

Nephroprotective Effects of Sarsasapogenin in Adenine-Induced Chronic Kidney Failure in Experimental Rats

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ABSTRACT

Background: Chronic Kidney Disease (CKD), characterized by a progressive decrease in kidney function, has become a prominent health issue worldwide. The limitations of existing therapeutics for CKD underscore the pressing need for safe and effective alternative therapies that might target the underlying pathogenic pathways and inhibit disease progression. **Objectives:** In this work, we studied the nephroprotective effects of sarsasapogenin in adenine-induced CKD model in rats. **Materials and Methods:** The experimental rats were administered 200 mg/kg of adenine for four weeks to induce CKD, and concurrently treated with sarsasapogenin (30 and 60 mg/kg, respectively) by oral route for four weeks. Rats were observed weekly for alterations in body weight and food intake. The concentrations of biochemical markers, including uric acid, creatinine, urea nitrogen, electrolytes, and liver function marker enzymes in the serum was evaluated using kits. The biomarkers of oxidative stress and inflammatory cytokines were evaluated using kits. The kidney tissues were subjected to the histopathological analysis. **Results:** The current findings indicated that sarsasapogenin treatment increased body weight and food intake of the adenine-induced rats. The serum levels of the creatinine, uric acid, and urea nitrogen in the adenine-induced rats were considerably reduced by the sarsasapogenin treatment. Furthermore, sarsasapogenin treatment significantly increased antioxidant levels, reduced inflammatory cytokines, and regulated electrolyte levels in the adenine-induced rats. Moreover, the findings of the histological study has further evidenced the nephroprotective properties of the sarsasapogenin. **Conclusion:** The present findings demonstrate that sarsasapogenin treatment can mitigate and protect against adenine-induced CKD in rats. The beneficial nephroprotective effects of sarsasapogenin may be due to its notable antioxidant and anti-inflammatory activities.

Keywords: Renal Fibrosis, Adenine, Creatinine, Inflammation, Sarsasapogenin.

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INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a progressive deterioration of kidney function and/or structure, persisting for a duration exceeding three months, thereby posing significant implications for overall health. This condition is characterized by its insidious nature, where the reduction in renal function develops independently of the primary cause of damage, or external factors such as infection, inflammation, or exposure

to toxins.¹ The classification of CKD is primarily based on the estimated Glomerular Filtration Rate (eGFR) and the presence of albuminuria, which are indicative of kidney function and damage, respectively. The GFR serves as a key marker for assessing the kidney's capacity to excrete waste products from the blood, while albuminuria signifies damage to the glomerular filtration barrier, resulting in abnormal protein leakage into the urine.² The worldwide prevalence of CKD is alarmingly high, affecting more than 10% of the world's population. Projections indicate that CKD will be the fifth major cause of mortality by 2040, highlighting the urgency for increased awareness, prevention, and effective management strategies.³ The increasing incidence of diabetes and hypertension, major causes for CKD, contributes to the escalating global burden of the disease. It is estimated that a significant proportion of individuals with CKD remain undiagnosed, further exacerbating the public health challenge.



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Timely diagnosis and management of modifiable risk factors are crucial to curb the rising prevalence of CKD and its associated complications.⁴

The etiology of CKD is multifactorial, encompassing a wide array of conditions and risk factors that can initiate or accelerate kidney damage. Diabetic nephropathy, a microvascular complication of diabetes, occurs when hyperglycemia damage the glomeruli, leading to proteinuria and progressive loss of kidney function.⁵ Glomerulonephritis, an inflammatory condition affecting the glomeruli, can arise from various causes, including autoimmune disorders, infections, and genetic factors. Other etiologies of CKD include polycystic kidney disease, obstructive uropathy, recurrent kidney infections, and exposure to nephrotoxic medications or environmental toxins.⁶ The pathogenesis of CKD involves a complex interplay of structural and functional alterations that ultimately lead to irreversible kidney damage and end-stage renal disease. The initial insult triggers a cascade of events, including nephron loss, compensatory hypertrophy of remaining nephrons, and glomerular hypertension.⁷ Nephron loss refers to the gradual destruction of functional kidney units, impairing the kidney's capacity to excrete wastes and regulate fluid balance. Compensatory hypertrophy occurs as the remaining nephrons enlarge to maintain overall kidney function, but this adaptation can lead to increased glomerular pressure and further damage. Oxidative stress plays a significant role in the pathophysiology of CKD, contributing to inflammation, fibrosis, and endothelial dysfunction. Inflammatory processes are activated, releasing cytokines and growth factors that promote fibrosis and scarring of the kidney tissue.⁸ As kidney function declines, various systemic complications arise, including anemia, mineral and bone disorders, cardiovascular disease, and impaired immune function. The progressive nature of CKD necessitates early detection and intervention to interrupt the pathophysiological cascade and preserve kidney function.⁹

