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Original Article

Tricin Ameliorates Renal Fibrosis and Inhibits the Progression of Chronic Kidney Disease in Adenine-Induced Rats

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ABSTRACT

Background: Renal fibrosis, a defining feature of Chronic Kidney Disease (CKD) development, is marked by the over deposition of extracellular matrix proteins, resulting in structural and functional impairment of the kidney. The limitations of existing therapies, together the escalating prevalence of CKD, highlight the pressing need for innovative therapeutic strategies that might proficiently avert or reverse renal fibrosis and maintain kidney functionality. **Objectives:** This study aimed to assess the impacts of tricin in a renal fibrosis induced by adenine in rats and to clarify the underlying pharmacological mechanisms of tricin. **Materials and Methods:** Renal fibrosis was induced in the experimental rats by administering 250 mg/kg of adenine daily for first two weeks, followed by every alternative day during the subsequent four weeks. Tricin at 50 and 100 mg/kg concentrations were administered to the rats daily from 2nd and 6th weeks. The body weights of the experimental rats were evaluated carefully on the weekly basis. Following the completion of the treatments, the levels of serum creatinine, Blood Urea Nitrogen (BUN), monophosphate levels, and inflammatory cytokine levels were evaluated. The kidneys of the experimental rats were subjected to histopathological analysis. **Results:** The treatment of tricin at 50 and 100 mg/kg concentrations markedly elevated body weight and subsequently reduced renal index in adenine-induced rats. Moreover, tricin treatment decreased the serum creatinine and BUN levels in the adenine-induced rats. Tricin treatment markedly reduced inflammatory cytokine levels and regulated the monophosphate levels in rats with renal fibrosis. The histological analysis confirmed the therapeutic effectiveness of tricin against the renal fibrosis. **Conclusion:** This study demonstrated that tricin ameliorated adenine-induced renal fibrosis and inhibited the progression of CKD in rats, which may be due to its anti-inflammatory properties.

Keywords: Creatinine, Inflammatory cytokines, Monophosphates, Renal fibrosis, Tricin.

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INTRODUCTION

Chronic Kidney Disease (CKD) is a major global health issue, defined by a gradual and irreversible decrease in kidney function over a period of months or years. CKD is not a single disease, but rather a group of heterogeneous conditions affecting the function and structure of the kidneys. Renal fibrosis, a hallmark of CKD development, is marked by the excessive deposition of Extracellular Matrix (ECM) proteins; resulting in structural and functional impairment of the kidney.[1] The incidence of CKD has reached epidemic levels, rendering it a significant public health issue that imposes a considerable financial burden on global healthcare systems. CKD is connected with increased risks of cardiovascular disease, kidney failure, and premature death. The insidious onset and variable progression of CKD often lead to delayed detection and treatment, contributing to its substantial morbidity and mortality.[2] As kidney function declines, individuals with CKD may experience a wide array of symptoms, including fatigue, edema, nausea, and shortness of breath, significantly impacting their quality of life. Furthermore, CKD imposes a heavy financial burden on healthcare systems due to the high costs associated with dialysis, kidney transplantation, and the management of associated complications.[3] The etiology of CKD is multifaceted and intricate, frequently encompassing a confluence of genetic, environmental, and lifestyle causes. Diabetes mellitus and hypertension are the primary contributors to CKD globally, representing a substantial percentage of cases. Additional

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prevalent etiologies of CKD encompass glomerulonephritis, polycystic kidney disease, obstructive uropathy, and exposure to nephrotoxic agents.[4]

The pathogenesis of renal fibrosis, the common endpoint of CKD progression, is a complex and dynamic mechanism involving multiple cell types, signaling pathways, and ECM components. Regardless of the initial insult, the kidneys undergo a cascade of structural and functional changes that ultimately lead to fibrosis, characterized by over deposition of ECM proteins in the renal interstitium.[5] The development of renal fibrosis involves a complex interplay of cellular and molecular events, including inflammation, tubular atrophy, and microvascular rarefaction. Inflammation plays a crucial role in the onset of renal fibrosis, with immune cells infiltrating the kidney and releasing cytokines and chemokines that promote fibroblast activation and matrix deposition.[6] Oxidative stress and endoplasmic reticulum stress also participate in the onset of renal fibrosis by promoting inflammation, apoptosis, and ECM production. Irreversible renal injury includes nephron loss resulting from glomerular or tubular cell deletion, fibrosis impacting both glomeruli and tubules, and abnormalities in renal vasculature. Necroinflammation, a self-amplifying cycle between tubular cell death and interstitial inflammation, exacerbates renal damage.[7] The interaction of molecular processes such as Epithelial-Mesenchymal Transition (EMT), cell cycle arrest, and metabolic disorder show tubular cells playing a role in progressive renal damage. Ultimately, the progressive accumulation of ECM leads to scarring, architectural distortion, and loss of functional nephrons, resulting in end-stage renal disease.[8]

