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Implications of Endothelin-1 antagonist, ACE Inhibitor and Statin on Experimentally Induced Hyperlipidemic Nephropathy in Rats

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ABSTRACT

Chronic kidney disease is a growing global health challenge, with prevalence steadily increasing worldwide. Current pharmacological interventions are often insufficient to completely prevent or slow the progression of nephropathy. To address this, the present study investigated the renoprotective efficacy of Ramipril, BQ123, and Atorvastatin in a rat model of hyperlipidemia-induced nephropathy. Hyperlipidemia was induced by a high-fat diet for six weeks, followed by two weeks of treatment. At the study endpoint, animals were sacrificed for biochemical and histopathological evaluation. Combination therapy produced significant improvements, including reductions in serum creatinine, blood urea nitrogen (BUN), total protein, and serum nitrite, along with amelioration of renal histopathology. Furthermore, the treatments reduced oxidative stress and reinstated the activity of antioxidant enzymes that had been impaired by hyperlipidemia.

Keywords: Chronic kidney disease, Hyperlipidemia, Ramipril, BQ123, Atorvastatin, Oxidative stress.

INTRODUCTION

Nephropathy is a major global health challenge that disproportionately affects poor and disadvantaged populations, contributing to significant individual, healthcare, and societal burdens. Globally, nearly 700 million people are estimated to have chronic kidney disease (CKD). When acute kidney injury (AKI) and end-stage renal failure (dialysis and transplant recipients) are considered, the prevalence of renal disease rises to approximately 850 million, affecting more than 10% of the global population[1,2].

The progression of nephropathy is largely driven by hyperlipidemia, hyperglycemia, and hypertension[3]. High-fat diets markedly increase circulating cholesterol and triglycerides, and elevated lipid levels represent a significant risk factor for renal injury[4]. Hypercholesterolemia has been demonstrated in several animal models to accelerate renal disease progression[5]. Hypercholesterolemia in endothelial cells enhances oxidative stress[6], which triggers the generation of unsaturated free fatty acids and initiates lipid peroxidation of cellular membranes[7]. The resulting oxidized low-density lipoproteins (Ox-LDL) interfere with key vasoactive mediators such as nitric oxide, angiotensin II, endothelin-1 (ET-1), and

transforming growth factor- β (TGF-β), thereby driving pathological changes within the kidney[4].

Statins, by blocking 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) reductase, demonstrate renoprotective actions in both experimental and clinical models of kidney disorders. Beyond their cholesterol-lowering capacity, they also help reduce lipid accumulation in renal tissue and protect against obesity-associated renal injury[8,9].

In addition, hyperlipidemia is often associated with overactivation of the renin-angiotensin-aldosterone system (RAAS)[10], which contributes to glomerular hyperfiltration and mesangial expansion[11]. Angiotensin II enhances albumin reabsorption within renal tubules[12], and sustained albumin overload further stimulates ET-1 release. Angiotensin-converting enzyme inhibitors (ACEIs) not only mitigate proteinuria but may also improve lipid profile, ultimately providing therapeutic benefit in chronic kidney disease[13]. Despite this, novel therapeutic strategies are required to enhance the protective effects of RAAS inhibition, particularly in patients with progressive renal disease[14].

Endothelin-1 (ET-1), one of the most potent endogenous vasoconstrictors, acts via ETA and ETB receptors[15]. Clinical and preclinical evidence indicates that ET-1 levels are elevated in nephropathy patients[16]. Endothelin-1 (ET-1) is a key mediator in the pathogenesis of chronic kidney disease (CKD), with its harmful effects largely exerted through ETA receptors[17]. Antagonism of ET receptors has been reported to improve lipid metabolism and attenuate atherosclerotic changes[18]. BQ-123, a selective ETA receptor antagonist, demonstrates notable renoprotective actions by reducing blood pressure, proteinuria, and renal damage in experimental models of CKD[19-21].

Recent investigations suggest that combining ACE inhibitors and statins provides greater renoprotection than either therapy alone, significantly reducing proteinuria, glomerulosclerosis, tubular damage, and interstitial inflammation[22]. Given the interplay between RAAS and ET systems, combined inhibition of these pathways may represent a promising therapeutic approach for hyperlipidemia-induced nephropathy[14].