Despite the advancements in modern medicine, current therapeutic interventions for CKD remain limited in their ability to halt disease progression or fully restore renal function. The worldwide prevalence of kidney disease is on the rise, surpassing other chronic diseases prioritized by global health organizations.¹⁰ The primary objectives of current therapeutic strategies encompass slowing the advancement of kidney injury, managing associated complications, and mitigating the risk of cardiovascular events. Pharmacological interventions, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, are frequently employed to regulate blood pressure and decrease proteinuria, thus exerting a renoprotective effect.¹¹ Nevertheless, these agents may not be universally effective, particularly in individuals with advanced kidney disease or those who do not tolerate their side effects. Furthermore, the efficacy of these interventions may be attenuated over time, necessitating the exploration of alternative or adjunctive therapies.¹²

Recently, there has been a surge of interest in alternative and complementary therapies for CKD, driven by the need for safer and more effective treatment options. Sarsasapogenin is a natural steroidal compound mostly present in *Zhimu* (*Rhizoma Anemarrhenae*). Sarsasapogenin has been thoroughly investigated for its pharmacological uses and it showed better therapeutic effects against Alzheimer's disease¹³ and age-related cognitive impairment.¹⁴ Furthermore, sarsasapogenin also demonstrated anti-asthma,¹⁵ anti-depressive,¹⁶ anti-ulcerative colitis,¹⁷ and anti-arthritic¹⁸ properties. Several previous studies indicated that sarsasapogenin showed better therapeutic activity against diabetic nephropathy through various mechanisms.¹⁹⁻²¹ Consequently, we hypothesized that sarsasapogenin may demonstrate the nephroprotective effects in experimental chronic kidney failure models. To verify these hypotheses, we evaluated the nephroprotective effects of sarsasapogenin in adenine-induced CKD model in rats.

MATERIALS AND METHODS

Experimental animals

The present investigation was conducted on male Wistar rats with an approximate weight of 240 ± 10 g. A total of 24 rats were housed in a laboratory environment with careful attention to their safety. The settings were maintained at a temperature of 22–26°C, humidity of 40–70%, and a 12-hr light-dark sequence. During the experimental period, rats were given purified water and a conventional rodent diet. The experimental protocols of the present study were verified and approved by the Institutional Animal Care and Use Committee. Before commencing the investigation, a one-week acclimatization time was designated for the rats to adapt to the laboratory environment.

Treatment groups

After a one-week acclimatization period, rats were randomly assigned to four groups with six animals in each ($n=6$) and subjected to treatment for four consecutive weeks. Group I was continued with standard diet without intervention for four weeks (control group). Group II was administered 200 mg/kg of adenine via oral route for four consecutive weeks.²² Groups III and IV received adenine as specified in Group II, and subsequently treated with the sarsasapogenin (30 and 60 mg/kg, respectively) by oral gavage with corn oil used as a vehicle for four weeks.

Rats were observed weekly for alterations in body weight and food intake. At the conclusion of the treatments, rats were permitted to undergo an overnight fast prior to blood collection. Animals were anesthetized with ketamine and xylazine injection. The blood was obtained, centrifuged at 4000 rpm for 10 min, serum was collected, and properly kept at -20°C for biochemical tests. Subsequent to blood collection, the kidneys were promptly dissected, rinsed, and weighed; a segment of the tissue was preserved in 10% formaldehyde for histological examination,

while the remaining tissue was maintained in an ice-cold buffer for additional investigation.

Analysis of biochemical marker levels

The concentrations of Serum Urea Nitrogen (SUN), uric acid, and creatinine in the serum samples were evaluated using commercial test kits according to the manufacturer's specifications (Abcam, USA). The concentrations of sodium and potassium in the serum samples were assessed using commercially available kits (Elabscience, USA). The activities of Alanine Transaminase (ALT), Aspartate Transaminase (AST), and Lactate Dehydrogenase (LDH) in the serum of experimental rats were assessed using kits (Cusabio, China). Each test was performed in triplicate in accordance with the manufacturer's specifications.

Analysis of inflammatory cytokines and oxidative stress marker levels

Serum concentrations of Interleukin-1 β (IL-1 β) and TNF- α in the experimental rats were quantified using kits. The kits were obtained from R&D Systems, USA, and the tests were performed in triplicate as per the protocols outlined in the kit booklet. The oxidative stress markers, including Glutathione (GSH), Superoxide Dismutase (SOD), and Malondialdehyde (MDA) were evaluated in the kidney tissue homogenates of the experimental rats using commercial test kits. All tests were performed in triplicate in accordance with the manufacturer's instructions (Elabscience, USA).

Histopathological analysis

The kidney tissue samples were obtained and processed with a 10% formalin to assess the histopathological alterations in kidney architecture. Thereafter, the tissues were paraffin-embedded, sectioned to 5 μ m, and stained with hematoxylin-eosin. Finally, the kidney tissues were examined microscopically to evaluate the histological changes.