Contemporary treatment approaches for CKD predominantly include the management of risk factors, including hypertension, proteinuria, and diabetes, with the mitigation of renal damage development. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers are frequently recommended to diminish proteinuria and lower blood pressure, therefore mitigating the progression of CKD. However, despite these interventions, a significant proportion of patients continue to experience disease progression, eventually requiring renal replacement therapy like dialysis or kidney transplantation.[9] The limitations of current treatment options, coupled with the rising incidence of CKD, underscore the urgent need for novel therapeutic approaches that can effectively prevent or reverse renal fibrosis and preserve kidney function. The search for safe and effective alternative therapies for CKD has led to growing interest in plant bioactive compounds, which have a long history of use in conventional medicine.[10] Tricin, a 5,7,4′-trihydroxy-3′,5′-dimethoxyflavone is an major bioactive compound found extensively in the rice bran and other grasses like wheat, maize, and barley. The various pharmacological properties of the tricin was already reported, including its anti-obesity,[11] anticancer,[12] antiallergic,[13] immunoregulatory,[14] hepatoprotective,[15] and neuroprotective activities.[16] Though, the influence of tricin on renal fibrosis caused by adenine is still remain unclear. Therefore, this work intended to assess the therapeutic impact of tricin in a renal fibrosis rat model caused by adenine and to elucidate the underlying pharmacological processes, therefore providing a more robust theoretical foundation for the use of tricin in treating renal fibrosis.

MATERIALS AND METHODS

Animals

The present work utilized the male Sprague-Dawley rats. The rats were caged in sterilized polypropylene confines under controlled laboratory environments, maintaining a temperature of 22-26°C and humidity of 50-60%. A 12-hr cycle of alternating illumination and darkness was established. During the entire experimental period, all rats were provided with free access to a conventional rodent meal and purified drinking water. Before the commencement of the research, all rats had one week acclimation phase in a laboratory environment.

Experimental groups and treatment protocol

Following a 7-day acclimatization period, the rats were arbitrarily allocated into four experimental groups (n=6/group). Group I was control consisted of rats that received 0.9% saline for a duration of 6 weeks. Group II consisted of rats administered 250 mg/kg of adenine daily for initial two weeks, followed by every alternative day during the subsequent four weeks.[17] Groups III and IV rats were administered 50 and 100 mg/kg of tricin (dissolved in 0.5% carboxymethyl cellulose [CMC]),[16] respectively daily, commencing in week 2 and continuing for the subsequent 4 weeks, alongside the adenine regimen as mentioned in Group II. The body weights of the experimental rats were evaluated carefully on the weekly basis. Upon conclusion of the treatments, the rats were anesthetized and subsequently killed. The kidneys were swiftly removed and weighed; one segment was preserved in paraformaldehyde (4%) for histological examination, while the remaining kidneys were quickly frozen for further studies. The renal index was determined using the equation:

$$\text{Renal Index (\%)} = (\text{Kidney Weight (g)} / \text{Body Weight (g)})*100$$

Analysis of biochemical marker levels

The concentrations of cyclic Adenosine Monophosphate (cAMP), cyclic Guanosine Monophosphate (cGMP), Blood Urea Nitrogen (BUN), and creatinine in the serum of experimental rats were assessed using commercial test kits. Each test was performed with three replicates using the manufacturer's recommended guidelines (Elabscience, USA).

Analysis of inflammatory cytokine levels

The removed kidneys were homogenized in saline, and the suspension was centrifuged at 5000 rpm for 20 min. The supernatant was utilized to assess inflammatory cytokine concentrations. The TNF-α, IL-6, and IL-1β concentrations were assessed using the kits. The tests were conducted in triplicate as per the manufacturer's specified protocols (Abcam, USA).

Histopathological analysis

The renal tissue samples were obtained and subjected to a 10% neutral formalin solution to assess the histopathological alterations. Subsequently, the tissues were paraffin-embedded, sectioned to 5 µm, and stained with eosin-hematoxylin. Finally, the kidney tissues were examined microscopically at 200× magnification to assess the histology.

Statistical analysis

The results were evaluated using GraphPad Prism and illustrated as the mean±SD of triplicates. The data were studied with one-way ANOVA and Tukey's *post hoc* test, with significance set at $p<0.05$.

RESULTS

Effect of tricin on the bodyweight of experimental rats

The body weights of the experimental rats were assessed, with findings illustrated in Figure 1. The rats with adenine-induced renal fibrosis had significantly reduced body weight over a period of weeks when compared with control. Whereas, the treatment of tricin at a doses of 50 and 100 mg/kg concentrations markedly increased the body weight of adenine-induced rats.

