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Guiera senegalensis Alleviates Ischemia Renal Reperfusion Injury in Albinos Wistar Rats

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Abstract

Introduction: Renal ischemia-reperfusion (IR) is responsible for injuries such as destruction or dysfunction of tubular epithelial cells with inflammatory reaction and oxidative stress. Several therapeutic methods have been tested to alleviate ischemia-perfusion injury, ranging from using anti-inflammatory drugs, antioxidants, and plants from traditional pharmacopeia to administering RNA interference. However, there is currently no effective therapeutic option available for the treatment of renal IR injury, other than supportive therapies such as renal replacement therapy or hydration. **Objective:** This present study aimed to evaluate the effect of *Guiera senegalensis* on renal ischemia reperfusion, a recognized plant for its antioxidant and anti-inflammatory properties. **Materials and Methods:** Twenty-four (24) adult male Wistar rats were divided into four following groups: SLAM (subjected to a median laparotomy with simulated ischemia); GUIERRA (animals that received 250 mg/kg of guierra senegalensis orally, once a day, for 5 days, with simulated renal ischemia); IR (animals that underwent laparotomy followed by clamping of bilateral renal pedicles for 45 min and followed by reperfusion); GUIERRA + IR (animals given GUIERRA at the dosage of 250 mg/kg per day, for 5 days and then subjected to renal ischemia-reperfusion). Data analysis was performed by ANOVA, and a significance level of $p < 0.05$ was chosen. Blood and renal tissue samples from all rats were collected after 24 h. Histopathological analysis of the kidneys was performed by evaluating the degree of tubular degeneration, the presence of interstitial lymphocytic infiltrate, proteinaceous casts, necrosis, and loss of the brush border appearance of the tubules using a dedicated score. In the blood samples, creatinine levels were evaluated. **Results:** Compared with the I/R group, rats in the GUIERRA + IR group showed reduced histopathological damage scores ($p < 0.05$). Although the differences in

creatinine levels were not statistically significant, these were significantly decreased in the treatment group. **Conclusion:** The results of this preliminary work suggest that *Guiera senegalensis* decreases the degree of tissue damage in renal ischemia-reperfusion cases. This plant seems to be a promising therapeutic; further studies could help to precise the targets of its compounds on ischemia-reperfusion pathways.

Keywords

Ischemia Reperfusion, Acute Kidney Injury, *Guiera senegalensis*, Tubular Degenerescence

1. Introduction

Renal Ischemia reperfusion (IR) is responsible for lesions damaging renal function. It is most often induced during a surgical procedure by clamping of the aorta, renal vascular surgery, shock and trauma situations. In renal transplantation in particular, it is responsible for significant renal dysfunction that can lead to rejection or postoperative complications that can lead to death. On the cellular level, the pathophysiology of the lesion remains unclear and the mechanisms of tissue damage remain the subject of numerous studies [1]. These lesions can induce destruction or dysfunction of tubular epithelial cells, microcirculatory disorders, inflammatory reaction and release of reactive oxygen species involved in oxidative stress [2]. Histopathologically, IR injury frequently manifests as damage to the tubular epithelium, primarily due to the high energy demands of renal tubules [3]. Several therapeutic methods have been tested in an attempt to alleviate the ischemia perfusion injury ranging from the use of anti-inflammatories, erythropoietin, antioxidants to the administration of RNA interference.

The pathophysiology of ischemia-reperfusion (I/R) implies acute kidney injury (AKI) that is a highly complex process reported to involve activation of neutrophils, release of reactive oxygen species (ROS) and secretion of various inflammatory mediators, including cytokines such as TNF-α and IL-6 [4]. However, there is currently no effective therapeutic option available for the treatment of renal IR injury, other than supportive therapies such as renal replacement therapy or hydration [4.] *Guiera senegalensis*, widely used in Senegalese pharmacopoeia and in West Africa, is a plant recognized pharmacologically for its antioxidant and anti-inflammatory properties [5] [6]. In the context of ischemia-reperfusion injuries, the anti-inflammatory and anti-oxidant properties of *Guiera senegalensis* have not yet been explored to date. Therefore, the present study aimed to assess the effects of *Guiera senegalensis* on this condition.

2. Material and Methods

2.1. Experiment Animals

This study involved twenty adult Wistar rats with body weight between 220 - 250

g. The animals were housed under standard laboratory conditions in the Animal House of the Laboratory of Toxicology, Faculty of Medicine, Pharmacy and Odontology University Cheikh Anta Diop, Dakar, Sénégal. They were fed with pelletized mash and given drinking water.