Statistical analysis

The data are shown as mean $\pm$ SD of triplicates. The values are analyzed using GraphPad Prism software. The differences in the values were assessed using a one-way ANOVA and Tukey's *post hoc* test. A significance threshold of $p < 0.05$ was used for group comparisons.

RESULTS

Effect of sarsasapogenin on the food intake, body weight, and kidney weight of experimental rats

The effects of sarsasapogenin on body weight, food intake, and kidney weight of the experimental rats were assessed, as seen in Figure 1. The rats with adenine-induced CKD illustrated a significant reduction in body weight and food intake, subsequently

elevated their kidney weight compared with control. Nonetheless, sarsasapogenin treatment at 30 and 60 mg/kg, respectively significantly enhanced the body weight and food consumption, and decreased the kidney weight of the adenine-induced rats.

Effect of sarsasapogenin on the renal function markers in experimental rats

Figure 2(A) depicts the concentrations of renal function markers of the experimental rats. The serum concentrations of creatinine, SUN, uric acid, and potassium was markedly elevated in the adenine-induced rats compared with control. The adenine-induced rats also showed slight reduction in serum sodium levels. In contrast, the levels of the creatinine, SUN, uric acid, and potassium were significantly reduced in the 30 and 60 mg/kg of sarsasapogenin-treated rats. The sarsasapogenin treatment also showed slight increase in the serum sodium levels of the adenine-induced rats.

Effect of sarsasapogenin on liver marker enzymes in experimental rats

The impact of sarsasapogenin on the liver marker enzymes in the serum samples were investigated, with results depicted in Figure 2(B). The rats with adenine-induced CKD showed a marked increase in AST, ALT, and LDH levels in their serum when compared with control. However, the sarsasapogenin treatment at a dosages of 30 and 60 mg/kg, respectively considerably reduced these enzymes in the serum of adenine-induced rats.

Effect of sarsasapogenin on oxidative stress markers in experimental rats

The concentrations of oxidative stress indicators in the kidney tissues of experimental rats were assessed, and the outcomes are illustrated in Figure 3(A). The results of this work demonstrated that the adenine-induced rats displayed a considerable reduction in SOD and GSH levels and a subsequent elevation in MDA concentrations in their kidney tissues compared with control. Notably, the 30 and 60 mg/kg dosages of sarsasapogenin demonstrated a marked reduction in the MDA levels and elevated the antioxidant levels in the kidneys of the adenine-induced rats, which proves its antioxidant capacity.

Effect of sarsasapogenin on the inflammatory cytokine levels in experimental rats

The effect of sarsasapogenin treatment on inflammatory cytokines in the serum samples were illustrated in Figure 3(B). The adenine-induced rats displayed a notable elevation in TNF- α and IL-1 β concentrations in their serum when compared with control. Interestingly, the treatment of 30 and 60 mg/kg of sarsasapogenin markedly decreased these pro-inflammatory cytokine concentrations in the adenine-induced rats, which evidences its anti-inflammatory effects.