Effect of tricin on the renal index, creatinine, and BUN levels in the experimental rats

Figure 2 illustrates the concentrations of serum creatinine, BUN, and renal index of the experimental rats. The adenine-induced rats demonstrated a marked elevation in renal index, BUN, and creatinine concentrations relative to the control group. Nonetheless, the tricin treatment at dosages of 50 and 100 mg/kg showed a considerable reduction in real index, creatinine, and BUN concentrations in rats with adenine-induced renal fibrosis.

Effect of tricin on the cAMP and cGMP levels in the experimental rats

Figure 3 illustrates the levels of cAMP, cGMP, and cAMP/cGMP ratio in the experimental rats. The experimental rats with adenine-induced renal fibrosis exhibited a significant increase in cGMP and subsequent reduction in cAMP and cAMP/cGMP ratio when compared with control. Interestingly, the treatment of 50 and 100 mg/kg concentrations of tricin to the adenine-induced rats resulted in a considerable reduction in cGMP and elevation in cAMP and cAMP/cGMP ratio when compared with adenine alone-induced rats.

Effect of tricin on the inflammatory cytokines in the experimental rats

The effect of tricin treatment on the inflammatory cytokines was evaluated, with results presented in Figure 4. The adenine-induced rats revealed a substantial elevation in TNF-α, IL-1β, and IL-6 levels in their kidney tissue compared with control group. The treatment of 50 and 100 mg/kg of tricin to the adenine-induced rats led to a substantial decrease in all these cytokine levels. These findings indicates the anti-inflammatory properties of the tricin.

Effect of tricin on kidney histology of the experimental rats

The histological examination was performed on the renal tissues of the rats, with the results illustrated in Figure 5. The kidneys of control rats exhibited characteristic morphology with clear renal histoarchitectures. Nevertheless, the kidneys of the adenine-induced rats exhibited renal tubular casts, glomerular atrophy, inflammatory cell infiltrations, and epithelial cell injury, and extensive adenine crystal depositions. Interestingly, the tricin treatment at doses of 50 and 100 mg/kg markedly ameliorated histological abnormalities in the kidneys of rats caused by adenine induction.

DISCUSSION

Renal fibrosis, a common endpoint of various CKDs, represents a critical area of unmet medical need due to its irreversible nature and contribution to renal failure. The pathophysiology of renal fibrosis is a complex process involving a cascade of events triggered by initial kidney injury, encompassing inflammation, immune cell infiltration, and the activation of fibroblasts.[18] Inflammation is intricately associated with fibrosis and significantly contributes to the initiation and advancement of renal disorders. The persistent advancement of CKD is believed to stem from a self-sustaining cycle of fibrosis triggered by an initial damage. This cycle of injury and repair can become maladaptive, resulting in excessive ECM deposition, tubular atrophy, and ultimately, the destruction of functional nephrons.[19] Renal tubules are recognized as active drivers of CKD progression through mechanisms like partial EMT, cell-cycle arrest, and metabolic condition. The relentless deposition of ECM, driven by activated fibroblasts, distorts the normal kidney architecture, leading to impaired filtration, tubular dysfunction, and compromised overall kidney function.[20]

The development of tubulointerstitial fibrosis encompasses many mechanisms, including senescence, EMT, inflammation, chronic hypoxia, and ROS, all stemming from sustained cellular damage and localized cell death. Furthermore, metabolic changes within immune cells and the influence of inflammation on fibroblast metabolism have emerged as critical factors in the progression of

