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Trandolapril improves renal ischemia-reperfusion injury in adult male rats via activation of the autophagy pathway and inhibition of inflammation, oxidative stress, and apoptosis

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Abstract

Acute kidney injury (AKI) frequently occurs due to renal ischemia/reperfusion injury (IRI), which is marked by damaged tissue and a decrease in blood flow to the kidneys. IRI causes Oxidative damage, inflammation, and cell death. Autophagy, which recycles cytoplasmic components and breaks them down into smaller pieces, may have a role in cell death or survival in certain pathological states.

Objective: Through antioxidant, anti-inflammatory, and anti-apoptotic actions, as well as activation of the autophagy system, this study explores the potential nephroprotective benefits of trandolapril against renal ischemia-reperfusion damage. **Material and method:** There were four groups of rats used in this study: sham, RIRI, Dimethyl sulfoxide, and Trandolapril pretreated groups. The sham group underwent the same anesthesia and surgical procedures except for ischemia. Other groups undergo bilateral renal ischemia for 30 minutes and then reperfusion for 24 hours. DMSO group vehicle for trandolapril and trandolapril group 0.3mg/kg given 2 hours before ischemia induction. **Results:** The study found that blood urea and serum creatinine levels increased in the RIRI and DMSO groups when compared with the sham group. Renal tissue levels of IL-6, Kim-1, caspase-3, LC-3, and Akt were also elevated in RIRI while GSH levels decreased in the RIRI. The Trandolapril group showed significant increases in GSH, LC-3, and Akt levels when compared to the sham group. Trandolapril reduced serum urea and creatinine levels, and renal tissue levels of IL-6, Kim-1, and caspase-3 also reduced.

Conclusion: Male rat models of ischemia-reperfusion injury showed that trandolapril significantly decreased kidney damage.

Keywords: Ischemia, trandolapril, autophagy, LC-3, RIRI, Akt

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1. Introduction

Reduced blood flow to an organ, such as the kidneys (two bean-shaped organs), causes hypoxia and reduces the delivery of oxygen to tissues, this situation is known as ischemia. Problems like electrolyte imbalance, pericarditis, fluid retention, anemia, and heart failure can arise from ischemia [1]. Right and left renal arteries branch out into numerous levels to create glomeruli, which are specialized capillary beds that feed blood to the kidneys [2]. Reduced renal blood flow and subsequent renal hypoxia induce renal ischemia and reperfusion injury (RIRI), the most common kind of acute kidney injury (AKI) [3]. This syndrome affects

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10–20% of patients who have received a kidney transplant [4]. Damage to the proximal tubule brush boundary casts in the distal tubule, and areas of cellular regeneration are hallmarks of RIRI [5]. Intrinsic renal, postrenal, and prerenal AKI are the three main types of AKI. The renal tubules, glomeruli, blood arteries, and interstitium are directly affected by intrinsic renal AKI, which is more common than prerenal and postrenal AKI [6]. While the exact mechanisms that caused renal damage by IRI remain unclear, it is believed that inflammation, cell death, and acute kidney injury (AKI) are all caused by reactive oxygen species (ROS) which are produced during the reperfusion period [7]. Chemokines such as neutrophils, lymphocytes, monocytes, and dendritic cells initiate inflammatory pathways that ultimately cause kidney damage in renal ischemia/reperfusion injury (RIRI) [8]. The use of anti-inflammatory therapies is crucial for protecting kidney cells and tissues during RIRI [9].

During ischemia, the kidneys are unable to eliminate waste products effectively, because of a reduction in blood flow and cell count. Reactive oxygen species (ROS), hydrogen peroxide, hydroxyl radicals, and superoxide anion are among the pathogenic processes that occur during renal ischemia-reperfusion injury. Injured cells go through a few different stages, the cell membrane and nucleus can be damaged in these reactions, [10].This damage in turn activates protease enzymes, reduces ATP generation, increases intracellular calcium ions, and oxidative phosphorylation in the mitochondria. [11] [12].