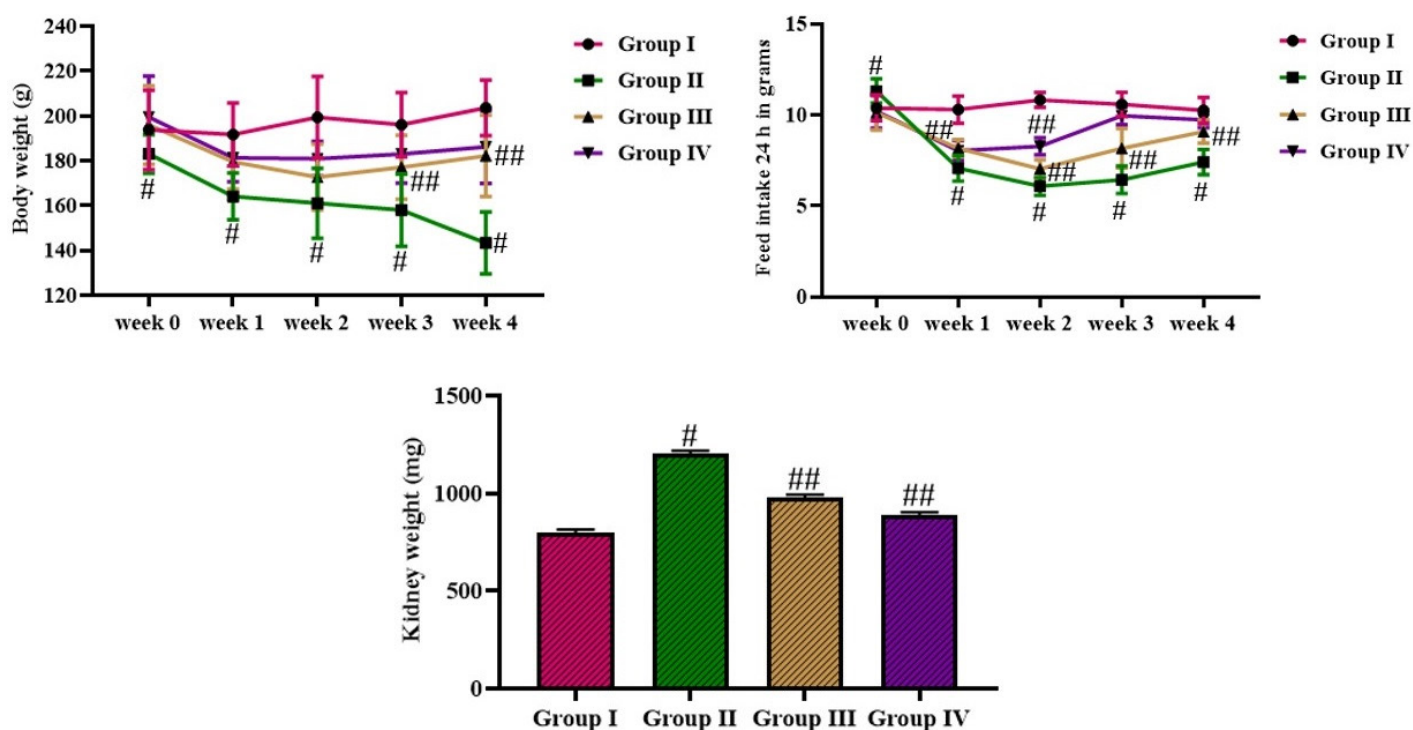


Figure 1: Effect of sarsasapogenin on the body weight, food intake, and kidney weight of the experimental rats. The data were evaluated using GraphPad Prism software, and results are depicted as Mean $\pm$ SD of triplicates. The significance level between treatment groups were set as '#' $p < 0.01$ for comparisons between the control and adenine-induced groups; '##' $p < 0.05$ for comparisons between the adenine-induced group and the adenine + sarsasapogenin-treated groups.

Effect of sarsasapogenin on the renal tissue histopathology of experimental rats

The histological study was conducted on the renal tissues of the experimental rats, with the findings depicted in Figure 4. The kidneys of control rats had distinct morphology with well-defined renal histoarchitectures. Nonetheless, the kidneys of the adenine-induced rats had glomerular shrinkage, renal tubular damages, inflammatory cell infiltrates, and significant adenine crystal deposits when compared with control. Interestingly, the sarsasapogenin treatment at dosages of 30 and 60 mg/kg, respectively considerably decreased histological abnormalities in the kidneys of rats with adenine-induced CKD.

DISCUSSION

CKD, defined by a progressive reduction in renal function, has become a prominent worldwide health issue. Defined by structural or functional abnormalities persisting for over three months, CKD arises from a multitude of clinical, sociodemographic, and environmental factors, with diabetes, hypertension, and glomerulonephritis being primary culprits.²³ Notably, the insidious nature of CKD often leads to delayed diagnosis, allowing the disease to progress to advanced stages before detection, further complicating management and increasing the risk of adverse outcomes. CKD is a progressive condition associated with kidney failure, cardiovascular events, and mortality.²⁴ The pathogenesis of CKD is multifaceted, involving a complex interplay of various causes that eventually leads to irreversible structural and functional damage to the kidneys. Progressive

loss of nephrons, the functional units of the kidney, results in decreased GFR, a hallmark of CKD progression.²⁵ Current pharmacological interventions are aimed at reducing proteinuria and lower blood pressure, thereby attenuating glomerular injury and slowing the reduction rate of renal function. Nonetheless, these agents are often associated with adverse effects, such as hyperkalemia and hypotension.²⁶ The limitations of current therapies for CKD highlight the urgent need for safe and effective alternative treatment approaches that can address the underlying pathogenic mechanisms and halt disease progression.

The progressive loss of glomerular filtration impairs the kidneys' ability to effectively eliminate toxic compounds from the bloodstream, resulting in their build-up within the body. This accumulation of toxins, normally cleared by the kidneys, results in uremia. The clinical manifestation of CKD is not only due to reduced kidney function but also the complex interplay of retained uremic solutes that exert toxic effects on multiple organ systems.²⁷ Serum creatinine, a commonly measured marker of renal function, is derived from the metabolism of creatine in muscle tissue and its levels are inversely correlated with glomerular filtration rate. Creatinine is readily filtered by the glomeruli and is not reabsorbed, with a minor quantity secreted by the proximal tubule, rendering it a valuable marker of renal function. Elevated serum creatinine levels indicate a decline in GFR, reflecting impaired renal clearance.²⁸ Uric acid, a product of purine metabolism, is primarily eliminated by the kidneys. Hyperuricemia, or elevated uric acid levels, has been implicated in the onset of CKD through various mechanisms, including

endothelial dysfunction, inflammation, and oxidative stress.²⁹ Uric acid can crystallize in the renal tubules and interstitium, leading to inflammation and fibrosis, thereby contributing to the progression of CKD.³⁰