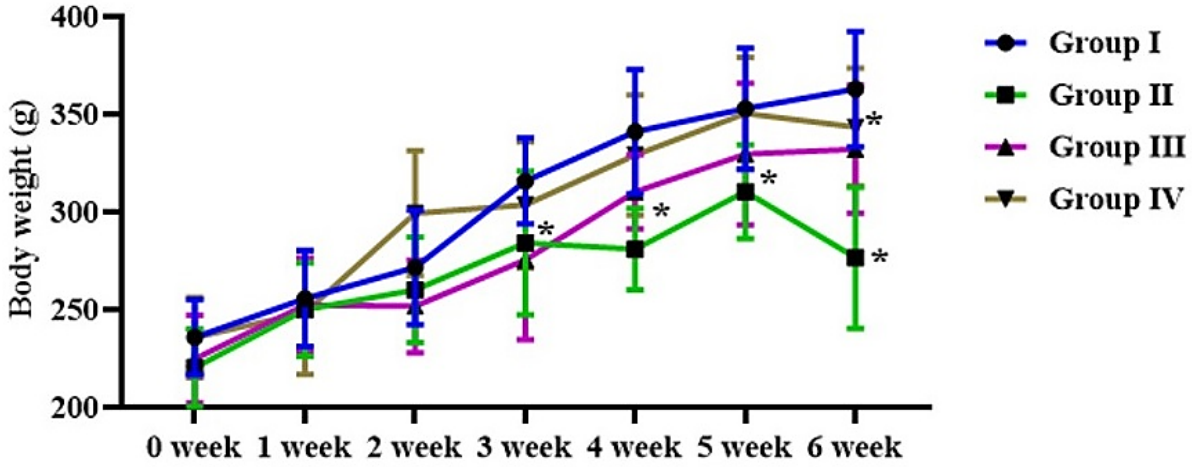

Figure 1: Effect of tricin on the bodyweight of experimental rats. The data depicted in each bar is the mean±SD of triplicate measurements. An one-way ANOVA and Tukey's *post hoc* test were conducted to ascertain the level of statistical significance. Note: '*' indicates that the values are significant at $p<0.01$ compared to the control group; '**' indicates that the values are significant at $p<0.05$ compared to the renal fibrosis-induced group.

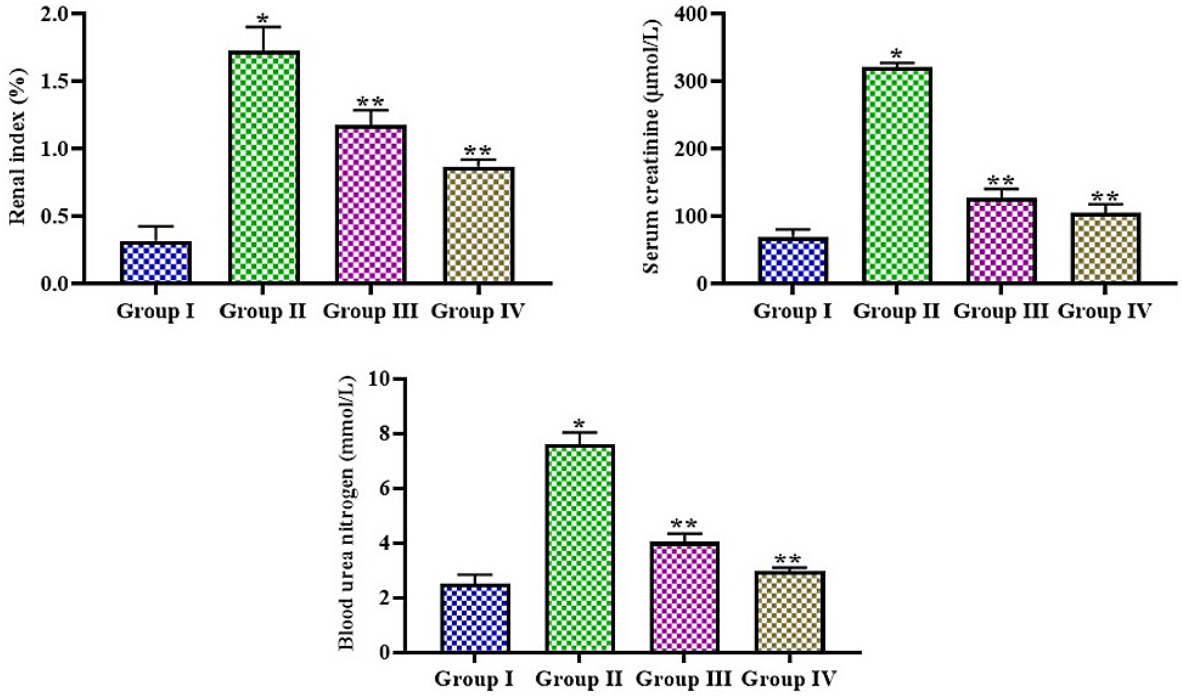

Figure 2: Effect of tricin on the renal index, creatinine, and BUN levels in the experimental rats. The data depicted in each bar is the mean±SD of triplicate measurements. An one-way ANOVA and Tukey's *post hoc* test were conducted to ascertain the level of statistical significance. Note: '*' indicates that the values are significant at $p<0.01$ compared to the control group; '**' indicates that the values are significant at $p<0.05$ compared to the renal fibrosis-induced group.

fibrosis.[21] Given the limitations of current therapies in effectively halting or reversing renal fibrosis, there is a pressing need for the development of safe and effective alternative treatments. Comprehending the mechanism by which tubular damage promotes inflammation and fibrosis is essential for developing therapies to impede the course of CKD.[22]

Early diagnosis and precise evaluation of renal fibrosis are essential for timely intervention and prevention of disease progression, highlighting the importance of reliable biomarkers that can reflect the underlying pathological processes.[23] While traditional markers like serum creatinine and BUN have been used for decades to assess kidney function, their utility in the context of renal fibrosis is limited due to their late elevation in the disease course and lack of specificity for fibrotic changes. Estimated glomerular filtration rate is often derived from serum creatinine levels, but it is not directly measurable in most clinical settings.[24] Creatinine, a breakdown product of creatine phosphate in muscle, is freely filtered by the glomeruli and excreted in the urine. BUN, an indicator of blood urea levels, is a frequently utilized test of renal function. Urea is a metabolic byproduct

generated in the liver during protein catabolism, then filtered by the glomeruli and eliminated in the urine.[25] The present findings indicated that adenine-induced rats illustrated an increased BUN and creatinine levels. Interestingly, the tricin treatment considerably reduced the creatinine and BUN levels in rats with adenine-induced renal fibrosis.