Glutathione (GSH) is an important antioxidant present in plants, fungi, animals, and even certain microbes. Protecting intracellular molecules against both internal and external reactive oxygen and nitrogen species and directly scavenging certain free radicals. It directly scavenges certain free radicals and provides crucial protection for intracellular molecules from both internal and external reactive oxygen and nitrogen species [13] [14]. Apoptosis is enzymes mediated process, these enzymes destroy cytoplasmic and nuclear proteins and damage cell DNA this leads to the initiation of apoptosis, the last stage of an undesired cell's life cycle [15]. Autophagy is a cellular process related to cell homeostasis, precisely controls and regulates cell degradation and the recycling of cellular elements and organelles, it is a catabolic state that is needed to maintain normal cell physiology in extreme conditions, it plays an important role in combating infectious, carcinogenic, and degenerative agents to maintain healthy bodily systems and processes through cell cycle regulation, many health problems and diseases are linked to malfunctions in the body's autophagy mechanisms [16] [17].

Trandolapril is a heavily studied ACE inhibitor, it is largely used in the treatment of hypertension, and cardiovascular diseases, and it plays a critical role in the prevention and management of proteinuria, initially, it was believed that ACE inhibitors (ACEI) reduce proteinuria and protect the kidneys by dilating the efferent arterioles, which leads to a decrease in glomerular capillary pressure [18]. However, current evidence suggests that ACEI changes the size and permeability of the glomerulus and increases the negative electric charge across the glomerular membrane [19].

Examining biochemical parameters and histopathological changes in adult male rats, this study seeks to discover whether trandolapril has any nephroprotective effects against renal ischemia-reperfusion injury.

Trandolapril is tested for its ability to activate the autophagy pathway, as well as its antioxidant, anti-inflammatory, and anti-apoptotic effects.

2. Method

2.1. Animal preparation

The Sprague Dawley rats utilized in this study were obtained from the University of Kufa/Faculty of Science. The rats stayed in an animal house on the

Faculty of Pharmacy campus, where they remained at a temperature of 24 ± 2℃ and changed every 12 hours between cycles of light and dark. They had access to drinking water and a typical meal. The participation of the rats was permitted by the University of Kufa's Animal Care and Research Committee

2.2. Study design

The study involved 28 male rats, divided into four groups seven rats in each group [20], sham group, RIRI group, vehicle group (DMSO + RIRI), and Trandolapril+ RIRI pretreated group. The sham group was anesthetized and underwent bilateral flank incisions without ischemia induction. The RIRI group was anesthetized and underwent bilateral flank incisions to induce renal ischemia for 30 minutes, followed by a 24-hour reperfusion period. The vehicle group received dimethyl sulfoxide (DMSO) vehicle for Trandolapril via oral administration 2 hours before ischemia, followed by 30 minutes of bilateral renal ischemia and reperfusion for another 24 hours [21]. Trandolapril pretreated group received 0.3mg/kg of Trandolapril orally two hours before ischemia, then underwent bilateral flank incisions to induce renal ischemia for 30 min. and 24 hours of reperfusion [22]. Following 24 hours of reperfusion, kidney and blood samples were obtained via a midline laparotomy incision. An intraperitoneal injection of anesthesia for the procedure was induced by administering ketamine and xylazine at a dose of 100 mg/kg and 10 mg/kg respectively.

2.3. Preparation of drug

Trandolapril powder was dissolved in DMSO (100 mg/ml) as described by the manufacturer’s guidelines (Shanghai Macklin Biochemical/China). The dose was administered orally according to the body weight [22].

2.4. The experimental model of renal ischemia/reperfusion injury

The procedure starts by weighing rats and anesthetizing them with intraperitoneal ketamine and xylazine. The rats are placed in a prone position over heating pads to maintain body temperature and stability. The operative site is disinfected with a povidone-iodine solution. A bilateral 1.5 cm vertical flank incision is made, and a layer-by-layer dissection is carried out. The kidney is found below the 13th rib, and the perinephric fat is dissected to expose the renal hilum. To avoid partial renal ischemia, the pedicle is skeletonized, and all fat has been removed. The ischemia time is determined by obstructing the renal pedicle and starting the timer. Renal arteries are left claimed for around 30 minutes after that the kidneys are returned to the retroperitoneal area. The clamps can be removed once the ischemia period is over, and reperfusion is visually observed. Before the wound is closed, 1 mL of 0.9% saline that has been preheated to 37°C is applied to the retroperitoneal region [21]. The skin wounds are closed into two layers. The rats are then moved back to their cages and provided with food. After 24 hours, the rats are anesthetized and sacrificed, and blood and kidney tissue samples are obtained for analysis.

