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The protective effects of lemongrass and N-acetylcysteine against adenine-induced chronic kidney disease in an animal model

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ABSTRACT

Chronic kidney disease (CKD) is prevalent in humans and leads to serious health issues, including increased cardiovascular risk and heart failure. The adenine-induced CKD model in rats is frequently used to assess nephroprotective agents. However, renal replacement therapies are often inaccessible due to limited resources in many regions. This study aimed to evaluate the nephroprotective effects of lemongrass (LG) and N-acetyl cysteine (NAC) on adenine-induced CKD. Fifty male rats were randomly divided into five groups (10 rats each). Group I (control) received normal saline orally, while Groups II to V received adenine via intraperitoneal injection (300 mg/kg) twice weekly for four weeks. Group III (LG + adenine) was given LG (360 mg/kg), Group IV (NAC + adenine) received NAC (150 mg/kg), and Group V (LG + NAC + adenine) received both LG and NAC, Both treatments were administered per OS daily for four weeks. After the end of the experiment, serum samples were analyzed for kidney function, and kidney tissues were assessed histopathologically. Adenine treatment significantly increased serum urea, creatinine, and uric acid levels, while decreased albumin concentration compared to the control group. However, LG or NAC administration with adenine significantly improved kidney function and increased albumin levels compared to the adenine group. Notably, the combination of LG and NAC proved more effective than either treatment alone. Thus, lemongrass and N-acetyl cysteine exhibit nephroprotective effects against adenine-induced CKD.

1. INTRODUCTION

Chronic kidney disease (CKD) is a life-threatening disorder linked to elevated rates of morbidity and mortality. Globally, 697.5 million people suffered from chronic kidney disease (CKD) in 2017. The mortality rate from CKD elevated by 41·5% for all age groups between 1990 and 2017 (Bikbov et al., 2020). According to WHO's Global Health Estimates, renal disorders ranked as the tenth cause of death Globally. Diabetes and hypertension are the main causes of CKD (Kalantar-Zadeh et al., 2021). The popular causes of this apparent rise are drug abuse and irrational use, environmental pollution, obesity, and the prevalence of schistosomiasis and malaria (Said et al., 2019). Lowering cardiovascular disorder, managing albumin urine levels, avoiding nephrotoxic substances, and modifying medication doses (Chen et al., 2019). The probability of CKD development is still rising (Perkovic et al., 2019). New treatments are required even though treatment options like angiotensin-converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) already exist (Inker et al., 2014) Additionally, sodium-glucose cotransporter 2 (SGLT2) inhibitors have recently become available for treating patients with CKD, both with and without diabetes (Cherney et al., 2020; Heerspink et al., 2020).

In the 1980s, chronic kidney disease (CKD) induced by adenine was first described as a substitute for the expensive and highly skilled surgical models (Al Za'abi et al., 2015). Basic processes of chronic renal failure (CRF) have been studied in rats using an adenine model, and its main mechanisms are renal tubular obstruction, oxidative stress, and inflammatory response (Zhao et al., 2013). Many organisms depend on oxidation to produce the energy needed for biological functions. However, renal impairment can be caused by excessive reactive oxygen species (ROS) generation (Dennis and Witting, 2017). When physical or chemical damage occurs, inflammatory mediators may be generated, which attracts more inflammatory cells to the location and affects the tubules (Humanes et al., 2017). One of the established mechanisms of CRF is tubular interstitial fibrosis, which induces excessive deposition of extracellular matrix after chronic damage (Cai et al., 2018).