MATERIAL AND METHODS

Chemicals and drugs

Atorvastatin, BQ123, and Ramipril were obtained from Sigma-Aldrich (St. Louis, MO, USA), All other reagents and chemicals used in the study were of analytical grade and procured from Merck Pvt. Ltd., New Delhi, India. Commercial assay kits for triglycerides, cholesterol, serum creatinine, blood urea nitrogen (BUN), and total protein were purchased from Uma Scientific Traders, Allahabad, India.

Animals

Healthy Wistar rats of either sex (100-150 g) were obtained from the Animal House, Teerthanker Mahaveer University (TMU), Moradabad, following approval from the Institutional Animal Ethics Committee (IAEC approval no. DVCP/IAEC/2023/06). Animals were maintained in polypropylene cages with husk bedding under controlled laboratory conditions (24±2°C, 45-55% relative humidity, and a 12 h light/dark cycle). For 24-h urine collection, rats were transferred to individual metabolic cages. A standard pellet diet (Lipton India Ltd., Mumbai) and water were provided ad libitum. All experimental procedures adhered to IAEC guidelines and complied with the regulations of the Committee for the Control and Supervision of Experiments on Animals (CCSEA), Government of India.

Induction of hyperlipidemia

Hyperlipidemia was induced by feeding rats a high-fat diet for six weeks (42 days). The diet consisted of butter (20 g), corn starch (44.74 g), sucrose (10 g), fiber (5 g), cholesterol (1 g), casein (14 g), vitamin mix (1 g), mineral mix (3.5 g), choline (0.25 g), tert-butylhydroquinone (0.0008 g), and cholic acid (0.5 g)[23]. At the end of the feeding period, serum lipid profiles were analyzed to confirm the establishment of hyperlipidemia.

EXPERIMENTAL

The animals were randomly divided

into ten groups, each comprising six rats. Group I served as the normal control and received a standard diet without any treatment. Group II was designated as the hyperlipidemic control and received a high-fat diet (HFD) only. Group III functioned as the vehicle control and was administered HFD along with the vehicle at an equivalent volume. Group IV received HFD combined with atorvastatin (10 mg/kg i.p.)[24], while Group V was given HFD with ramipril (1 mg/kg, i.p.)[25,26]. Group VI was administered HFD along with BQ-123 (1 mg/kg i.p.)[27,28]. The combination treatment groups included Group VII, which received HFD with atorvastatin and ramipril; Group VIII, which received HFD with atorvastatin and BQ-123; and Group IX, which received HFD with ramipril and BQ-123. Finally, Group X received HFD along with all three agents-atorvastatin, ramipril, and BQ-123-representing the triple combination treatment group.

Biochemical estimation

At the end of treatment, overnight-fasted rats underwent retro-orbital blood collection under light anesthesia. Serum was separated by centrifugation (2000 rpm, 10-20 min) for biochemical estimations. Rats were also housed in metabolic cages for 24-h urine collection prior to sacrifice. Primary outcomes included serum creatinine, blood urea nitrogen (BUN), total protein, cholesterol, triglycerides, and nitrite (Griess method)[29] using standard diagnostic kit using spectrophotometer as per leveled instructions.

Antioxidant estimation of kidney tissue

Kidneys were excised from each rat and rinsed immediately with ice-cold normal saline (0.9% NaCl) to remove blood and debris. The tissues were blotted dry with sterile filter paper and stored at -70°C until analysis. For biochemical assays, kidney samples were homogenized in 0.15 M Tris buffer (pH 7.4) for 10 min at 1,000 rpm, and the resulting supernatant was collected. Oxidative stress markers, including glutathione (GSH), superoxide dismutase (SOD), and catalase (CAT), were measured using commercial colorimetric kits (Abcam, Cambridge, USA) at 450 nm. Lipid peroxidation (LPO) was assessed following the method of Ohkawa *et al.,* with absorbance recorded at 532 nm[30,31].

Renal Hypertrophy and Fibrosis Measurements

Renal hypertrophy was assessed by calculating the kidney-to-body weight ratio. The kidneys were carefully excised, cleaned of surrounding tissues, and weighed. The percentage of kidney mass relative to body mass was determined using the standard methodology.

Statistical Analysis

All data are presented as mean ± standard error of the mean (SEM, n = 6). Statistical analyses were carried out using GraphPad Prism software, version 5.01 (GraphPad Inc., San Diego, CA, USA). Comparisons among groups were performed using one-way analysis of variance (ANOVA), followed by Newman-Keuls post hoc test. Differences were considered statistically significant at $p<0.05$.

