. Current therapies can only decelerate the course of the disease and may cause adverse effects. This study aimed to investigate the potential reno-protective effects and modulation of gut integrity by the glucagon-like peptide-1 receptor agonist liraglutide and probiotics, separately and in combination, in a rat model of CKD.

Methods: CKD was induced in male rats (n=40) by intraperitoneal injection of high-dose folic acid. Animals were randomly distributed into five equal groups: control negative, control positive, liraglutide group, probiotics group, and combination group. Serum levels of creatinine, blood urea nitrogen, cystatin-C and C-reactive protein were measured. Histological assessment of the kidney and colon was also performed.

Results: High-dosefolic acid significantly increased markers of impaired kidney function and systemic inflammation. Treatment with liraglutide, probiotics, and their combination significantly reduced these markers' levels. Histopathological analysis revealed improved renal and gastrointestinal integrity in all treatment groups, with the combination treatment group demonstrating the most substantial recovery.

Conclusion: The combination therapy effectively protected renal and intestinal tissues from the damage of high-dose folic acid. The current findings suggest potential additive or synergistic benefits of combining liraglutide with probiotics and support its use as a novel strategy for managing CKD via gut and renal regulation.

Keywords: Glucagon-like peptide-1 receptor agonists, Gutmicrobiota, Renoprotection, Folic acid, Gut-kidney axis.

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Introduction

Chronic kidney disease (CKD) is a progressive, incurable condition characterised by a steady decline in renal function, nephron damage, and severe cardiovascular complications (1). Conventional treatments merely slow disease progression and are often associated with adverse effects. Growing evidence indicates that CKD progression impairs gut function, highlighting gut microbiota modulation as a promising therapeutical approach (2). Declining kidney function shifts the gut microflora composition in favour of urea-degrading bacteria that produce exces suremic toxin and worsen systemic inflammation. CKD also disrupts intestinal tight junctions, allowing bacterial lipopolysaccharides (LPS) to persistently leak into circulation and trigger the release of inflammatory mediators interleukin (IL)-1, IL-6, tumor necrosis factor-alpha, and C-reactive protein (CRP) (3).

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs), such as liraglutide, and probiotics have demonstrated promising reno-protective benefits in prior research (4-7). GLP-1RAs improve kidney function through both direct and indirect mechanisms (8). For instance, they antagonize endothelin-1 and promote renal vasodilation (9). They also modulate the gut microbiota population (10) and reinforcethe gut mucous barrier (10, 11), limiting pathogenic microflora growth and uremic toxinaccumulation, which ultimately reduces systemic inflammation (12). Despite these individual advantages, no study has examined the combined impact of liraglutide and probiotics in this context. This research hypothesizes that their co-administration may offer a synergistic or additive reno-protective advantage by regulating the gut–kidney axis. This approach may represent anovel and effective approach for the management of CKD in non-diabetic CKD animal models.

Methods

Animals

Forty male Wistar rats (8-10 weeks old, 230-350 g) were housed in polypropylene cages with sawdust bedding. The animals were acclimatized for two weeks before the study. They were maintained at 22 ± 2°C under a 12-hour light/dark cycle with unrestricted access to standard rat chow and water. This study was carried out from September 2024 to mid-January 2025. Ethical approval was granted by the Hawler Medical University College of Medicine Ethics Committee on November 14th, 2024 (Meeting code: 2; Paper code: 13).

Drugs and chemicals

Pure folic acid (LOBA Chemie, India) stock solution was prepared in 0.3 M

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$NaHCO_3$ (Laborate Pharmaceuticals, India). Liraglutide (Saxenda®) and probiotics mix (Velavit®) were purchased from a licensed pharmacy. The probiotic mix (1×10^{10} CFU) contained four *Bifidobacterium* strains (*bifidum, longum, lactis,* and *infantis*), seven *Lactobacillus* strains (*acidophilus, bulgaricus, plantarum, gasseri, salivarius, casei, paracasei,* and *lactis*), *Enterococcus faecium*, and *Streptococcus thermophilus*, each at concentrations ranging from 7×10^8 to 9×10^9 CFU.