Sex differences in ischemia-reperfusion injury were reported [7] and male could be more sensitive, so we selected a group of males to begin the experiment.

The experimental animal handling was in accordance with the guidelines of OECD [8].

This study was approved by Research and Ethics Committee of the University.

2.2. The Plant Extraction

Leaves of *G. senegalensis* were washed and shade-dried for five (5) days and powdered using a plant grinder. Double extraction by maceration technique was used. For the current study, 250 g of the grinder leaves power was dissolved to 1.5 liters of methanol in a 3 liters stoppered container, for a period of 72 hours with gentle agitation at room temperature. The resulting mixtures were filtered using cotton wool then Grade I Whatman filter paper. The extraction and filtration procedure were repeated further in 750 mL of methanol. The methanol filtrate was concentrated to dryness in-vacuo using an evaporator (LB-RE2000-3000 Rotary Evaporator) and the resulting powder was kept in an air-tight container and refrigerated before any further test.

2.3. Experimental Design

Adult Wistar albinos' rats were divided into the following four groups at random (n = 6). A median laparotomy was performed under anesthesia (intraperitoneal injection of choral hydrate 10% (250 mg/kg). Renal ischemia was induced by using clamps on renal pedicles, including the renal artery, for 45 min and reperfusion was obtained by removing the clamps. The animals were euthanized by exsanguination through intracardiac puncture and blood samples were collected. Bilateral nephrectomy was then performed by relaparotomy. Both kidneys were removed from each animal and were preserved in 10% formalin at room temperature for 48 h for histological analysis. The centrifugation of blood samples was performed at 2110× g for 10 min at 2˚C - 8˚C. Serum was stored in Eppendorf tubes at −80˚C for creatinine levels assessment. The experimental groups were the following:

Control group (SLAM)

In this group, rats were subjected to a median laparotomy with simulated ischemia.

***Guiera senegalensis* group (GUIERA)**

Animals received 250 mg/kg of *Guiera senegalensis* orally, once a day, for 5 days and had simulated renal ischemia.

Ischemia reperfusion group (IR)

Rats received the administration of intraperitoneal saline (40 mg/kg/j), 5 days before the surgery and then ischemia was applied in right and left main renal arteries for 45 min.

Therapy group (GUIERA + IR)

Guiera senegalensis (250 mg/kg/j) was administrated 5 days before the surgery. A median laparotomy was performed under anesthesia. Right and left main renal arteries were subjected to ischemia for 45 min.

2.4. Histological Preparation

After formalin fixation, the samples went through a series of graded ethanol solutions to dehydrate them (70%, 95% and 100%). Alcohol was replaced by xylene to clear the tissue samples. Molten paraffin wax was then infiltrated to impregnate them and imbedded the tissues. After cooling, blocks were obtained and cut in microtomes adjusted for 4 microns of lamel size. The staining process started with deparaffinization in a 60˚C laboratory oven for 5 min. The rest of the staining process was performed using a Tissue automatic tissue stainer with baths calibrated for Hematoxylin eosin staining protocol (Leica station). Finally, the slides were cleared in xylene and covered manually with Eukitt.

2.5. Histopathological Analysis

Histological analysis was performed by two pathologists and blinded to the subjects. After overall assessment of the injuries, 10 high power fields were analyzed under a light microscope (Leica DM1000) at 200 magnification, using a score considering a mean percentage of registered lesion *i.e.* tubular dilatation, presence of cytoplasmic vacuoles, interstitial lymphocyte infiltration, protein cylinders, necrosis and loss of brush borders. Tubular injury score was graded depending on the percentage of the injured area [9]. (0: no tubular injury; 1: ≤10% injured tubules; 2: 11% - 25% injured tubules; 3: 26% - 50% injured tubules; 4: 51% - 74% injured tubules; and 5: ≥75% injured tubules.)

2.6. Biochemical Parameters

Biochemical tests were performed by the Sysmex XS-500i Coulter and Biosystem BTS-350. Serum creatinine was determined according to the method description by the manufacturer of the Biosystem kits.

2.7. Statistical Analysis

Histopathological injury scores are reported as mean with standard deviation. The parameters of the different groups were presented as an average standard deviation of the number of animals used for each group. The difference of distribution between the different groups was assessed using a test of variance one-way ANOVA. The confidence interval level was 95% and differences with values of $p < 0.05$ were considered statistically significant. The data was processed and analyzed using SPSS software.