RESULTS

Impact of therapeutic interventions on body weight and kidney weight vs body wight ratio in experimentally induced hyperlipidemic nephropathy

Rats subjected to a high-fat diet (HFD) demonstrated a significant increase in body weight compared to the normal control group ($p<0.05$), indicating the successful induction of obesity-associated metabolic alterations. Treatment with atorvastatin (ATO), ramipril (RAM), and the endothelin receptor antagonist BQ-123, administered individually or in combination, resulted in a marked attenuation of body weight gain, with combination therapy showing the most pronounced effect. Furthermore, the kidney-to-body weight ratio was significantly elevated in HFD-fed rats compared to controls ($p<0.05$), reflecting renal hypertrophy and pathological changes associated with hyperlipidemic nephropathy. Pharmacological interventions significantly reduced this ratio, with the triple combination of ATO, RAM, and BQ-123 demonstrating the most substantial improvement, approaching near-normal values. These findings suggest that combined therapy provides superior protection against HFD-induced weight gain and renal hypertrophy compared to monotherapy Figure 1.

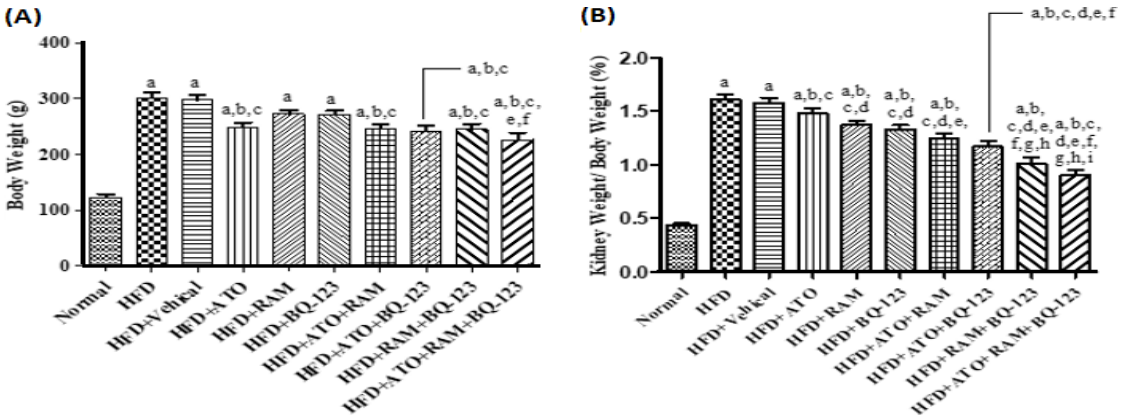

Fig. 1. Effect of ATO, RAM and BQ-123 and their combination of HFD induced body weight (A), and kinney weight vs body weight ratio (B), All values mena+SEM (n=6). [a]p<0.05 compared to normal, [b]p<0.05 compared to HFD, [c]p<0.05 compared to HFD+vehicle, [d]p<0.05 compared to HFD+ATO, [e]p<0.05 compared to HFD+RAM, [f]p<0.05 compared to HFD+BQ-123 [g]p<0.05 compared to HFD+ATO+RAM, [h]p<0.05 compared to HFD+ATO+BQ-123 and [i]p<0.05 compared to HFD+RAM+BQ-123 (one-way ANOVA followed by Student-Newman-Keuls test)

Impact of therapeutic interventions on lipid profile in experimentally induced hyperlipidemic nephropathy

The high-fat diet (HFD) group exhibited a significant elevation in serum triglycerides and total cholesterol levels compared to the normal control group ($p<0.05$), confirming the successful induction of hyperlipidemia. Treatment with atorvastatin (ATO), ramipril (RAM), or BQ-123 individually resulted in a moderate reduction in both lipid parameters, whereas combination therapies showed more pronounced effects. Dual combinations of ATO+RAM, ATO+BQ-123, and RAM+BQ-123 produced significantly greater reductions compared to individual treatments, indicating synergistic lipid-lowering potential. The most substantial improvement was observed in the triple combination group (ATO+RAM+BQ-123), where serum triglyceride and cholesterol levels were restored close to normal values ($p<0.05$ vs. HFD). These findings demonstrate that combined pharmacological intervention provides superior protection against HFD-induced dyslipidemia compared to monotherapy Figure 2.