Study design

CKD and gut dysbiosis were induced in accordance with previous studies (13) by a single intraperitoneal (IP) injection of folic acid (250 mg/kg) on day 1. Rats were randomly divided into five equal groups:

- Control negative (CN): Received 0.3 M $NaHCO_3$ IP on day 1, along with daily subcutaneous (SC) administration of water for injection and oral gavage of distilled water throughout the experiment.
- Control positive (CP): Received a single IP dose of 250 mg/kg folic acid on day 1, with the same daily SC and oral placebo treatments as the CN group.

The remaining three groups served as treatment groups. Starting on day 28 post-folic acid injection, the following medications were administered daily for 8 weeks:

- Liraglutide group: Received 0.4 mg/kg liraglutide (Saxenda®) SC.
- Probiotics group: Received 0.08 mg of a probiotic mix (Velavit®) containing $1x10^9$ CFU via oral gavage.
- Combination group: Received both liraglutide SC and the probiotic mix orally, as described above.

The rats' weights were recorded weekly. After 8 weeks of treatment, the rats were anesthetized by IP injection of 12 mg/kg of xylazine and 80 mg/kg of ketamine (14).

Biochemical evaluation

Blood samples were withdrawn via cardiac puncture into non-heparinized tubes, left to coagulate for 30 minutes, and then centrifuged for 10 minutes at 400 rpm. Serum was stored at -20˚C for biochemical investigation. Serum creatinine (SCr) and blood urea nitrogen (BUN) were measured spectrophotometrically whereas CRP and cystatin-C (CysC) were quantified using anenzyme-linked immunosorbent assay (ELISA) rat kit.

Histopathological evaluation

Kidneys and large intestines were harvested and preserved in 10% formaldehyde and subsequently stained byhematoxylin and eosin for histopathological analysis.

Statistical analysis

One-way ANOVA (Analysis of Variance) test was employed to statistically compare the research groups, with

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Tukey's post-hoc test to investigate multiple comparisons (software: SPSS; version: 27.0).

Results

As shown in Table 1, high-dose folic acid significantly (P ≤0.05) elevated mean SCr, BUN, and CRP concentrations in the CP group as opposed to the CN. Liraglutide, probiotics, and their combination led to lower (P ≤0.05) mean concentrations for all markers relative to the CP.

Table 1. Treatment impact on the mean (± SEM) serum levels of CKD biomarkers

	CN	CP	Liraglutide	Probiotics	Combination
SCr (mg/dl)	0.45±0.07^b	1.10±0.11^a	0.58±0.07^b	0.65±0.12^b	0.52±0.08^b
P-value	<0.001	-	0.003	0.013	<0.001
BUN (mg/dl)	33.49±1.99^b	50.95±1.67^a	38.48±3.18^b	40.22±3.33^b	37.00±2.12^b
P-value	<0.001	-	0.012	0.039	0.004
CysC (ng/dl)	9.49±0.44^b	14.63±1.24^a	10.51±0.82^b	10.97±0.87^b	9.74±0.63^b
P-value	<0.001	-	0.024	0.033	0.002
CRP (ng/ml)	4.71±0.44^b	7.80±0.38^a	5.78±0.50^b	6.12±0.25^b	5.24±0.27^b
P-value	<0.001	-	0.008	0.033	<0.001

All values are expressed as mean ± SEM.
Different signs indicate different significances:
a: P ≤0.05 significantly different when compared with the CN group.
b: P ≤0.05 significantly different when compared with the CP group.

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The CN kidney histopathological assessment showed typical renal tissue structures (Figure 1).

In contrast, kidneys from the CP group showed severe histopathological changes, including:

- Dense inflammatory cell infiltration (II) in the interstitium (Figure 2A)
- Numerous dilated tubules (DT) with lumens invaded by inflammatory cells (IT) (Figure 2A).
- Congested and/or hemorrhagicblood vessels (Figure 2B).
- Epithelial cell damage with prominent vacuolation (Figure 2C).
- Renal thyrodization (RT), characterized by tubular inflammation andpink colloidal material in the lumens (Figure 2A).

Focal infiltration of inflammatory cells into the glomeruli (IG), with distorted Bowman's spaces (Figure 2A).