SUN, also known as BUN, is a waste product derived from protein metabolism, and its levels are elevated in CKD due to impaired renal excretion. Urea is synthesized in the liver as part of the urea cycle, a metabolic pathway that eliminates ammonia, a toxic byproduct of protein metabolism. Elevated levels of SUN in CKD reflect the reduced capacity of the kidneys to filter and excrete urea, resulting in its buildup in the bloodstream.³¹ Elevated urea levels contribute to uremic toxicity, affecting various organ systems, including the gastrointestinal, cardiovascular, and nervous systems.³² Serum electrolytes, including sodium and potassium, are tightly regulated by the kidneys to maintain fluid balance, nerve and muscle function, and overall cellular homeostasis. In CKD, the capacity of the kidneys to regulate sodium and potassium balance is impaired, resulting in electrolyte abnormalities like hyperkalemia (elevated potassium levels) and hyponatremia (low sodium levels).³³ Hyperkalemia, or elevated serum potassium levels, is a common and life-threatening condition of CKD, especially in advanced stages. The kidneys play a central role in potassium excretion, and reduced GFR and tubular dysfunction in CKD can lead to potassium retention.³⁴ Hyponatremia, or low serum sodium

levels, can also occur in CKD, particularly in patients with fluid overload or those taking diuretics. Impaired sodium handling can result in either sodium retention, resulting in edema and hypertension, or sodium wasting, contributing to hypovolemia and hypotension.³⁵ The present results evidenced the elevated concentrations of creatinine, SUN, uric acid, and potassium in the serum of adenine-induced rats. A slight reduction in sodium levels were also found in the adenine-induced rats. Contrastingly, the treatment with sarsasapogenin effectively decreased the levels of creatinine, SUN, uric acid, and potassium in the adenine-induced rats. It also showed increase in the serum sodium levels of the adenine-induced rats. These results suggest that sarsasapogenin can improve the renal function and assist in excreting the toxic wastes from the serum of CKD rats.

CKD is frequently accompanied by heightened oxidative stress, stemming from an imbalance between the accumulation of ROS and the body's antioxidant systems. This oxidative stress contributes significantly to the progression and complications of CKD. The heightened generation of ROS has been directly implicated in various disease mechanisms connected with the initiation of CKD.³⁶ Oxidative stress arises from an increased production of ROS, encompassing superoxide anion, hydrogen peroxide, and hydroxyl radicals, which are byproducts of normal aerobic metabolism. The accumulation of these ROS overwhelms the intrinsic antioxidant systems of the kidneys,