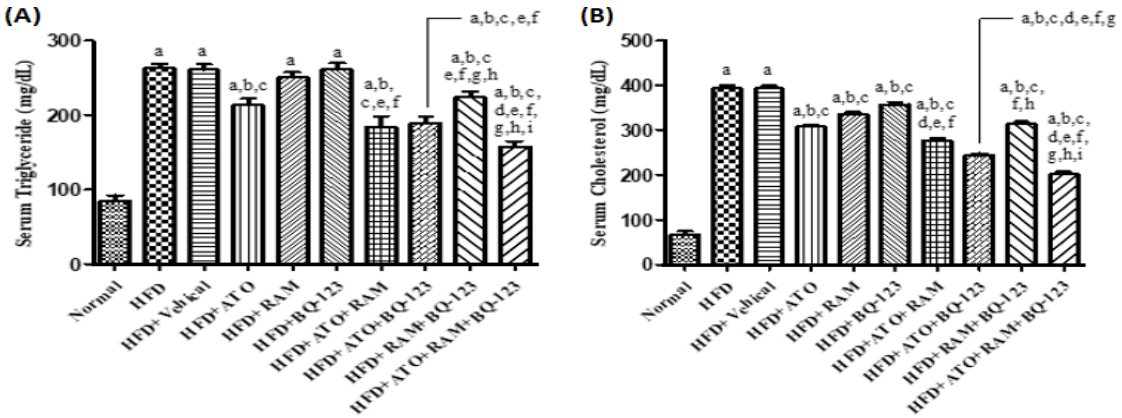

Fig. 2. Effect of ATO, RAM and BQ-123 and their combination of HFD induced body weight (A) serum triglyceride (A), and serum cholesterol (B), All values mena + SEM (n=6). [a]p<0.05 compared to normal, [b]p<0.05 compared to HFD, [c]p<0.05 compared to HFD+vehicle, [d]p<0.05 compared to HFD+ATO, [e]p<0.05 compared to HFD+RAM, [f]p<0.05 compared to HFD+BQ-123 [g]p<0.05 compared to HFD+ATO+RAM, [h]p<0.05 compared to HFD+ATO+BQ-123 and ip<0.05 compared to HFD+RAM+BQ-123 (one-way ANOVA followed by Student-Newman-Keuls test)

Impact of therapeutic interventions on biochemical parameters in experimentally induced hyperlipidemic nephropathy

High-fat diet (HFD) administration induced significant alterations in renal function biomarkers, as evident from marked elevations in serum creatinine, blood urea nitrogen (BUN), and total urinary protein levels, alongside a pronounced reduction

in serum nitrite/nitrate concentrations compared to normal controls ($p<0.05$). These changes indicate compromised renal function and impaired nitric oxide bioavailability in HFD-fed rats. Treatment with atorvastatin (ATO), ramipril (RAM), and the endothelin receptor antagonist BQ-123, either individually or in combination, resulted in substantial improvements in these parameters. Combination therapies demonstrated superior efficacy, with the triple combination of ATO+RAM+BQ-123 producing the most pronounced reduction in serum creatinine, BUN, and urinary protein levels, restoring them near normal values ($p<0.05$ vs. HFD group). Concurrently, serum nitrite/nitrate levels significantly increased in treatment groups, indicating enhanced endothelial function and nitric oxide availability. These findings suggest that multi-targeted therapeutic interventions provide additive or synergistic renoprotective effects in experimentally induced hyperlipidemic nephropathy Figure 3.