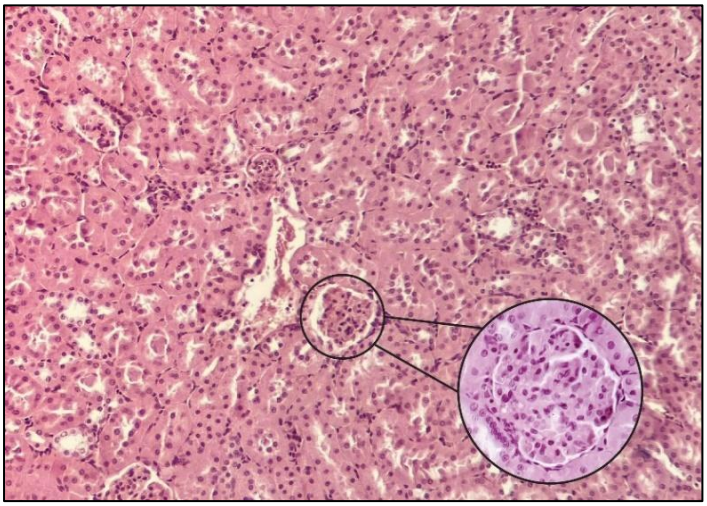

Figure 1. Micrograph of CN kidney sections (200x, 400x)

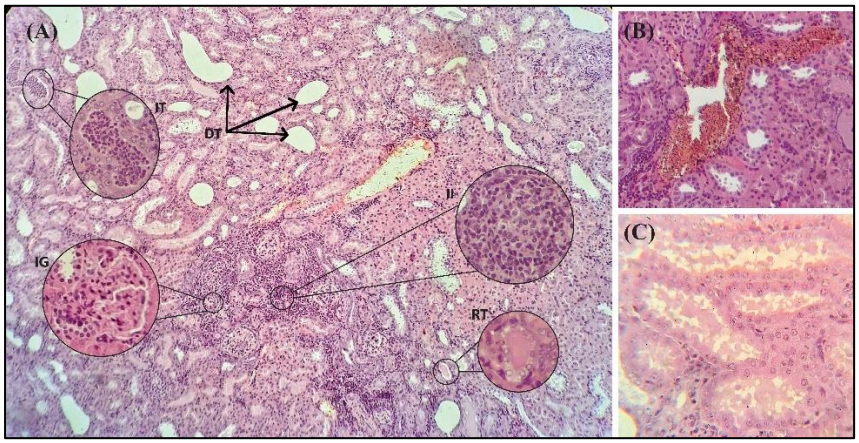

Figure 2. Micrographs of CP kidneys:A – 200x, 400x.; B – 400x; C – 400x

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In the liraglutide-treated group, only a single focal area in one sample exhibited mild inflammatory cell infiltration in the interstitium (II) (Figure 3C). No glomerular infiltration or irregularities were observed, indicating minimal to no glomerular damage. Tubular dilatation (DT) was mild (Figure 3A) and renal thyrodization (RT) was rare (Figure 3B).

In the probiotics group, moderate interstitial inflammatory cell infiltration (II) was observed (Figure 4A), along with persistent but reduced tubular dilation (DT) and inflammatory infiltration (Figures 4A and 4B). Renal thyrodization (RT) remained rare (Figure 4C).

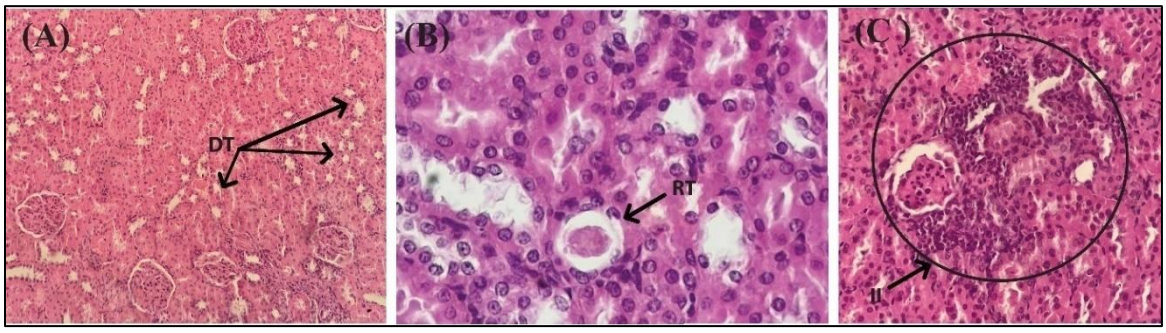

Figure 3. Micrographs of kidneys from the liraglutide group: A – 200x; B – 400x; C – 400x