Herbal medicines have become recognized as a dietary supplement in recent years for managing various types of diseases, including diabetes, cancer, and CKD. Lemongrass is scientifically known as *Cymbopogon citratus*, it is a tall perennial grass that is a member of the Poaceae family. It is unique due to its potent lemon-like flavor and medicinal benefits (Ali et al., 2023). According to reports, lemongrass contain phenolics, flavonoids, terpenoids, alkaloids, and tannins, all of which support its usage in both the food and medical industries. Lemongrass or *Cymbopogon citratus* Stapf. (Poaceae) has been a common herb in tropical regions for over 2,000 years (Tarkang et al., 2012; Said et al., 2019). Lemongrass contains a variety of phytochemicals, including flavonoids, volatile and nonvolatile terpenoids, carotenoids, and tannins (Alzobaay and Kadhim, 2018). According to earlier studies, lemongrass is used in traditional therapy as

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an anti-inflammatory, hypoglycemic, and cardioprotective agent (Trang et al., 2020). It also elicits cytotoxic activities, making it a potential source of phytochemicals against cancer (Abdel-Wahab and Moussa, 2019). Although this plant has been used for a long time and has many nutritional uses, there haven't been any extensive studies performed on how it affects kidney disease, particularly CKD.

N-acetyl cysteine (NAC) is an amino acid that contains thiols, having the ability to block lipid peroxidation (LPO), neutralize free radicals, and stop glutathione (GSH) from being depleted (Samuni et al., 2013; Abdel-Wahab and Moussa, 2019). Furthermore, NAC has the ability to chelate metals, which can restore balance or correct the unbalanced levels of pro- and anti-oxidants (Giampreti et al., 2016). NAC also protects against nephrotoxicity by lowering inflammation and oxidative stress (Shahripour et al., 2014; Bhatti et al., 2018). N-acetyl cysteine is known as the acetyl form of L-cysteine. It is transformed by the body into metabolites that help eliminate free radicals, help make glutathione, and aid in detoxification. It can be utilized in several therapeutic conditions, including drug addiction, bronchitis, schizophrenia, and acetaminophen toxicity. NAC works as a precursor that is transformed into cysteine by aminoacylase-1 in the intestine and then absorbed into the blood circulation (Mokhtari et al., 2017). Because cysteine is an essential part of glutathione, NAC supplementation replenishes glutathione stores. As a broad anti-oxidant, NAC can also lessen the symptoms of many diseases which reactive oxygen species (ROS) have worsened. N-acetylcysteine (NAC), a synthetic thiol with strong oxidative damage suppressor properties, primarily contributes a sulfhydryl group to GSH production (Aldini et al., 2018). Clinical applications of NAC include treating a variety of inflammatory conditions (Faghfouri et al., 2020).

This study assesses the protective effects of oral LG and NAC treatment in a rat model of adenine-induced chronic kidney disease (CKD) using serum biochemical analysis and histopathological evaluation.

2. MATERIAL AND METHODS

The procedures used in this study followed the animal care and use criteria approved by Scientific Research Ethical Committee, Faculty of Veterinary Medicine, Benha University, with ethical approval number (BUFVTM33-11-23)

2.1. Chemicals and herbal plant

Adenine is a crystalline powder bought from Sigma-Aldrich (St. Louis, Missouri, United States). It was dissolved in distilled water and given to male rats intraperitoneally at a dose of 300 mg/kg twice weekly for 4 weeks (Said et al., 2019).

Lemongrass was purchased from a local herbal market in Benha as a dry powder. It was prepared by heat decoction method and given orally to male rats at a dose of 360 mg/kg body weight daily for four weeks (Said et al., 2019)

N-Acetylcysteine was bought from SEDICO company in the form of sachets. It is effervescent instant granules. It was dissolved in distilled water and given orally to male rats at 150 mg/kg body weight daily for four weeks (Feng et al., 2015).

2.2. Experimental animals:

Fifty male albino rats, 180±40 g, 7-8 weeks old, were used in this investigation. They were acquired from the Laboratory Animal Research Center, Faculty of Veterinary Medicine, Benha University. The rats were given free access to water and a standard pellet chow diet. They were housed in cages with hardwood shavings for bedding and maintained under appropriate living conditions, including a temperature range of 21 to 24 °C, a 12-hour light/dark cycle, and humidity levels not to exceed 60%. The rats were housed in these circumstances for a week before the experiment.