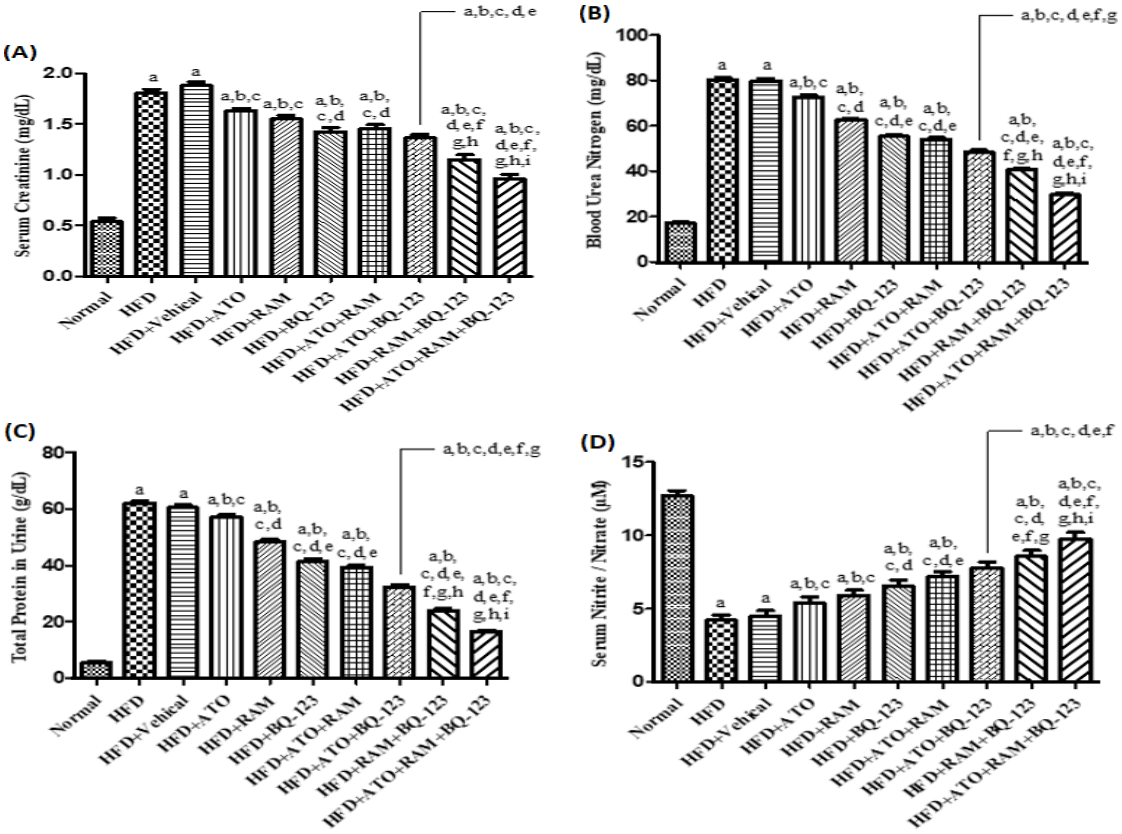

Fig. 3. Effect of ATO, RAM and BQ-123 and their combination of HFD induced serum creatinine (A) blood urea nitrogen (B), total protein in urine (C), and serum nitrite/nitrate (D). All values mean+SEM (n=6). [a]p<0.05 compared to normal, [b]p<0.05 compared to HFD, [c]p<0.05 compared to HFD+vehicle, [d]p<0.05 compared to HFD+ATO, [e]p<0.05 compared to HFD+RAM, [f]p<0.05 compared to HFD+BQ-123 [g]p<0.05 compared to HFD+ATO+RAM, [h]p<0.05 compared to HFD+ATO+BQ-123 and [i]p<0.05 compared to HFD+RAM+BQ-123 (one-way ANOVA followed by Student-Newman-Keuls test)

Impact of therapeutic interventions on antioxidant profile of kidney in experimentally induced hyperlipidemic nephropathy

Feeding rats a HFD led to a significant increase in renal lipid peroxidation, as reflected by elevated MDA levels compared with normal controls ($p<0.05$). This was accompanied by a marked decline in antioxidant defense mechanisms, including SOD, GSH, and CAT, indicating disruption of redox balance in HFD-fed animals. Treatment with ATO, RAM, and the endothelin receptor antagonist BQ-123, either alone or in combination, significantly mitigated oxidative stress, demonstrated by reduced MDA levels ($p<0.05$ vs. HFD). Antioxidant enzyme activities were simultaneously restored, with combination therapies producing greater improvement than monotherapies. Notably, the triple therapy group (ATO+RAM+BQ-123) showed the most substantial recovery, with oxidative stress parameters approaching those of normal controls.

These results highlight the synergistic efficacy of multi-targeted therapy in counteracting oxidative damage associated with hyperlipidemia-induced nephropathy Figure 4.