2.5. Collection of samples

2.5.1. Blood samples collection for measurement of renal function

After 24 h of reperfusion, the rats are anesthetized, and blood samples are aspirated directly from the heart. Approximately 2-5 mL of blood was inserted in a simple tube at 37°C with no anticoagulant. To separate the serum, the tube was centrifuged at 3000 rpm for ten minutes. The manufacturer's instructions were followed while measuring urea and creatinine levels in serum

2.5.2. Tissue preparation for measurement of apoptotic, autophagy, and oxidative parameters

Following the completion of the trial, each animal's kidney is removed and divided into two halves. One half was placed in a deep freezer at -80°C. The frozen half was subsequently homogenized. Using a protease inhibitor cocktail, 1% Triton X-100, and phosphate-buffered saline (at a weight/volume ratio

of 1:10), the mixture was homogenized in a powerful ultrasonic liquid processor [23]. The homogenate was then centrifuged at 5000 rpm for 10 min. at 4°C, the resulting supernatant was used for the measurement of IL-6, Caspase-3, LC-3, GSH, KIM-1, and Akt using the ELISA technique according to the manufacturer's guidelines.

2.5.3. Preparation of tissue samples for Histopathology

Before being embedded in a paraffin block, the other kidney half was soaked in 10% Neutral-Buffered Formalin, dehydrated in alcohol, and cleaned in xylene. The staining technique employed for the horizontal slide sections, which were approximately 5µm thick, involved the application of hematoxylin and eosin stain [24].

2.6. Measure study parameters

2.6.1. Measurement of urea and creatinine

The Urea and Creatinine Kits, manufactured by Sunlong Biotech Co., Ltd. of China, were used to measure Urea and Creatinine levels according to the manufacturer's instructions.

2.6.2. Measurement of IL-6

The IL-6 Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. of China, was used to measure IL-6 levels according to the manufacturer's instructions.

2.6.3. Measurement of KIM

KIM-1 Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. of China, was used to measure KIM-1 according to the manufacturer's instructions.

2.6.4. Measurement of GSH

The GSH Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. of China, was used to measure GSH levels according to the manufacturer's instructions.

2.6.5. Measurement of Caspase-3

The Caspase-3 Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. of China, was used to measure Caspase levels according to the manufacturer's instructions.

2.6.6. Measurement of LC-3

The LC-3 Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. of China, was used to measure LC-3 levels according to the manufacturer's instructions.

2.6.7. Measurement of Akt

The Akt Elisa Kit, manufactured by Sunlong Biotech Co., Ltd. (China) Akt Elisa was used to measure Akt levels following the directions provided by the manufacturer.

2.7. Statistical Analyses

The data collected in this study was analyzed using GraphPad Prism 8.0.1 (GraphPad Software, La Jolla, California, USA). Results were shown as mean ± Standard Error Mean (SEM). One-way analysis of Variance (ANOVA) followed by the Bonferroni multiple comparison test was used to analyze the data. $P < 0.05$ was used to indicate statistical significance in all tests. Additionally, the Jablonski Score system criteria were used to compare alterations in histopathology between the study groups.

3. Results

The study found that blood urea and serum creatinine levels increased in the RIRI and vehicle groups when compared with the sham group. Renal tissue levels of IL-6, Kim-1, caspase-3, LC-3, and Akt were also increased in RIRI and vehicle groups when compared with the sham group. GSH levels decreased in the RIRI and vehicle groups when compared with the sham group. Trandolapril significantly reduced serum urea and creatinine levels, and renal tissue levels of IL-6, Kim-1, and caspase-3 were significantly reduced **(Figure 1, Figure 2, Figure 3, figure 4, Figure 6**) respectively. Trandolapril pretreated groups showed significant increases in GSH, LC-3, and Akt levels **(Figure 5, Figure 7, and Figure 8**). Trandolapril reduced the severity of kidney damage in ischemia-reperfusion injury, but the RIRI group showed substantial renal damage when compared with the sham group that occurred in histopathologic examination (**Figure 9**).