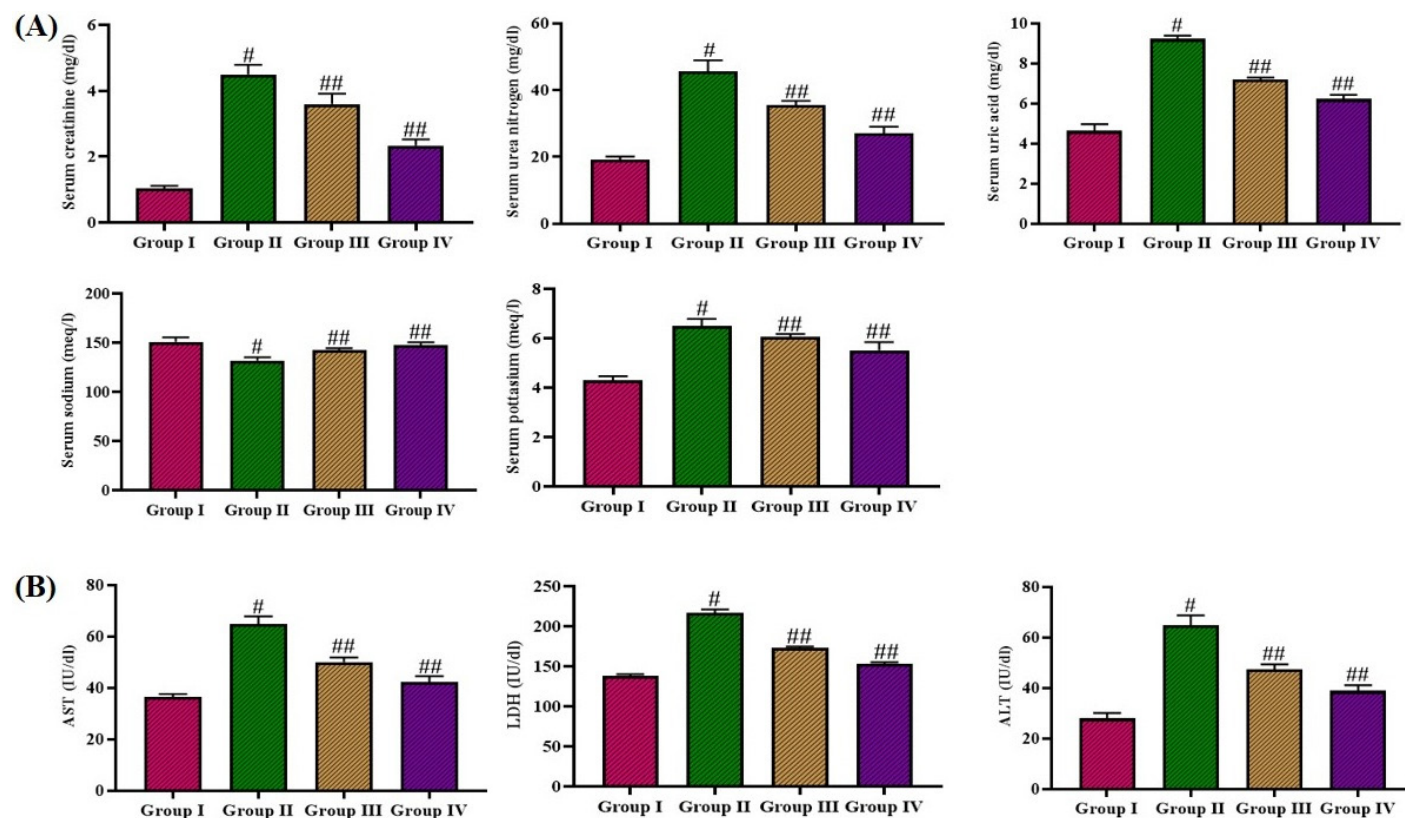


Figure 2: Effect of sarsasapogenin on the renal and liver function markers in the experimental rats. The data were evaluated using GraphPad Prism software, and results are depicted as mean $\pm$ SD of triplicates. The significance level between treatment groups were set as '[#]' $p < 0.01$ for comparisons between the control and adenine-induced groups; '^{##}' $p < 0.05$ for comparisons between the adenine-induced group and the adenine + sarsasapogenin-treated groups.

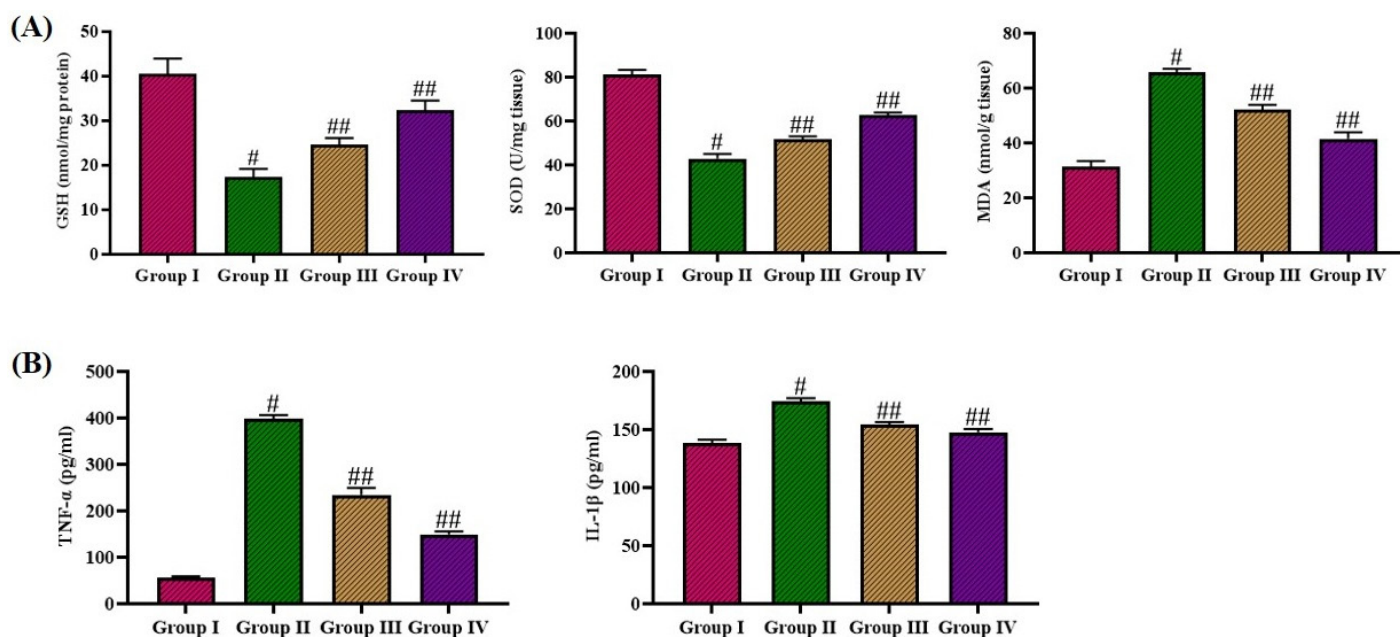


Figure 3: Effect of sarsasapogenin on the oxidative stress markers and inflammatory cytokine levels in the experimental rats. The data were evaluated using GraphPad Prism software, and results are depicted as Mean $\pm$ SD of triplicates. The significance level between treatment groups were set as '#' p <0.01 for comparisons between the control and adenine-induced groups; '##' p <0.05 for comparisons between the adenine-induced group and the adenine + sarsasapogenin-treated groups.