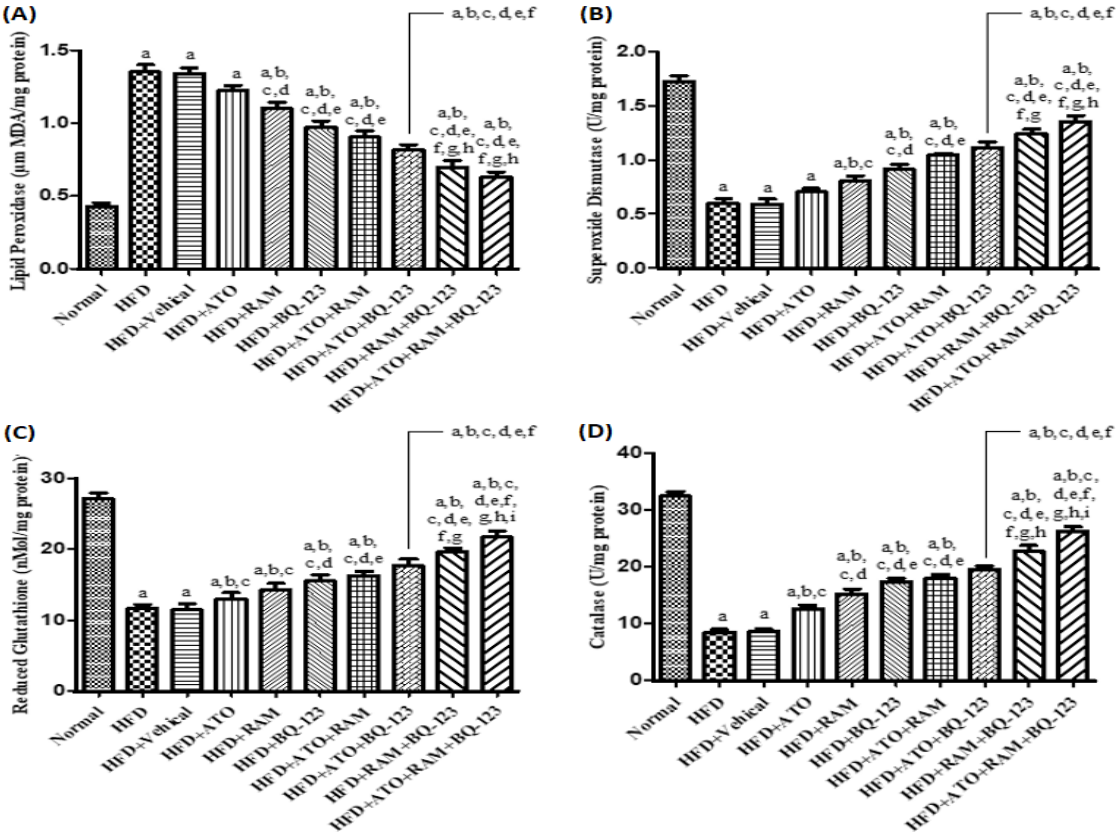

Fig. 4. Effect of ATO, RAM and BQ-123 and their combination of HFD induced alteration in lipid peroxidase (A) superoxide dismutase (B), reduced glutathione (c), and catalase (D). All values mean+SEM (n=6). [a]p<0.05 compared to normal, [b]p<0.05 compared to HFD, [c]p<0.05 compared to HFD+vehicle, [d]p<0.05 compared to HFD+ATO, [e]p<0.05 compared to HFD+RAM, [f]p<0.05 compared to HFD+BQ-123 [g]p<0.05 compared to HFD+ATO+RAM, [h]p<0.05 compared to HFD+ATO+BQ-123 and [i]p<0.05 compared to HFD+RAM+BQ-123 (one-way ANOVA followed by Student-Newman-Keuls test)

Impact of therapeutic interventions on histopathological changes of kidney in experimentally induced hyperlipidemic nephropathy

Histopathological analysis revealed that kidney sections from the normal control group (A) displayed well-preserved architecture with intact glomeruli, normal proximal (PCT) and distal convoluted tubules (DCT), and absence of pathological alterations. In contrast, the hyperlipidemic (B) and vehicle control (C) groups exhibited severe renal damage characterized by marked glomerular atrophy, tubular cast formation, interstitial infiltration, and degeneration of renal tubular structures, indicating pronounced nephrotoxicity. Treatment with atorvastatin (D), ramipril (E), or BQ-123 (F) individually led to partial histological recovery, with reduced glomerular atrophy and moderate improvement in tubular morphology, though signs of interstitial infiltration were still evident. Combination therapy with atorvastatin and ramipril (G) or atorvastatin and BQ-123 (H) demonstrated more substantial preservation of renal tissue, showing milder degenerative changes compared to monotherapy groups. The dual therapy of ramipril and BQ-123 (1) produced similar protective effects, while the triple combination of atorvastatin, ramipril, and BQ-123 (J) showed the most remarkable improvement, with nearly restored renal histoarchitecture resembling that of the normal control. These findings indicate that combination therapy, particularly the triple regimen, offers superior protection against hyperlipidemia-induced renal damage compared to individual drug treatments Figure 5.