The advancement of CKD entails the activation of cellular mechanisms coming from several kidney compartments, with biochemical routes of cellular damage that contribute to these mechanisms. cAMP and cGMP are ubiquitous second messengers that mediate the effects of a wide range of hormones and neurotransmitters, exerting multifaceted regulatory actions in various tissues, including the kidney.[26] In the context of renal fibrosis, cAMP and cGMP have emerged as important signaling molecules with both protective and pathogenic roles, relying on the specific context and stage of the disease. The understanding of pathogenic factors that contribute to renal fibrosis in nephropathy has expanded considerably.[27] Lesions in nephropathy and chronic renal failure progress over time due to intricate pathophysiological processes, with many cellular pathways typically functioning concurrently. Disruption of these signaling pathways may facilitate the onset and advancement of renal fibrosis.[28]

Aberrant cAMP signaling has been participated in the development of renal fibrosis, with studies demonstrating that elevated cAMP levels can promote the production of ECM components by renal cells.[29] Conversely, cGMP signaling has generally been connected with renoprotective effects, like vasodilation, inhibition of cell proliferation, and suppression of inflammation. However, the precise roles of cAMP and cGMP in renal fibrosis are complex and context-dependent, warranting further investigation to fully elucidate their contributions to the disease process. It has been revealed that the increase of cAMP levels stimulates ECM production.[30] Emerging evidence suggests that renal tubular EMT is an important event in renal interstitial fibrosis. The process of EMT implicates cAMP and cGMP signaling in modulating cellular plasticity and phenotype transition.[31] Given the involvement of cAMP and cGMP in renal fibrosis, these cyclic nucleotides and their downstream targets represent potential diagnostic biomarkers for the disease. Measuring the levels of cAMP and cGMP in urine or plasma may provide valuable information about the severity and advancement of renal fibrosis, and the effectiveness of therapeutic interventions.[32] In this work, the findings exhibited that rats with adenine-induced renal fibrosis has increased cGMP and subsequently reduced cAMP and cAMP/cGMP ratio when compared with control. Whereas, the tricin treatment to the adenine-induced rats resulted in decrease of cGMP and elevation in cAMP and cAMP/cGMP ratio.

Inflammation, orchestrated by a complex interplay of immune cells and signaling molecules, plays a pivotal role in the onset of renal fibrosis.[33] The intricate process involves a cascade of events, beginning with tissue injury that triggers an inflammatory response, leading to influx of immune cells, the