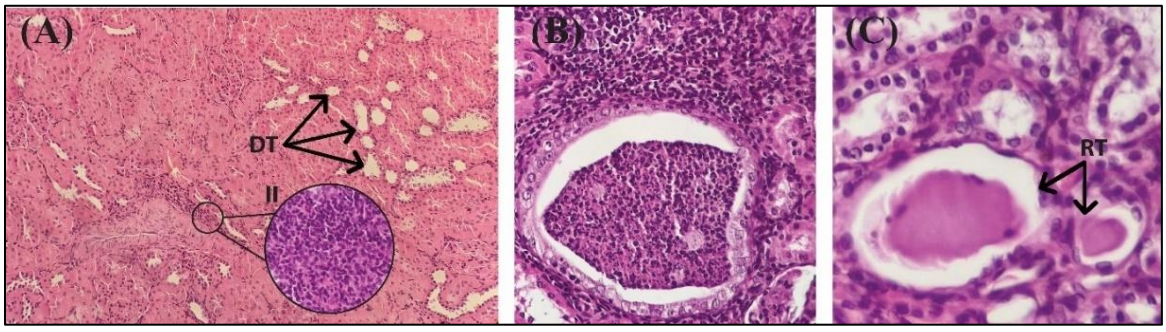

Figure 4. Micrographs of kidneys from probiotics group: A – 100x, 400x; B – 400x; C – 400x

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The combination-treated group showed minimal to no interstitial infiltration (Figure 5A). Tubular dilation (DT) was rare with no tubular infiltration (Figure 5A). Renal thyrodization (RT) was very rare (Figure 5B), and no glomerular abnormalities or infiltration were reported.

A histopathological scoring was given to the study groups based on the nephropathy grading score of Jozi *et al.* (15):

- CN: 0 (normal histology);
- CP: 4 (51-75% involvement of inflammatory and structural changes observed in glomeruli and tubules);
- Liraglutide group: 2 (1-25% involvement);
- Probiotics group: 3 (26-50% involvement);
- Combination group: 1 (<1% involvement).

Histological assessment of the CN group colon showed regular mucosa, submucosa, muscularis propria, and well-formed crypts (Figure 6).

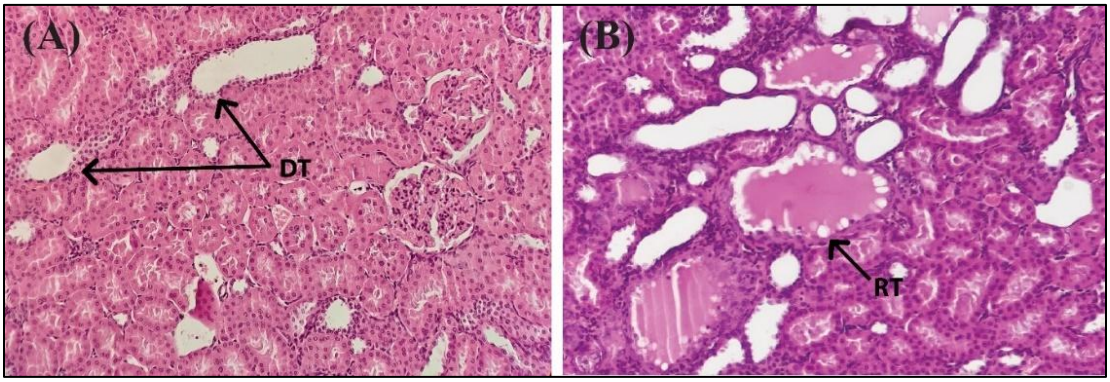

Figure 5. Micrographs of kidneys from the combination group: A – 200x; B – 400x

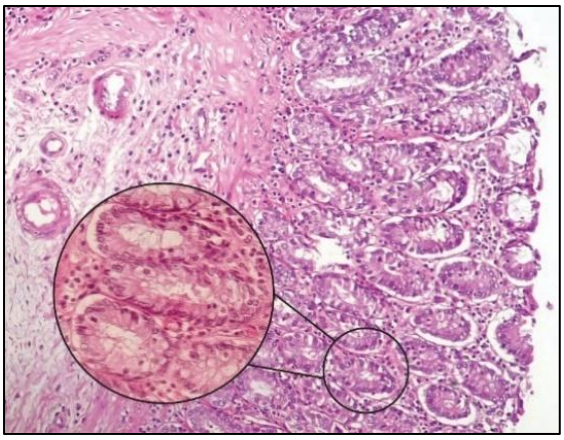

Figure 6. Micrographs of CN colon (200x, 400x)

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In contrast, the CP group showed dense mixed inflammatory infiltration in the surface epithelium and lamina propria (Figure 7A). Inflammatory cells extended into the crypt walls (cryptitis) and crypt lumens (crypt abscesses) (Figure 7B) but did not penetrate past the mucosa (unaffected submucosa) (Figure 7C).