2.3. Experimental design

Five equal groups of rats were randomly assigned (10 rats/ group):

Group I (control) rats were received orally normal saline, Group II (adenine) rats were administered intraperitoneal injections of adenine (300 mg/kg body weight) twice weekly for 4 weeks (Said et al., 2019), Group III (LG + adenine) rats were administered lemongrass orally (360 mg/kg b. w. daily P.O) (Said et al., 2019), Group IV (NAC+ adenine) rats were administered N-Acetylcysteine orally (150 mg/kg/daily, P.O.) (Feng et al., 2015). Group V (LG + NAC + adenine) rats were administered lemongrass (360 mg/kg b. w. daily P.O.) and NAC (150 mg/kg/daily, P.O.).

(Group III - V) the rats received adenine by intraperitoneal injection (300 mg/kg body weight) twice weekly for four weeks, after a 2-hour interval following the oral administration of each treatment. The experiment continued for four weeks.

2.4. Sampling

2.4.1. Blood sampling

As soon as the experiment had finished after four weeks, All of the animals were fasted for a whole night and euthanized. Using a capillary tube, blood samples were taken from the eye's medial canthus. To separate the serum, the obtained samples were centrifuged at 3000 rpm for 15 minutes and then kept at -20 °C till the biochemical analysis.

2.4.2. Tissue sampling

As soon as the blood samples were taken, the rats were euthanized, and the small tissue specimens from the kidneys were taken out and quickly cleaned and preserved in a 10% formalin solution for the histological examination.

2.5. Biochemical analysis

Urea and creatinine concentrations were spectrophotometrically determined following the procedures stated before (Kaplan, 1984; Schirmeister et al., 1984). Additionally, the concentration of uric acid was measured by spectrophotometer using the protocol described by Schultz, (1984). The albumin concentration was measured according to the procedure outlined before (Doumas et al., 1971). All of them measured by an automatic analyzer using a commercial kit supplied by (Diamond Diagnostics, Cairo, Egypt).

2.6. Histopathological analysis

Small tissue samples were taken from the rats' kidneys and immediately stored in 10% neutral buffered formalin for 72 hours. After the proper fixation process, The specimens were dehydrated in progressively increasing concentrations of ethyl alcohol, cleared with xylene, and embedded in paraffin wax. Tissue sections of 5 µm thickness were cut and stained with H&E stain (Bancroft and Layton, 2013). These sections were histopathologically evaluated using a Nikon Eclipse E800 light microscope, and photomicrographs were captured using an Olympus digital camera.

2.7. Statistical analysis:

The data was analyzed using One-Way Analysis of Variance (ANOVA). Duncan post-hoc test was employed with SPSS

25 (SPSS Inc., Chicago, USA). The results were shown as Mean ± SE. P-values in the data below 0.05 indicated statistical significance.

3. RESULTS

3.1. Biochemical results

The data obtained demonstrated that intraperitoneal injections of adenine induced a significant increase in serum urea, creatinine, and uric acid concentration with a significant decrease in albumin concentration when compared to the control group (Fig1A). On the other hand, oral administration of lemongrass or NAC with adenine showed a significant decrease in serum urea, creatinine, and uric acid concentration compared to adenine group. Moreover, lemon grass administration showed a significant increase in albumin concentration, while NAC administration showed a non-significant increase when compared to the adenine group (Fig1B). Furthermore, when rats were administered a combination of lemongrass and N-Acetylcysteine with adenine, the results of urea, creatinine, and albumin levels were noticeably improved when compared to the other treatment groups while uric acid concentration showed a non-significant decrease compared to lemongrass group and significant decrease compared to NAC group (Fig1C).