resulting in oxidative injury to major cellular components.³⁷ Moreover, oxidative stress directly impacts the function of various cell types within the kidney, including podocytes, mesangial cells, and tubular epithelial cells. The ensuing cellular dysfunction contributes to the initiation of glomerulosclerosis, and tubulointerstitial fibrosis.³⁸

MDA is a lipid peroxidation product, serving as an indicator of oxidative damage to lipids in cell membranes and lipoproteins. Elevated levels of MDA in plasma and urine are observed in CKD patients, and it reflects the cumulative effect of oxidative damage in the kidney and systemic circulation.³⁹ SOD is a primary antioxidant that catalyzes the dismutation of superoxide radicals into H_2O_2 and O_2 , representing a crucial component of the enzymatic antioxidant defense system. In CKD, SOD activity may be altered, with some studies reporting decreased activity, indicating impaired antioxidant capacity, while others suggest increased activity as a compensatory response to elevated oxidative stress.⁴⁰ GSH is a tripeptide antioxidant that plays a central role in cellular defense against oxidative stress. The levels of GSH are often decreased in CKD patients, reflecting increased utilization in combating oxidative stress and diminished synthesis or regeneration.⁴¹ Therapeutic strategies aimed at reducing oxidative stress, such as antioxidant supplementation or lifestyle modifications, hold promise to inhibit the advancement of renal fibrosis and enhancing outcomes in CKD patients.⁴² In this work, we found that the adenine-induced rats displayed a diminished SOD and GSH levels and subsequently elevated MDA levels in their kidney tissues. Captivatingly, the sarsasapogenin treatment illustrated a marked reduction in MDA levels and increased

the antioxidant concentrations in the kidney tissues of the adenine-induced rats, which proves its antioxidant capacity.

CKD is increasingly recognized as a systemic disorder characterized not only by declining renal function but also by profound disturbances in the immune system and persistent inflammation. The progression of CKD involves intricate interactions between hemodynamic, immunological, metabolic, and inflammatory factors, with inflammation now recognized as a fundamental component even in cases of non-immune-mediated CKD.⁴³ Regardless of the initial cause of CKD, sustained inflammation is invariably present in the kidneys, with immune cell recruitment resulting in a local accumulation of growth factors and pro-fibrotic markers. The escalation of inflammation from a mere observation to a well-established element in CKD has occurred over numerous years, solidifying its importance. Uncontrolled inflammation can inflict damage on glomeruli, tubules, and the kidney's interstitial components.⁴⁴

TNF- α and IL-1 β are pivotal pro-inflammatory markers that have been participated in the pathogenesis of CKD. TNF- α promotes inflammation by increasing leukocyte adhesion to endothelial cells, stimulating the production of chemokines that recruit immune cells to the kidney, and enhancing the release of other pro-inflammatory markers, contributing to tissue damage and fibrosis.⁴⁵ IL-1 β , another crucial cytokine, is primarily secreted by activated macrophages and other immune cells and exerts its effects by binding to the IL-1 receptor, activating intracellular pathways that activate NF- κ B and MAPK, thereby exaggerating the inflammation. IL-1 β promotes inflammation by inducing the production of chemokines, stimulating the