Colons from the liraglutide-treated group showed no active inflammatory cells in the mucosa, submucosa, lamina propria, or crypts (Figure 8A). In the probiotics group, scattered mixed inflammatory cells were observed in the lamina propria with mild focal vascular congestion, while the crypts remained unaffected (Figure 8B). The combination group exhibited entirely normal histology, with no signs of inflammation or crypt involvement (Figure 8C).

Histopathological scoring, based on Remke *et al.* (16), assessed immune cell presence (0 to 3), injury to the epithelial layer (0 to 3), and mucosal architecture/atypia (0 to 3). The scores resulted as follows:

- CNliraglutide group and combination group : 0 (normal histology);
- CP: 6 (moderate-severe inflammation);
- Probiotics group: 1 (minimal-mild inflammation).

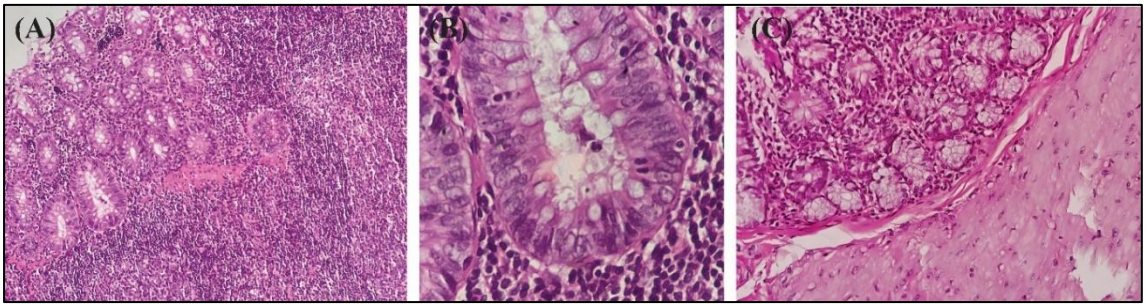

Figure 7. Micrographs of CP colon: A – 200x; B – 400x; C – 200x

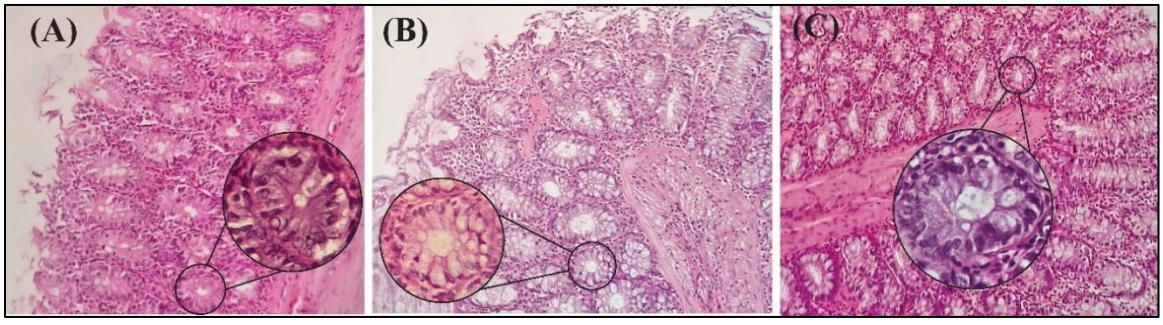

Figure 8. Micrographs of the colon from the (A) liraglutide, (B) colon, and (C) combination groups (200x, 400x)

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Discussion

Increasing evidence emphasizes the key role of the gut–kidney axis in the advancement of CKD, wherein renal impairment and intestinal dysbiosis mutually exacerbate one another (17). In this study, the significant elevation ($P < 0.001$) in the mean SCr and BUN levels in the CP group compared to the CN confirmed that IP injection of 250 mg/kg folic acid successfully induced kidney damage. This is further supported by the clear signs of inflammation observed in the CP kidney micrographs. Such outcomes align with earlier research models showing comparable elevation in these parameters (18). Folic acid crystallizes rapidly in the proximal tubules and obstructs flow, increasing intra-tubular pressure. This causes cellular stress, apoptosis, and inflammation (19). Once normal kidney function is impaired, urea and other toxins accumulate and permeate into the large intestine, disrupting normal microflora balance. This shift promotes the proliferation of urea-degrading and other pathogenic bacteria while impairing the intestinal barrier integrity, ultimately resulting in gut dysbiosis (2).