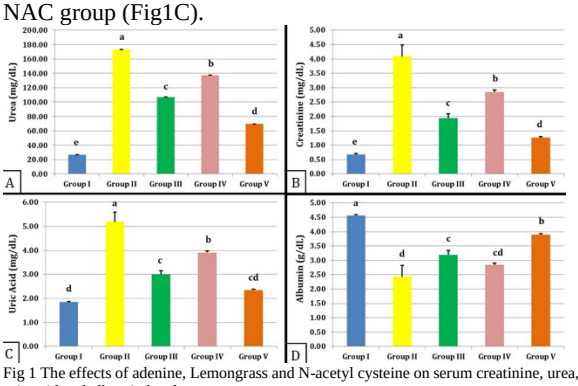

Fig 1 The effects of adenine, Lemongrass and N-acetyl cysteine on serum creatinine, urea, uric acid and albumin levels.
A: serum urea level (mg/dL); B: serum creatinine level (mg/dL); C: serum uric acid level (mg/dL), D: serum albumin (g/dl); Group I (control), Group II (adenine), Group III (LG + adenine), Group IV (NAC+ adenine), Group V (LG + NAC + adenine).

3.2. Histopathological changes in kidney tissue

In the control group, the majority of the examined kidney sections of the rats showed typical histological structures of the renal cortex and medulla (Fig. 2A).

Most kidney sections in rats receiving intraperitoneal adenine injections showed significant tubulointerstitial damage, characterized by chronic interstitial nephritis, fibrosis, and crystal deposits. Various sizes of needle-like crystals were found throughout the renal parenchyma, causing granulomatous inflammation with macrophages, lymphocytes, plasma cells, and giant cells (Fig. 2B). This was accompanied by marked tubular cystic dilatation in the renal medulla and cortex, along with cellular debris and denuded epithelium obstructing many tubules (Fig. 2C). There was also increased interstitial collagen, multifocal tubular degeneration, necrosis, atrophy, and severe interstitial edema with inflammatory cell infiltration, primarily of lymphocytes and macrophages.

Co-treatment with NAC reduced adenine-induced renal damage, improving overall renal histo-architecture compared to the adenine group. In this group, most kidney sections showed significant decreases in crystal deposits, tubular epithelial damage, cystic dilatation, and interstitial inflammation. However, some renal tubules were still dilated with flattened cells, and a few exhibited degenerative and necrotic changes (Fig. 2D). Mild edema and slight increases in interstitial collagen were occasionally observed. Lemongrass co-treatment also mitigated adenine-induced renal damage, represented by a significant reduction in the size and number of crystal deposits and their associated inflammation compared to NAC, indicating superior protective effects. Most kidney sections displayed only minor abnormalities, such as mild tubular degeneration and slight cystic dilatation, suggesting that lemongrass preserved the renal parenchyma's architecture (Fig. 2E). However, focal interstitial fibrosis was occasionally observed in a few sections.

Remarkably, co-treatment with lemongrass and NAC markedly reduced adenine-induced histopathological changes in the kidneys, with most sections showing no signs of necrosis, inflammation, or fibrosis. The renal tubular histo-architecture was nearly normal, resembling that of the control group, and crystal deposits were rarely observed. Additionally, the interstitial stroma showed no changes. However, some kidney sections displayed mildly dilated tubules and slight degenerative alterations (Fig.2F).