3. Results

In our series a pattern of tubular injury was identified as tubular dilatation,

necrosis, degeneration of the tubular epithelium, loss of brush border, eosinophilic hyaline cast, leucocyt infiltration and glomerulus retraction. Those lesions were assessed to be able to establish a tubular damage score for each animal with observation of 10 fields and calculation of the mean. The different observed lesions are reported in Figure 1.

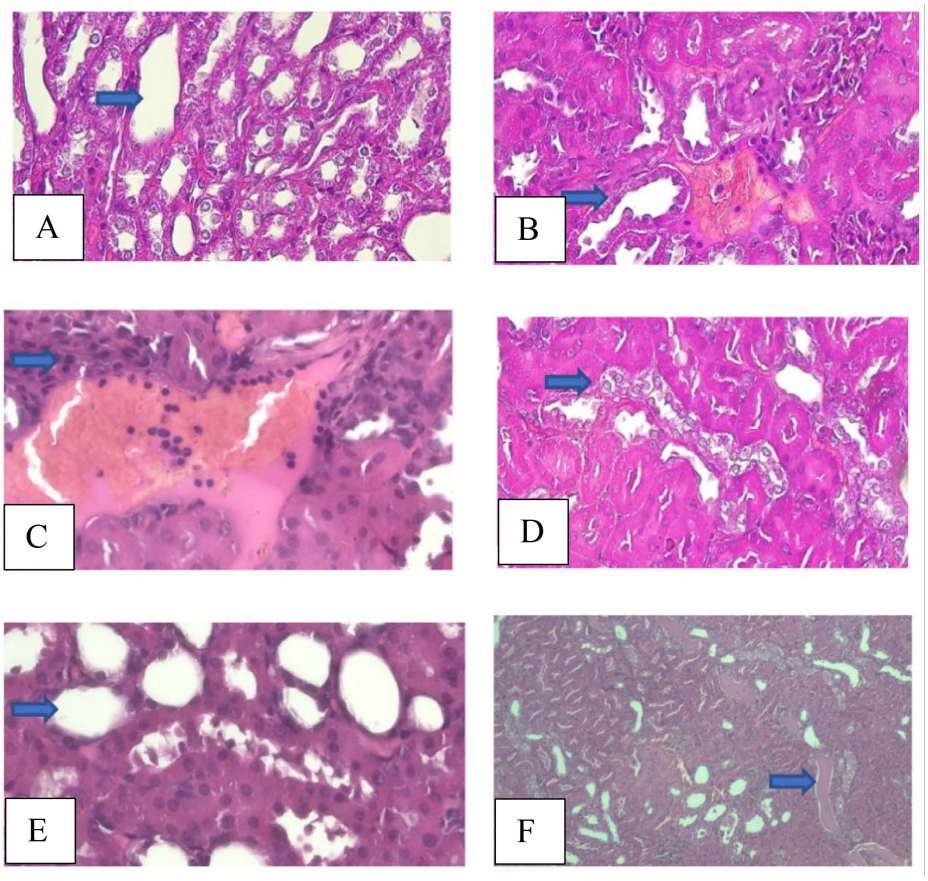

Figure 1. Illustration of Histopathological images of each of the criteria used to score the different groups. (A) arrows showing tubular dilatation ×200. (B) Tubular degeneration ×200. (C)Arrows indicating leucocyte infiltration, ×400. (D) Arrow indicates tubular necrosis, ×200. (E) Loss of brush border of the tubules, ×200. (F) Eosinophilic hyaline cats (protein cylinders), ×100.

3.1. Tubular Injury Score

A significant difference, concerning data repartition was noted within the different groups ($p = 4.196e{-}10$). Group IR had a significantly higher score of renal injury compared to the other groups including the therapy group (GUIERA + IR), ($p < 0.05$). In the IR Group, the mean injury score was 4 ± 0.66 and in the therapy group (GUIERA + IR) the mean score was 3.2 ± 0.91. In SHAM and GUIERA groups, the score was under 1 with respectively 0.4 ± 0.51 and 0.6 ± 0.69, of tubular injury score. The profile of tubular injury score in the different experimental groups is represented in Figure 2 and representative histopathological images of IR group and GUIERA + IR are represented in Figure 3.