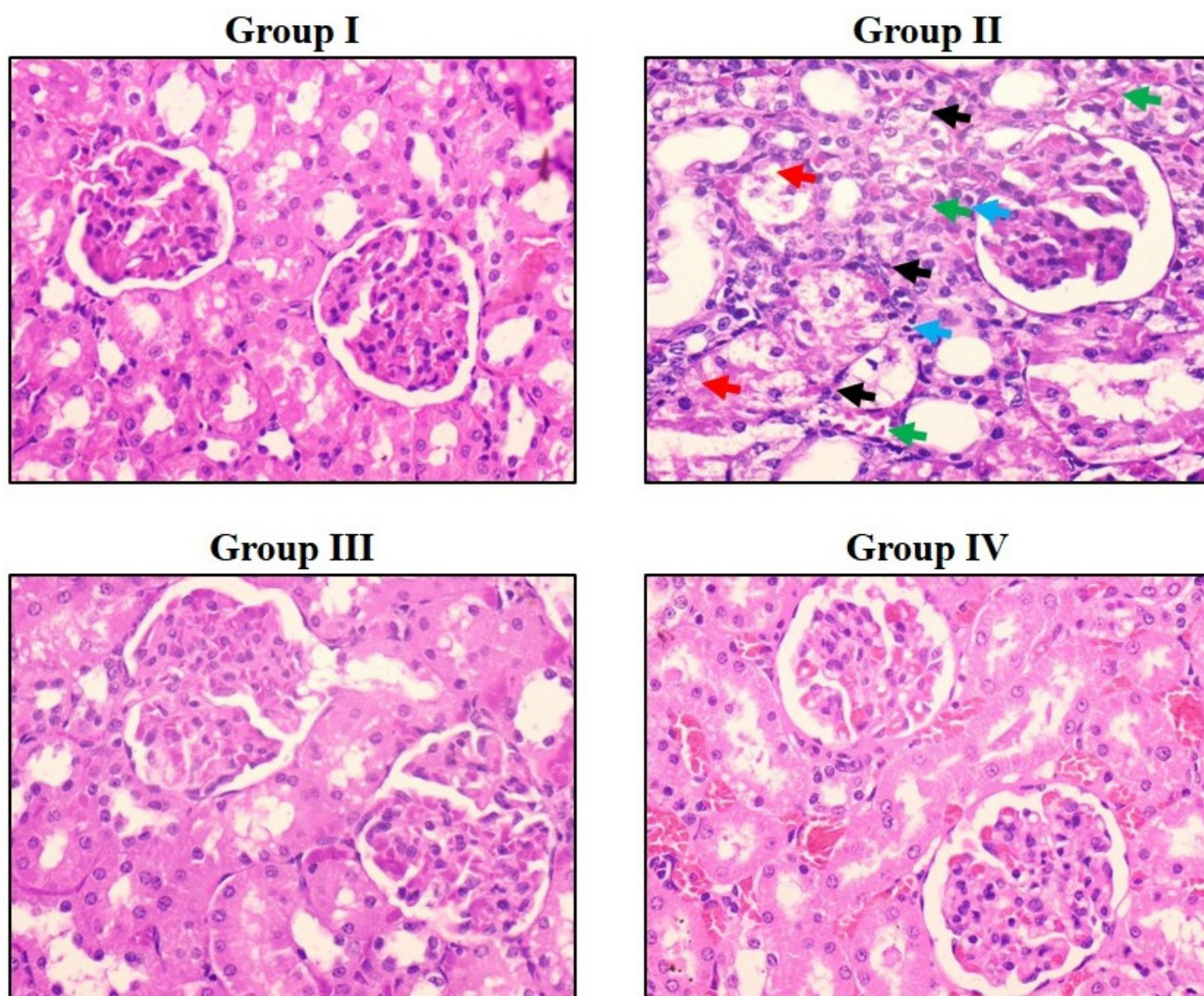


Figure 4: Effect of sarsasapogenin on the renal tissue histopathology of the experimental rats. Group I: Normal control; Group II: Adenine-induced CKD; Group III: Adenine-induced CKD + 30 mg/kg of sarsapogenin treatment; Group IV: Adenine-induced CKD + 60 mg/kg of sarsapogenin treatment. Black arrows: Glomerular shrinkage; Red arrows: Renal tubular damages; Blue arrows: Inflammatory cell infiltrates; Green arrows: Adenine crystal deposits.

synthesis of prostaglandins and other inflammatory mediators, and enhancing the activity of immune cells, contributing to tissue damage and fibrosis in the kidney.⁴⁶ The current results evidenced that the adenine-induced rats demonstrated a marked increase in TNF- α and IL-1 β levels in their serum. Fascinatingly, the treatment of sarsasapogenin considerably decreased these cytokine levels in the serum of adenine-induced rats, which supports its anti-inflammatory effects.

CONCLUSION

The present findings demonstrate that sarsasapogenin treatment can mitigate and protect against adenine-induced CKD in rats. The beneficial nephroprotective effects of sarsasapogenin may be due to its notable antioxidant and anti-inflammatory activities. Thus, sarsasapogenin treatment may represent a promising

therapeutic candidate to treat and/or prevent CKD. Further investigations are required to extend our understanding of the antioxidant, anti-inflammatory, and nephroprotective activities of sarsasapogenin in alleviating and protecting against CKD.

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None.

ABBREVIATIONS

CKD: Chronic Kidney Disease; **eGFR:** estimated Glomerular Filtration Rate; **SUN:** Serum Urea Nitrogen; **AST:** Aspartate Transaminase; **LDH:** Lactate Dehydrogenase; **IL:** Interleukin; **GSH:** Glutathione; **SOD:** Superoxide Dismutase; **MDA:** Malondialdehyde.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

CKD is a progressive loss of renal function, which become a prominent worldwide health issue. The pathogenesis of CKD is multifaceted, involving a complex interplay of various causes that eventually leads to irreversible structural and functional damage to the kidneys. The results of this study demonstrated that sarsasapogenin treatment can mitigate and protect against adenine-induced CKD in rats. Therefore, it can be a promising therapeutic candidate to treat and/or prevent CKD.

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