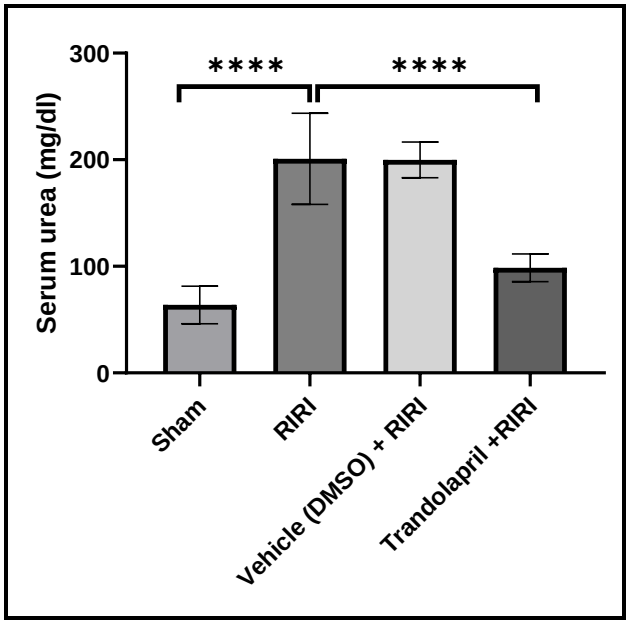

Figure 1: **Blood urea level of study groups.** Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 hr. Rats pretreated with either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, ****P< 0.0001 vs sham and RIRI.

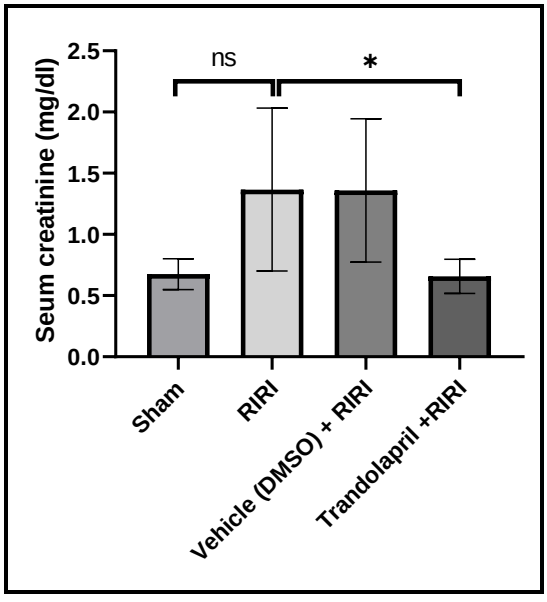

Figure 2: creatinine level of study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats were administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, *P< 0.05 vs RIRI.

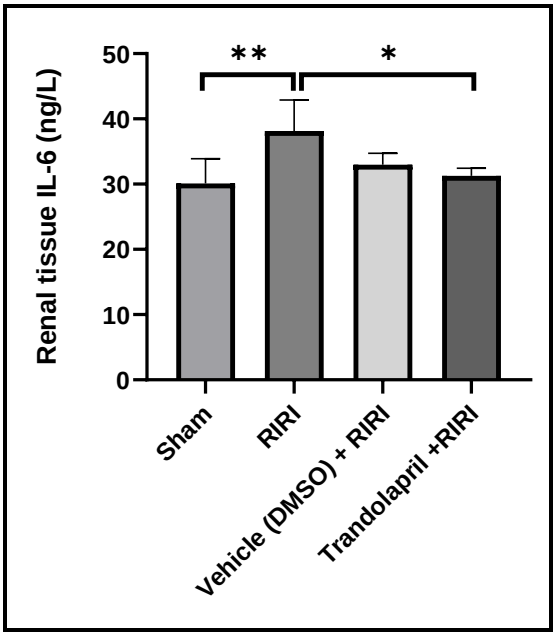

Figure 2: IL-6 level in study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats were administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). The tissue concentration levels of IL-6 were measured by using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, *P< 0.05 vs RIRI, **P<0.01 vs sham.