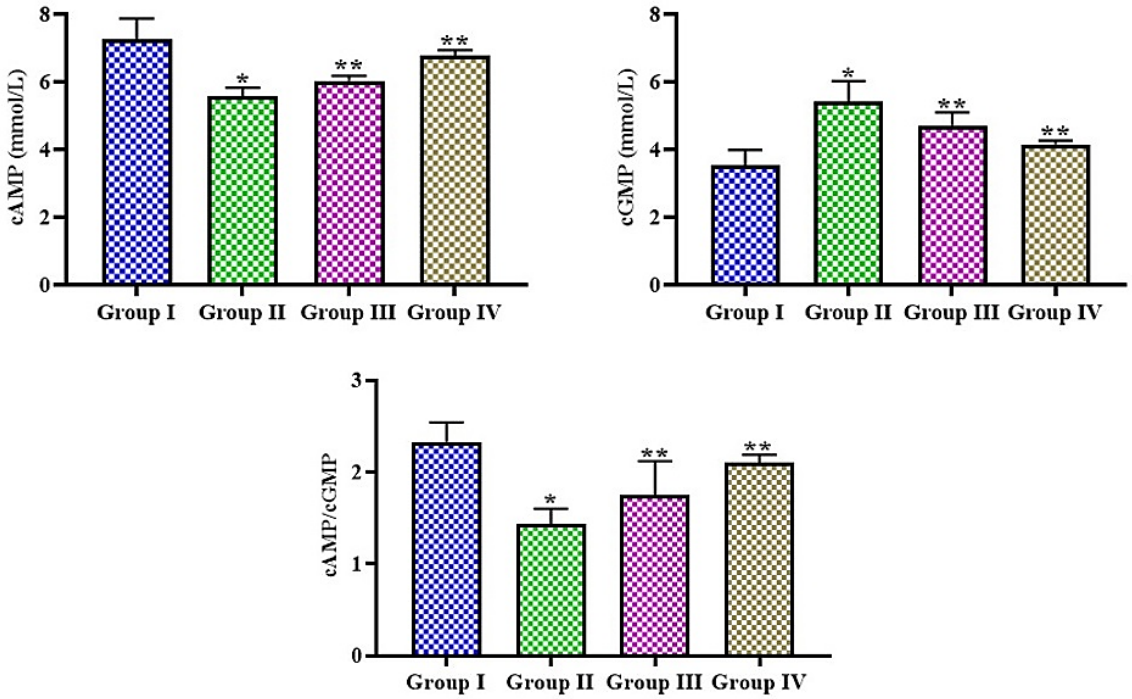

Figure 3: Effect of tricin on the cAMP and cGMP levels in the experimental rats. The data depicted in each bar is the mean±SD of triplicate measurements. An one-way ANOVA and Tukey's *post hoc* test were conducted to ascertain the level of statistical significance. Note: '*' indicates that the values are significant at $p<0.01$ compared to the control group; '**' indicates that the values are significant at $p<0.05$ compared to the renal fibrosis-induced group.

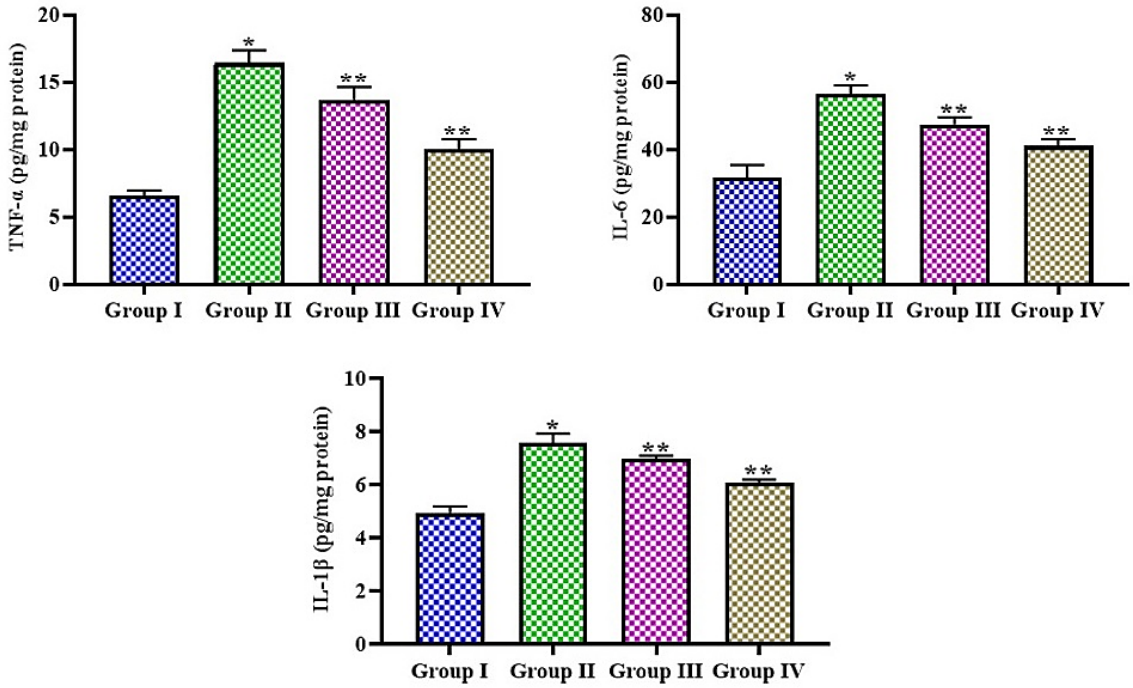

Figure 4: Effect of tricin on the inflammatory cytokine levels in the experimental rats. The data depicted in each bar is the mean±SD of triplicate measurements. An one-way ANOVA and Tukey's *post hoc* test were conducted to ascertain the level of statistical significance. Note: '*' indicates that the values are significant at $p<0.01$ compared to the control group; '**' indicates that the values are significant at $p<0.05$ compared to the renal fibrosis-induced group.

release of pro-fibrotic regulators, and ultimately, the activation of matrix-producing cells. Renal fibrosis represents a critical determinant of disease progression, impacting all kidney structures and disrupting tissue homeostasis, ultimately leading to kidney failure.[34] The inflammatory reaction in the kidney involves an array of immune cells, including macrophages, monocytes, and other leukocytes, which infiltrate the renal tissue in response to injury signals. These cells release a variety of inflammatory markers, including cytokines and chemokines that participate in the onset of fibrosis. Among the key inflammatory cytokines implicated in renal fibrosis, TNF-α, IL-6, and IL-1β have garnered considerable attention due to their multifaceted roles in promoting inflammation and fibrogenesis.[35]