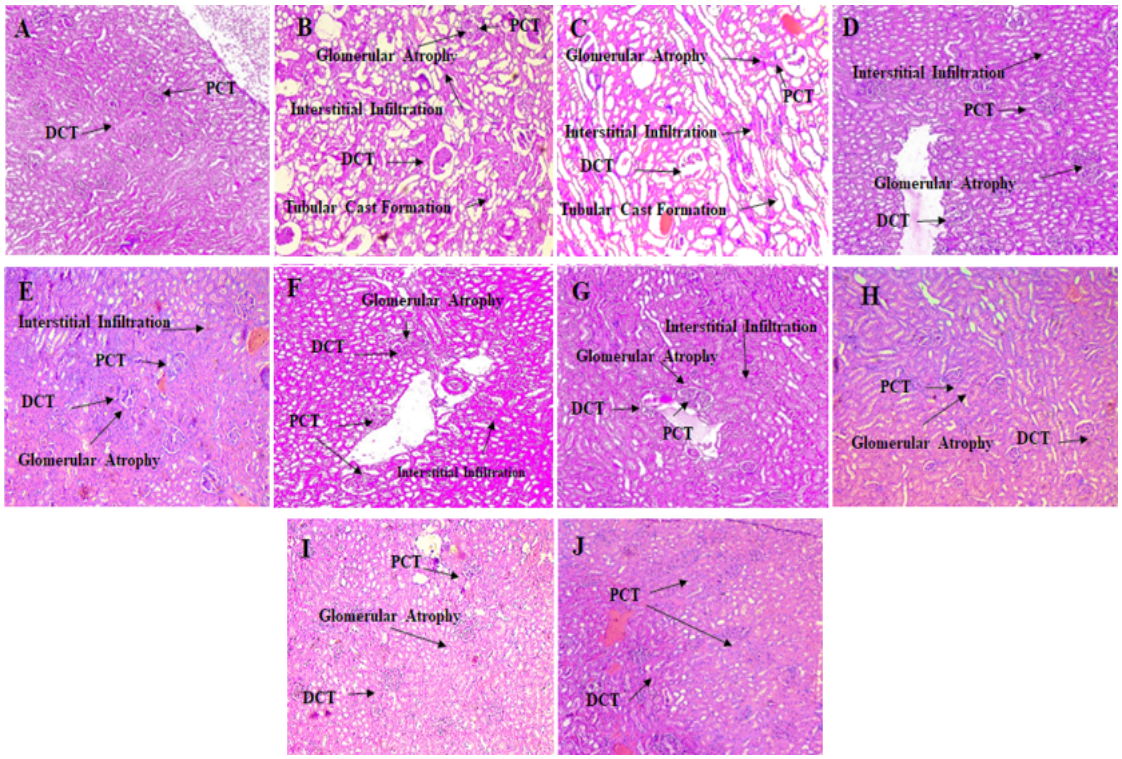

Fig. 5. Representative histopathological images of kidney sections from (A) normal control group, (B and C) hyperlipidemic and vehicle control groups, (D) atorvastatin-treated group, (E) ramipril-treated group, (F) BQ-123-treated group, (G) atorvastatin+ramipril-treated group, (H) atorvastatin+BQ-123-treated group, (1) ramipril+BQ-123-treated group, and (J) atorvastatin+ramipril+BQ-123-treated group

DISCUSSION

The study also assessed the therapeutic potency of these medications against hyperlipidemia promote nephropathy in animals. Biochemical investigations revealed that a six-week[33] high-fat diet significantly boosted the amount of cholesterol and triglycerides in bloodstream; higher lipid levels are considerd as a substantial theat for the development of nephropathy[4]. Excessive lipids may be harmful to the kidneys, according to several studies (renal lipotoxicity)[34,35]. Furthermore, elevated creatinine, blood urea nitrogen, urine protein have all identified as markers of nephropathy[36]. Consistent with research, our investigation revealed that a high-fat meal administered over six weeks markedly elevated serum creatinine levels, urinary protein, blood urea nitrogen in affected rat. In rats with hyperlipidemic diet induced nephropathy, atorvastatin and ramipril treatment notably reduced serum creatinine, urine protein, BUN and albuminuria levels. There is also evidence of the synergistic effects of lipid-lowering medications and renin-angiotensin-aldosterone system blockers in renal protection[37]. The outcome of BQ123's therapy was essentially the same as well. Our results therefore supported the renoprotective effect of atorvastatin, ramipril and BQ-123 in animals. The greatest effect of each of these variables was facilitated by the combination of treatments, demonstrating the impact of atorvastatin, ramipril and BQ-123. Moreover, a decrease in the serum nitrite levels and an increases the weight of kidney and body ratio had been identified as indicators of nephropathy[38]. In rats with hyperlipidemia, the weight of kidney and body ratio increased concurrently. Serum NO levels can be substantially changed by ramipril treatment. Still, BQ-123[39], either by itself and in combination with atorvastatin & ramipril, considerably increased the systemic circulation's lowered level of blood nitrite and reduced the experimental animals kidney weight/body weight ratio.