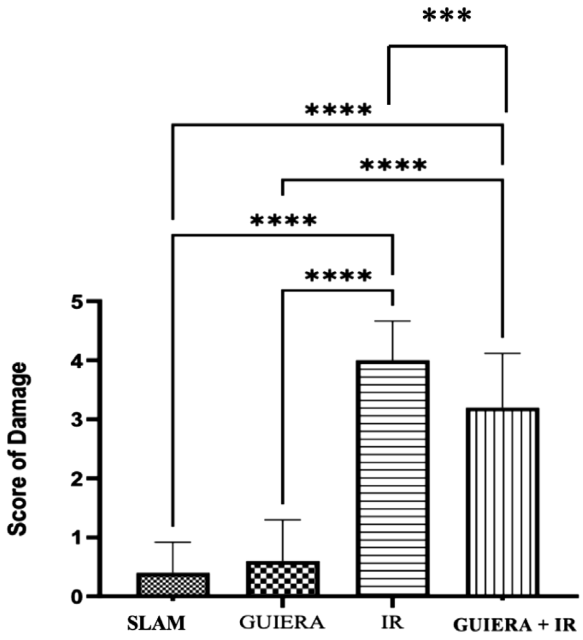

Figure 2. Tubular injury score observed in each group.

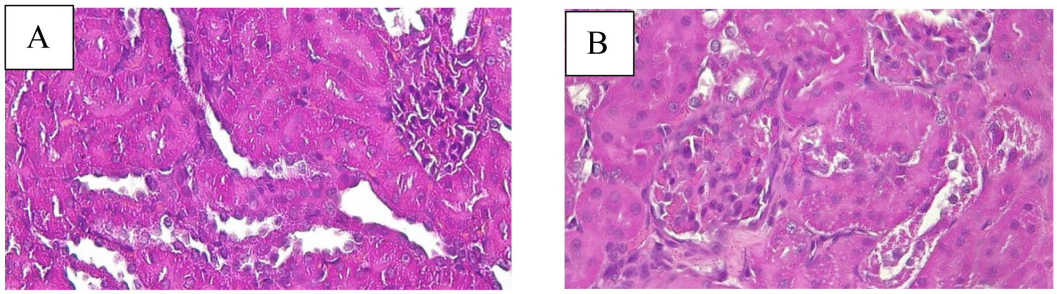

Figure 3. Representative histopathological images from group (A) IR, with tubular dilatation, necrosis, dilatation and glomerulus retraction (scored 4: 51% - 74% injured tubules) and group, (B) GUIERA + IR group with tubular necrosis and dilatation (scored 3: 26% - 50% injured tubules).

3.2. Biochemical Analysis

There was no significant difference between IR group and the therapy group (GUIERA + IR), on a statistical point of view. In Table 1, mean levels of creatinine are reported.

Table 1. Creatinine levels in serum from animals in the experimental groups.

Animal Group	Control group (C)	Guierra group (G)	Renal ischemia group (IR)	Guierra therapy group (T)
Serum Creatinine, mg/l	5.7 ± 0.8	6 ± 0.4	11 ± 0.5	10 ± 0.7

4. Discussion

4.1. Physiopathology and Cellular Mechanisms of IR Injury

Ischemia-reperfusion (IR) is a complex pathological process that occurs in many

organs and diseases and is a challenge in the management of kidney transplantation [1]. Ischemia combines lesions associated with oxidative stress and inflammation in connection with the recruitment and the activation of immunity cells. Late reperfusion induces tissue injury and cell necrosis caused by ischemia, leading to irreversible injury.

Histological lesions associate acute tubular necrosis and interstitial œdema, which can progress to interstitial fibrosis. IR induces Acute kidney injury (AKI) that is a major kidney disease associated with mortality in human patients and involved in the development and the progression of chronic kidney disease [2]. Preclinical models, such as murine and porcine models, have furthered help a lot in understanding the pathophysiological mechanisms of ischemia-reperfusion injury.

At the cellular level, the pathophysiology of the lesion remains unclear, and the mechanisms of tissue damage are the subject of numerous studies. Among them are mainly described immunological pathways with an inflammatory response, oxidative stress, perturbation of cell physiology with change of polarity, and cell death both by necrosis and apoptosis.

4.2. Inflammatory Response

Inflammatory response can be initiated by several mechanisms as the activation of DAMP, the production of cytokines, and the activation of immune cells.