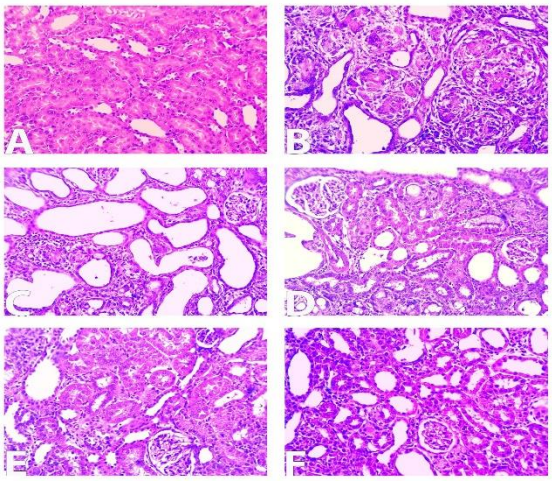

Fig. 2 Representative photomicrographs of H&E-stained kidney sectionsX200. The control group showed typical renal tubules lined by simple cuboidal epithelium with spherical vesicular nuclei and eosinophilic cytoplasm (A). Adenine group showed multiple crystal deposits surrounded by granulomatous inflammatory reaction (B) and severe cystic dilatation of the renal tubules (C), NAC+ Adenine group showed moderate cystic dilatation of some renal tubules that lined with flattened cells with degeneration and necrosis of some tubular epithelium (D) Lemongrass+ Adenine group showed mild renal degeneration and slight tubular cystic dilatation (E). Lemongrass+ NAC+ Adenine group showing dilated renal tubules and slight degenerated tubular epithelium (F).

4. DISCUSSION

Chronic kidney disease (CKD) is characterized by persistent and permanent damage to the kidneys' structure and function, which can result from different causes. Nowadays, the specific cause of CKD is still unknown (Lin et al., 2019). The advancement of CKD is associated with various factors, including fibrosis, destruction of parenchymal cells, injury to the microvasculature, disturbances in metabolism, oxidative damage, persistent inflammation, and diminished renal regenerative ability (Ruiz-Ortega et al., 2020).

It is necessary to investigate new approaches for delaying the start of dialysis or reducing the symptoms of uremia due to the rising prevalence of chronic kidney disease (CKD) and the limitations of renal replacement therapy, such as transplantation or dialysis. It is particularly necessary in developing countries where there is a lack of clinical and financial resources (Jain et al., 2012). Adenine is a purine nucleobase and one of the four crucial nucleobases that make up the structure of DNA (Dos Santos et al., 2019). Adenine-induced renal injury is a model that is widely used to investigate many parts of kidney function to determine the

efficiency of prospective drugs in avoiding and repairing kidney damage (Yi et al., 2021). Depending on the current study's biochemical results, intraperitoneal injections of adenine at a dose level of 300 mg/kg body weight twice a week for 4 weeks cause chronic renal failure (CRF) (Chang et al., 2017). Our study's findings revealed notable changes in both histopathological and kidney function biomarkers in the adenine group, indicating a marked deterioration in renal function when compared to the control group. Specifically, the adenine group exhibited a significant elevation in serum urea, creatinine, and uric acid concentrations, accompanied by a substantial reduction in albumin level compared to the control group. These findings agreed with those of Dos Santos et al., (2019), (Chang et al., 2017), and Kinugasa, (2011). This may be related to catalyzing adenine in the kidney by xanthine oxidoreductase into 2,8-dihydroxyadenine, 2,8-dihydroxyadenine is weakly soluble and precipitates in the renal tubules and causes fibrotic alterations, inflammation, damage to tubular epithelial cells and tubular occlusion (Nasr et al., 2010). Tubular obstruction caused by 2,8-dihydroxyadenine elevates stress in tubular cells and peritubular capillaries, leading to tubular hypoxia and reduced renal perfusion (Ito et al., 2005). Also, there is evidence of inflammation and oxidative stress in the renal tissue in adenine-induced chronic kidney disease. In the current study, intraperitoneal injection of adenine reduced albumin concentration in serum. This result agreed with Hailu et al. (2016) who recorded that the adenine group showed a substantial increase in the rate of protein excretion together with low serum albumin levels. The decrease in albumin concentration in serum could be attributed to proteinuria (Hailu et al., 2016) This is attributed to decreased food intake and reduced albumin production, indicating glomerular and tubular damage. In the adenine group, there was clear evidence of glomerular and tubular injury, along with significant disruption of renal architecture (Allahyari et al., 2021). This is also confirmed by the previous finding of Sabra et al. (2023).

This study evaluates the possible preventive benefits of lemongrass and N-Acetylcysteine against adenine-induced chronic kidney disease, focusing on their influence on renal function. On the other hand, concurrent oral administration of lemon grass or N-Acetylcysteine with adenine significantly improved renal functions compared to the adenine group.