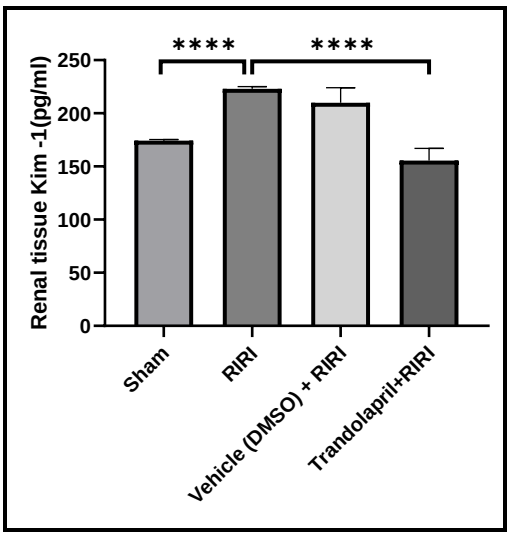

Figure 3:kim-1 level of study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). The tissue kim-1 concentration levels were measured by using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, ****P< 0.0001 vs sham & vs RIRI.

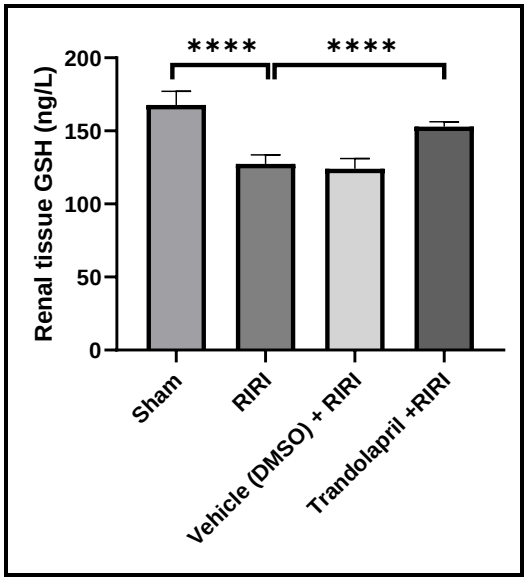

Figure 4: **GSH level in study groups.** Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats were administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). Tissue GSH concentration levels were measured by using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, ****P <0.0001 vs sham and RIRI.

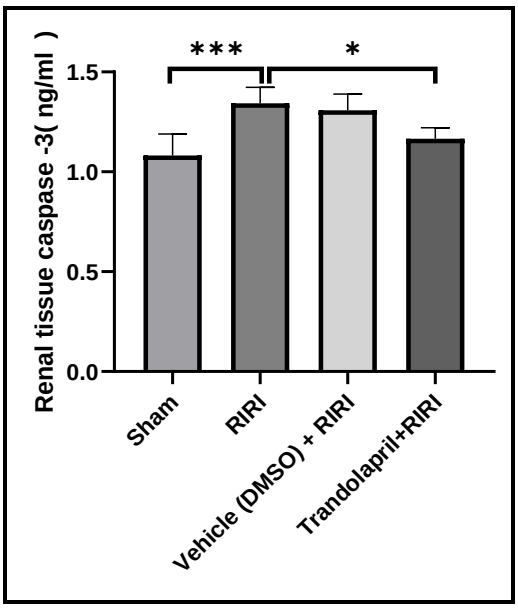

Figure 5: Caspase-3 level of study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 hr. Rats administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). The tissue concentration levels of caspase were measured by using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group *P< 0.05 vs RIRI, ***P<0.001 vs sham.

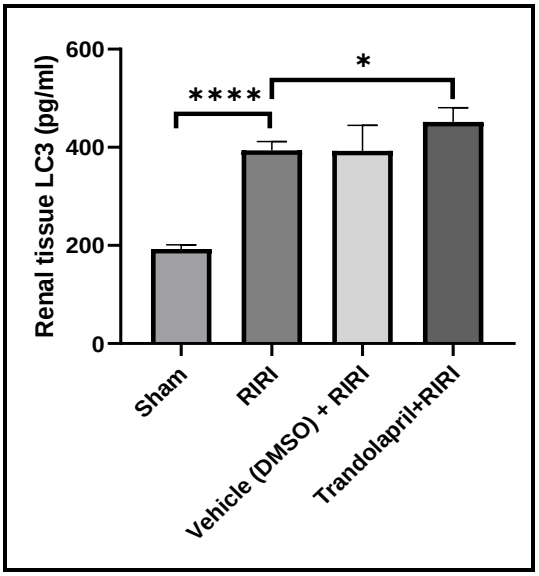

Figure 6: LC3 level of study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats administered either DMSO, and Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). The tissue concentration levels of LC-3 were measured by using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, *P< 0.05 vs RIRI ****P< 0.0001 vs sham.