Eight-week treatment with liraglutide and probiotics, administered separately and in combination, significantly reduced SCr, BUN, and CysC levels ($P = 0.003$, $P = 0.013$, and $P < 0.001$ for SCr; $P = 0.012$, $P = 0.039$, and $P = 0.004$ for BUN; $P = 0.024$, $P = 0.033$, and $P = 0.002$ respectively), indicating improved renal function. It is worthy of mention that CysC is a sensitive marker of kidney function, superior to SrCr, as it rises earlier and is less affected by age, sex, or muscle mass (20). In this study, elevated CysC levels indicated tubular injury from folic acid-induced CKD, supporting its use in evaluating treatment effects alongside conventional markers. Liraglutide protects renal function independently of its glycemic control (21, 22), possibly by suppressing nuclear transcription factor-κB (NF-κB) (23). It also promotes the growth of beneficial gut microbes species (*Lactobacilli* and *Bifidobacteria*) (24), and enhances intestinal barrier integrity through the upregulation of tight junction proteins (25). Similarly, probiotics also improve kidney function, likely by restoring normal gut permeability (24), limiting uremic toxin generation, and suppressing inflammatory cytokines production via the generation of short-chain fatty acids (26, 27). In the present study, the combination therapy exhibited the most significant improvement in renal function, suggesting a more complete recovery than each treatment alone. This may be attributed to the shared ability of both agents to boost the abundance and viability of commensal gut microflora, suppress inflammation, and restore the gut barrier's integrity. These effects collectively result in an

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amplification of their individual anti-uremic and anti-inflammatory.

The significantly elevated (P <0.001) CRP levels of the CP group confirmed the development of generalized inflammation in this CKD model (28). Liraglutide significantly reduced (P = 0.008) mean CRP levels. This aligns with its well-established role in downregulating inflammatory signaling pathways by antagonizing NF-kB (23) and reversing inflammatory and fibrotic gene expression (9). Probiotic treatment also significantly lowered (P = 0.033) CRP levels, possibly by promoting anti-inflammatory immune responses through upregulation of IL-10 (29), T-regulatory cell activation (30), and by stabilizing the gut barrier, thereby limiting endotoxin translocation (31). The combination therapy normalized CRP levels to near-control values (P <0.001), demonstrating that the gut-oriented anti-inflammatory actions of liraglutide and probiotics augmented each other to more effectively suppress systemic inflammation than each treatment alone. Histological findings supported these biochemical results: while liraglutide and probiotics each improved kidney architecture (reduced inflammatory infiltration, tubular dilation, and renal thyrodization), the combination group demonstrated the most preserved kidney architecture and the healthiest nephropathy score. This points to a superior reno-protective effect of the combination therapy. The severe colitis observed in the CP, characterized by cryptitis, crypt abscess, and dense inflammatory infiltration, supports the involvement of the gut-kidney axis in CKD pathogenesis (32). Liraglutide treatment restored normal colonic mucosa, whereas the probiotics-only group showed mild residual inflammation. The combination group, however, demonstrated fully normal colon histology, comparable to the healthy control. Such findings emphasize the added value of combined treatment in restoring both renal and gastrointestinal integrity.

Conclusion

In this study, liraglutide, probiotics, and their combination preserved renal and gut integrity to varying degrees following CKD induction with high-dose folic acid, likely through anti-inflammatory mechanisms. The combination therapy provided the greatest protection, as reflected by improved kidney function, reduced inflammatory markers, and the most favorable histological scores compared to either treatment alone. These findings suggest that liraglutide and probiotics combination may act synergistically to enhance renal protection and reduce inflammation in CKD beyond their individual effects.

Competing interest

The authors declare that they have no competing interests.

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