The decrease of other lipid profiles may be attributed to the restoration of NO-mediated endothelial activities, whilst the increase of HDL levels may be linked to the suppression of ET-1

secretion[40]. An increased concentration of nitric oxide in serum indicated enhanced kidney function, potentially attributable to improved renal blood flow resulting from the vasodilatory effects of BQ-123[41]. These alterations in the hyperlipidemic group could be the result of HFD deregulating lipid metabolism, primarily by reducing β-oxidation and raising cholesterol production, and oxidative stress by reducing the expression of genes for free radical scavenger enzymes[42]. In this investigation, hyperlipidemia elevates oxidative stress indicators, including LPO, ROS and GSH in the tissue of kidney in experimental rat. This analysis indicates that the heightened level of ROS (reactive oxygen species) is corroborated by the increased concentration of the malondialdehyde (MDA), an indicator of lipid peroxidation[43]. HFD caused aberrant elevations in lipid peroxidation, blood total cholesterol, triacylglycerol, and LDL, with reduced lipoprotein lipase activity and a compromised antioxidant defense system[42]. By decreasing MDA levels and raising SOD, GSH levels and catalase in kidney tissue activity, the current study demonstrated that atorvastatin, ramipril and BQ-123 had a protective impact on kidney tissue. A possible reason for ramipril's antioxidant activity is the thiol group, which enhances the oxidative balance by reacting with hydroxyl or superoxide anion radicals and scavenging them[44].

Hyperlipidemic rats also displayed an increased kidney-to-body weight ratio and reduced serum nitrite levels, both of which are indicative of nephropathy[38]. Ramipril treatment significantly restored serum nitrite levels, while BQ-123-alone or in combination-further improved nitric oxide (NO) availability and reduced the kidney-to-body weight ratio[39]. Restoration of NO levels is likely linked to improved endothelial function and renal blood flow, while increased high-density lipoprotein (HDL) levels may be associated with the suppression of endothelin-1 (ET-1) secretion[40,41].

Additionally, hyperlipidemia induced oxidative stress in renal tissues, evidenced by elevated levels of lipid peroxidation (MDA), reactive oxygen species (ROS), and reduced antioxidant enzyme activity, including superoxide dismutase (SOD), glutathione (GSH), and catalase. This imbalance is consistent with previous findings that HFD impairs lipid metabolism, enhances cholesterol synthesis, and downregulates antioxidant defense genes[42,43]. Treatment with atorvastatin, ramipril, and BQ-123 significantly reduced MDA levels while restoring SOD, GSH, and catalase activity, indicating attenuation of oxidative damage. Ramipril's antioxidant effects may be partially attributed to its thiol group, which scavenge free radicals such as hydroxyl and superoxide anion species[44].

Overall, the findings suggest that atorvastatin, ramipril, and BQ-123 exert complementary renoprotective effects through lipid-lowering, antioxidant, and endothelial function-enhancing mechanisms, with combination therapy offering maximal benefit in hyperlipidemia-induced nephropathy.

CONCLUSION

The findings of this study demonstrate that combined treatment with atorvastatin, ramipril, and BQ-123 effectively mitigates biochemical disturbances, oxidative stress, and structural renal damage associated with hyperlipidemia-induced nephropathy in rats. The synergistic effects observed suggest that this therapeutic combination not only improves lipid metabolism and renal function but also enhances antioxidant defense and endothelial integrity. These results highlight the potential of atorvastatin, ramipril, and BQ-123 as a promising adjunctive strategy for the management of hyperlipidemic nephropathy, warranting further investigation in preclinical and clinical settings.

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Conflict of interest

The author declare that we have no conflict of interest.

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