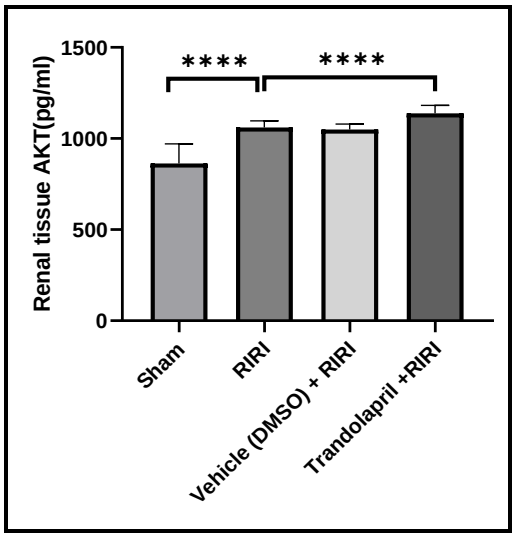

Figure 7: Akt level of study groups. Rats of the RIRI group were exposed to 30 min. of ischemia and then reperfusion for 24 h. Rats administered with either DMSO, Trandolapril (0.3mg/kg), or remained without treatment (sham and RIRI). The tissue concentration levels of AKT were measured by Using the ELISA technique. One-way ANOVA followed by the Bonferroni comparison test was used for analysis. Data are presented as mean ± SEM, n=7 rats in each group, ****P <0.0001 vs sham and RIRI.