Administration of LG orally together with adenine at a dose of 360 mg/kg body weight daily for 4 weeks resulted in a significant reduction in serum levels of urea, creatinine, and uric acid. This shows that LG has a beneficial effect on renal health, which may be associated with its diuretic action. Due to the flavonoid components of LG, the renal tubules fail to reabsorb water and electrolytes, which increases the excretion of nitrogenous substances (Said et al., 2019).

Also, this noticeable improvement in kidney function may be due to the presence of phytochemicals, volatile and nonvolatile terpenoids, carotenoids, and tannins in lemon grass as well as their potent anti-oxidant properties and ability to activate free radical-scavenging enzymes, This is also confirmed by the previous finding of Arhoghro and Kpomah (2013).

Due primarily to its anti-oxidant and free radical-scavenging characteristics, it was found that the aquatic extract of the leaf of LG had ameliorative advantages on oxidative damage in the liver caused by cisplatin (Arhoghro et al., 2014). Moreover, LG showed protection for the kidneys against gentamicin-induced toxicity; this is mainly due to the high concentration of flavonoids and strong anti-oxidant attributes in LG (Ullah et al., 2013). Moreover, *Cymbopogon citratus* has the anti-oxidant capacity to protect the kidney and liver from renal damage caused by lead acetate (Sousa et al., 2021; Asiwe et al., 2022).

Concurrent oral administration of NAC significantly improved renal functions when compared to the adenine group. The previous record by Elsayed et al. (2021). supported the results of the current study. They found that NAC, which was administrated orally every day (150 mg/kg body weight) with adenine for four weeks resulted in a significant reduction in serum levels of urea, creatinine, and uric acid with a significant increase in albumin level showing that NAC has a beneficial effect on renal function compared to the group which injected intraperitoneal with adenine only. In addition, Malmir et al. (2018) observed that oral administration of NAC in a dose (150 mg/kg) for 4 weeks to rats showed a significant decrease in serum urea, creatinine, and uric acid, with a significant increase in albumin compared to the group which injected intraperitoneal with methotrexate (Mahmoud et al., 2019).

This noticeable improvement in kidney function is due to the antioxidant properties of NAC, its ability to activate free radical-scavenging enzymes, act as a precursor for cellular glutathione (GSH) synthesis, and treat a wide range of inflammatory conditions (Faghfouri et al., 2020 and Aldini et al., 2018).

According to the results of biochemical analysis, the serum kidney biomarkers markedly declined in group V compared to the adenine group. These results were nearly similar to the reported studies of Zavala-Valencia et al. (2024) and Tuba Yalçin et al. (2024), who proved that NAC has a nephroprotective effect against cisplatin and spexin, respectively. This effectiveness could result from strong antioxidant properties that protect cells by preventing ROS production and lowering apoptosis (Kahraman et al., 2013; Yalçın et al., 2023) and act by scavenging free radicals (Nouri and Heidarian, 2019). NAC protects kidney tissue from oxidative damage in two ways: first, through a direct reaction with OH– and H_2O_2, and second, by indirectly promoting glutathione production, which represents a key defensive mechanism for cells against oxidative damage (Azarkish et al., 2013; Sehirli et al., 2003). Finally, the above result indicated that when rats were administered a combination of lemongrass and N-Acetylcysteine along with adenine, this treatment produced the most favorable outcomes compared to the other treatment groups. This may be due to their potent anti-oxidant properties and ability to activate free radical-scavenging enzymes. This is also confirmed by the previous findings of Haggag et al. (2015) and Honma et al. (2020).

5. CONCLUSIONS

The daily oral administration of lemongrass and N-acetylcysteine (NAC) for four weeks alleviated adenine-induced renal damage, as evidenced by biochemical and histopathological assessments. However, the combination of LG and NAC proved more effective than either. The positive effects of LG and NAC might be related to their antioxidant and anti-inflammatory properties.

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