TNF-α is a pleiotropic cytokine that exerts its pro-inflammatory and pro-fibrotic effects through diverse mechanisms. TNF-α influences renal fibrosis by promoting the pro-inflammatory molecule expressions, stimulating the accumulation of ROS, and activating intracellular signaling that result in increased synthesis of ECM components.[36] TNF-α directly stimulates fibroblasts, the primary matrix-producing cells in the kidney, to synthesize collagen and other ECM proteins, resulting in matrix accumulation and fibrosis. TNF-α also enhances the generation of other pro-inflammatory cytokines, further amplifying the inflammatory cascade and contributing to renal damage.[37] The cytokine induces the EMT, augmenting the population of fibroblasts and promoting fibrosis. The persistent inflammatory state, characterized by elevated levels of TNF-α and other pro-inflammatory mediators, perpetuates renal injury, creating a vicious cycle of inflammation, fibrosis, and progressive loss of renal function.[38]

IL-6, another key inflammatory cytokine, plays a complex role in renal fibrosis, exhibiting both pro-inflammatory and pro-fibrotic effects. IL-6 induces the production of acute-phase proteins, stimulates the growth of mesangial cells, and enhances the generation of ECM components. The cytokine enhances the production of pro-fibrotic mediators, like TGF-β, further amplifying the fibrotic response.[39] By stimulating the production of pro-angiogenic factors, IL-6 promotes neovascularization, which can participate in the onset of renal fibrosis. The cytokine enhances the expression of adhesion molecules on endothelial cells, facilitating the recruitment of leukocytes to the kidney and perpetuating the inflammatory response.[40] IL-1β, a potent pro-inflammatory cytokine, exerts its detrimental effects on renal tissue through multiple mechanisms. IL-1β promotes the expression of adhesion molecules on endothelial cells, facilitating the infiltration of leukocytes into the kidney and amplifying the inflammatory response.[41] IL-1β also stimulates the accumulation of ROS, leading to oxidative stress and cellular damage, which further participates in the advancement of renal fibrosis. The cytokine also enhances the release of other pro-inflammatory cytokines, developing a positive feedback loop that extends the inflammation. The cytokine directly stimulates fibroblasts to synthesize collagen and other ECM proteins, resulting in matrix accumulation and fibrosis.[42] In this work, we found that adenine-induced rats displayed increased TNF-α, IL-1β, and IL-6 levels in their renal tissues compared to the control. Interestingly,