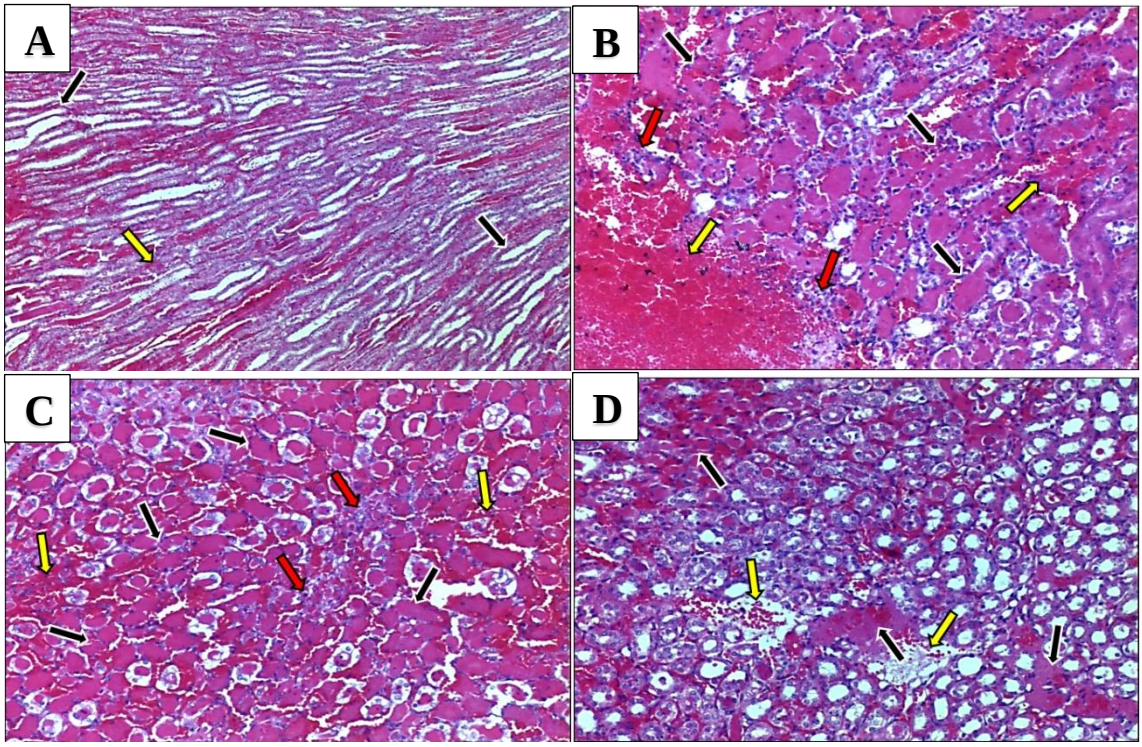

Figure 9: (A) Sham group normal histological architectures of kidney medulla, note the loop of Henle tubules (black arrow) and collecting ducts (yellow arrow). H&E.100x. **(B)** RIRI groups, the massive severe coagulative necrosis (black arrow) that involved all affected medulla areas led to the loss of normal architectures of the medulla observed, with the presence of inflammatory cell infiltrations (red arrow) in the affected area. Coagulative necrosis was observed as the absence of the nucleus of renal tubules epithelial cells in most renal tubules of the loop of Henle. Also, severe hemorrhage (yellow arrow) was observed in the affected area of the medulla. H&E.100x. **(C)** DMSO groups, the massive severe coagulative necrosis (black arrow) that involved all affected medulla areas led to the loss of normal architectures of the medulla was observed, with the presence of inflammatory cell infiltrations (red arrow) in the affected area. Coagulative necrosis was observed as the absence of the nucleus of renal tubules epithelial cells in most renal tubules of the loop of Henle. H&E.100x. **(D)** Trandolapril pretreated group, the coagulative necrosis (black arrow) of the loop of Henle's renal tubules epithelial cells was observed in affected medulla areas, however, the coagulative necrosis did not involve all medulla areas, where coagulative necrosis involved about 10%-15% of the medulla area. Also, the hemorrhage (yellow arrow) was observed in the affected area of the medulla. H&E. 100x.

4. Discussion

Reduced urine production and an increase in serum creatinine are signs of acute kidney injury (AKI), a fast decline in renal function. Ischemia/reperfusion injury, hypoxia, inflammation, oxidative stress, medications, and sepsis are the main causes of AKI. A complicated chain of events of ischemia/reperfusion injury involves fast energy loss, a decrease in membrane potential, a breakdown of ionic hemostasis, and cell death. In addition to being involved in the start and progression of ischemia injury, mitochondria also play a part in the healing process and other procedures that lead to the development of chronic kidney disease (CKD). [25] [26] [27]

Drugs that reduce inflammation and boost antioxidant levels, such as trandolapril have been studied for their potential to protect against experimental RIRI rat models. This medication has been shown to lower blood urea nitrogen and creatinine concentrations while having a reno-protective impact against IR injury.

When trandolapril is administered two hours before ischemia induction, blood urea, and serum creatinine levels are considerably lower than in the RIRI and vehicle groups **(Figure 1, Figure 2)**. This protective effect is comparable to that of a study by Yashida et al., which showed that trandolapril exerts its reno-protective effect without causing any obvious side effects in hypertensive patients with chronic renal failure by considerably lowering the serum creatinine levels. [28]

According to this study, compared to the sham group, the RIRI and vehicle groups had higher levels of interleukin-6 (IL-6) and kidney injury molecule-1 (KIM-1) following renal ischemia/reperfusion (**Figure3, Figure 4**)

Another well-known indicator of renal injury is KIM-1, which is particularly active when RIRI is present. According to published research, early RIRI was associated with a significant increase in KIM-1 mRNA and protein expression in rat kidneys, suggesting that KIM-1 is a sensitive marker for tubular injury in RIRI [29].

It has also been discovered that trandolapril, a different medication that has been demonstrated to lower KIM-1 and IL-6 levels in rats, has a positive reno-protective impact on RIRI by regulating the RAS system and lowering inflammation and oxidative stress. Their advantages typically exceed their disadvantages when utilized and supervised appropriately. ACEI inhibitors that block the renin-angiotensin system (RAS) can help lower inflammation and enhance renal function [30] [31]

According to this study, compared to the sham group, the RIRI and vehicle groups had lower GSH levels following I/R (**Figure 5).** The research shows that GSH concentrations significantly fall in response to renal ischemia, suggesting a deterioration in the kidney's ability to function as an antioxidant [25]. Previous research by Ahmadvand et al., Baltaci and associates, and Scaduto Jr. and colleagues support this study. Within 35 minutes of renal artery closure, the renal level of GSH dropped to 40%, and after 120 minutes of blood flow, it only partially recovered [33] [34] [35]. ACE inhibitors reduce the synthesis of angiotensin II, a powerful vasoconstrictor that aggravates oxidative stress and damage in the heart and kidneys. It was shown that trandolapril dramatically increased the activity of mitochondrial enzymes I, II, and IV and decreased oxidative stress in the rat brain by decreasing lipid peroxidation and raising glutathione and catalase levels. By slowing the rate of ATP and mitochondrial oxygen consumption drop, it also avoids mitochondrial dysfunction that occurs after an acute myocardial infarction [36] [37].

When compared to the sham group, renal ischemia/reperfusion injury causes a substantial increase in the levels of the kidney marker of apoptosis, caspase-3 (**Figure 6**) [25] [27]. This study supports the findings of earlier research by Eraslan et al. [40]

The research indicates that trandolapril pretreatment two hours before ischemia induction causes considerably reduced tissue levels of caspase-3, suggesting that trandolapril protects the kidneys by reducing renal apoptosis. Caspase-3 activity is significantly reduced when Angiotensin II synthesis is blocked. Angiotensin II promotes apoptosis and elevates apoptotic markers like caspase-3. This indicates that trandolapril inhibits the release of cytochrome C from the mitochondria and the activation of intracellular caspase-3, hence preventing apoptosis in cardiac cells [41]

Rats with acute myocardial infarction were given trandolapril as part of an experimental investigation. This improved mitochondrial dysfunction by decreasing the decrease in mitochondrial oxygen consumption and ATP generation and elevating the amounts of mitochondrial thiobarbiturate-reacting chemicals. Additionally, trandolapril has antioxidant qualities. By decreasing lipid peroxidation, and raising catalase and glutathione levels, it reduces oxidative stress markers in the rat brain. These

results imply that trandolapril inhibits caspase-3 activity through enhancement of mitochondrial efficiency and reduction of oxidative stress [42] [41]

Furthermore, the study demonstrates that in comparison to the sham group, the LC-3 and Akt levels of autophagy indicators were significantly higher in the RIRI and vehicle groups of rats that underwent 30 minutes of ischemia followed by 24 hours of reperfusion **(Figure 7, Figure 8**). This implies that autophagy might be activated in response to ischemia/reperfusion injury, perhaps acting as protective against I/R damage [43] [44].

Additionally, the study discovered that rather than causing autophagy through ischemia, reperfusion significantly increases it, possibly averting cell death. An active PI3K/Akt signaling system can control oxidative stress, inflammation, autophagy, and anti-apoptosis to lessen the damage caused by hepatic ischemia-reperfusion. It is anticipated that management of the PI3K and Akt signaling pathway would prove to be a successful focused strategy in the therapeutic prevention and mitigation of liver ischemia-reperfusion injury. In rats undergoing renal ischemia/reperfusion, the effects of trandolapril on autophagy markers are examined in this study. Administration of trandolapril two hours before ischemia causes a considerable rise in LC-3 and Akt levels, which is in line with another research. When administered two hours before ischemia induction, trandolapril raises tissue levels of LC-3 and Akt, Administration of Trandolapril Significantly increased tissue levels of LC-3 and Akt are found two hours before ischemia induction, suggesting that this time has a protective impact on the kidneys by encouraging autophagy. This is in line with earlier studies that demonstrated that in rats with acute myocardial infarction generated by inhibiting Angiotensin II, the PTP1B/PI3K/Akt pathway was upregulated, leading to a substantial increase in Akt phosphorylation [43]

In this study, renal parenchyma is also investigated. Significant changes were observed in the histological analysis of the RIRI and vehicle groups, including coagulative necrosis, loss of normal architecture, infiltration of inflammatory cells, and significant bleeding **(Figure 9)**. When compared to the RIRI and vehicle groups, Treatment with trandolapril lessened renal tubular injuries and decreased the severity of renal injury in the group receiving trandolapril [45]

This study demonstrates the possible advantages of trandolapril in the treatment of ischemia and kidney injury and how trandolapril may encourage autophagy and lessen the degree of kidney damage in ischemia patients. The precise mechanisms behind its protective effects on the kidneys and renal parenchyma require more investigation.

5. Conclusion

This study showed that trandolapril dramatically reduced renal damage from ischemia-reperfusion injury in male rat models through its antioxidant effect by elevation of antioxidant marker GSH, anti-inflammatory by reducing inflammatory markers IL-6 and KIM-1, anti-apoptotic by decreasing apoptotic marker Caspase-3, activation autophagy by increasing LC-3, Akt, and ameliorating histopathological changes.

Conflict of interest: NIL

Funding: NIL

Reference:

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