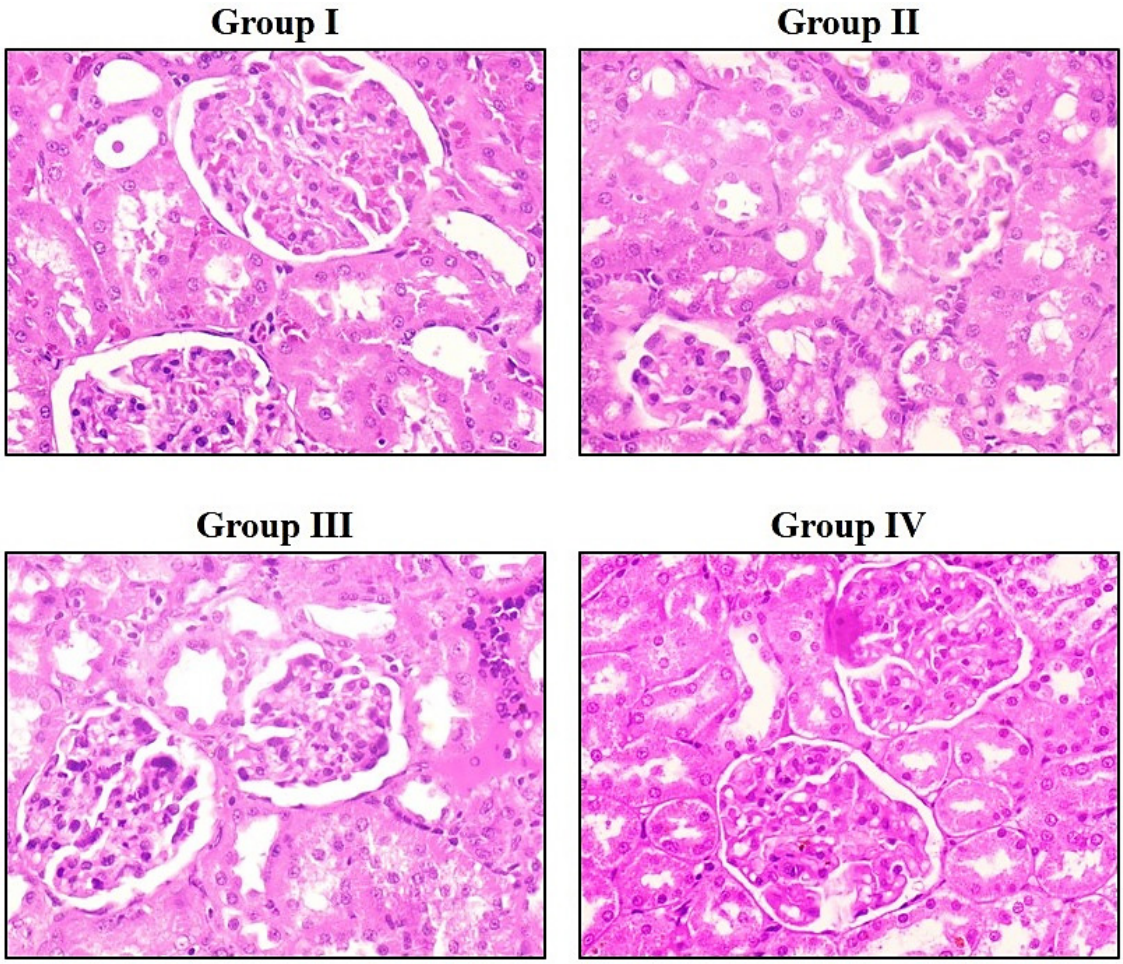

Figure 5: Effect of tricin on kidney histology of the experimental rats. Group I: Normal control group; Group II: Rats with 250 mg/kg of adenine-induced renal fibrosis; Groups III and IV: Renal fibrosis + 50 and 100 mg/kg of tricin, respectively treated rats.

the tricin treatment substantially reduced all the cytokine levels in the renal tissues of adenine-induced rats, which evidences its anti-inflammatory properties. In addition, it must be considered that the present study has several limitations. This study only investigated the effects of tricin in a single model of CKD and did not assess fibrosis markers, ROS-related markers, or functionally relevant indicators of CKD progression. Additionally, the study lacked a positive control, and the pharmacokinetics and toxicity profile of tricin were not thoroughly evaluated. These limitations will be rectified in future studies, which will focus on evaluating tricin's effects in multiple CKD models, assessing fibrosis markers and ROS-related markers, including a positive control, and thoroughly evaluating tricin's pharmacokinetics and toxicity profile to provide a more comprehensive understanding of tricin's therapeutic potential.

CONCLUSION

This study demonstrated that tricin ameliorated adenine-induced renal fibrosis and inhibited the progression of CKD in rats. Tricin treatment significantly increased the body weight, reduced the renal index, creatinine, and BUN concentrations in the adenine-induced rats. Furthermore, the tricin treatment considerably decreased the cGMP levels and subsequently reduced the cAMP levels and cAMP/cGMP ratio in the adenine-induced rats. Additionally, the tricin treatment decreased inflammatory cytokines in the kidneys and improved renal histology of the adenine-induced rats. This may be because to its anti-inflammatory properties. Further research is necessary to investigate the impact of tricin in various models of acute and chronic renal disorders. The precise mechanism behind the therapeutic action of tricin requires more investigation.

ACKNOWLEDGEMENT

Nil.

ABBREVIATIONS

CKD: Chronic Kidney Disease; ECM: Extracellular matrix; EMT: Epithelial-mesenchymal transition; cAMP: cyclic Adenosine monophosphate; cGMP: cyclic Guanosine monophosphate; BUN: Blood urea nitrogen; IL-1β: Interleukin-1β; IL-6: Interleukin-6; TNF-α: Tumor necrosis factor-α.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ETHICAL APPROVAL

Animal approval: the project has been approved by committee of affiliated hospital of hebei university. (Approval no. HDFYLL-KY-2023-159).

SUMMARY

This study demonstrated that tricin ameliorated adenine-induced renal fibrosis and inhibited the progression of CKD in rats. The body weights of the experimental rats were evaluated carefully on the weekly basis. Following the completion of the treatments, the levels of serum creatinine, Blood Urea Nitrogen (BUN), monophosphate levels, and inflammatory cytokine levels were evaluated. The kidneys of the experimental rats were subjected to histopathological analysis. Tricin treatment significantly increased the body weight, reduced the renal index, creatinine, and BUN concentrations in the adenine-induced rats. Furthermore, the tricin treatment considerably decreased the cGMP levels and subsequently reduced the cAMP levels and cAMP/cGMP ratio in the adenine-induced rats. Additionally, the tricin treatment decreased inflammatory cytokines in the kidneys and improved renal histology of the adenine-induced rats. The precise mechanism behind the therapeutic action of tricin requires further investigations.

DATA AVAILABILITY

Data will be made available on request.

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