4.3. Activation of DAMP

Damage-associated molecular patterns are endogenous molecules of intracellular origin or from fragments of the extracellular matrix. They are released after major cellular stress and are capable of inducing inflammation in a sterile context by acting on the pattern recognition receptors (PRRs) associated with innate immunity, in particular their specific receptors, Toll-like receptors (TLRs) and receptors for advanced glycation (RAGEs) [10].

4.4. Production of Cytokines

Tubular cells express class II molecules of the major histocompatibility complex and T lymphocyte costimulatory molecules. By this mechanism, tubular cells participate in the production of cytokines (TNF and [TNFα]) and in the recruitment of inflammatory cells [11]. Tubular cells will also express on their surface the Toll-like receptor TLR, in particular TLR2 and TLR4 whose activation also contributes to the release of pro-inflammatory cytokines (Tumor necrosis factor α [TNFα], IL-6, IL-1β) and chemoattractant cytokines such as RANTES [12].

4.5. Activation of Immune Cells

In the hours following ischemia-reperfusion, the renal interstitium is the site of an inflammatory infiltrate. The nature of the cells that compose this infiltrate varies over time. The first cells activated and/or recruited in response to renal

ischemia-reperfusion belong to innate immunity (dendritic cells, monocytes/macrophages, polymorphonuclear neutrophils, natural killer (NK) cells and invariant natural killer T (iNKT) cells). Among the resident leukocytes, dendritic cells are the most represented [12]. The activation of dendritic cells allows the early recruitment of polymorphonuclear neutrophils by interaction with their adhesion molecules expressed on the surface of the activated endothelium. Activation of neutrophils induces their own production of the pro-inflammatory cytokines IL-17 and interferon γ (IFN-γ) [13].

4.6. Oxidative Stress

Endothelial injury increases inducible nitric oxide synthase (iNOS), and so increases the nitric oxide produced, reacting with oxygen radicals to form peroxynitrite that may aggravate the inflammatory response [14]. Cytokines and reactive oxygen species (ROS) produced by IR injury upregulate the expression of adhesion molecules like ICAM, VCAM and P selectin [15]. The combination of chemokines, cytokines and adhesion molecules leads to recruitment, activation and sequestration of leukocytes, which generates further ROS and cytokines and potentiates the injury.

4.7. Change of Polarisation

With I/R injury, there is disruption of the actin cytoskeleton, loss of tight junctions and adherent junctions in the proximal tubular epithelium. This is responsible for change in the localization of polarized membrane proteins, especially sodium-potassium ATPase (NKA). NKA is normally localized to the basolateral plasma membrane and will appear on the apical plasma membrane [16]. Consequences are reduction of the efficiency of transcellular Na+ transport and increase Na+ delivery to the distal tubules leading to glomerular vasoconstriction and decreased Glomerular Filtration through tubuloglomerular feedback [3]. In addition, I/R causes decreased NaK ATPase activity, due to ATP depletion, leading to increased intracellular Na+ concentration, which increases intracellular Ca^{2+} and causes increased injury.

4.8. I/R Injury Causes Cell Death by Both Apoptosis and Necrosis

Renal ischemia-reperfusion injury (IRI) is histologically characterized by tubular cell death. Diverse pathways of cell death (RCD) have been reported and concerns apoptosis and necrosis. Concerning apoptosis, pathways lead to activation of the downstream effector caspase-3. It can be apoptosis through death domains (TNF receptor associated and Fas associated which activate caspase-8 followed by caspase-3 (through mitochondrial release of cytochrome c, which activates caspase-9 and then caspase-3). Many molecules regulate these apoptotic pathways among them are phosphatidylinositol 3 kinase (PI3K) and members of the Bcl-2 family [17]. Necrosis can occur through TLR (Toll-like receptor) and TIR-domain-containing adapter inducing interferon-β, necrostain 1 (Nec-1) and

Necrosul-fonamide (NSA) [18]. A better understanding of these mechanisms may allow selective targeting and therapeutic strategy to decrease deletere consequences of acute renal failure caused by ischemic. The understanding of the different pathways remains a domain of research.

4.9. Tested Molecules and Drugs

Several drugs and molecules have been tested to ameliorate IR injury. Flavonoids through 15 identified molecules have been reported to alleviate IR injury and their precise target was precised for each pathway involved in the process (Oxidative stress, Inflammatory response, cell death, endoplasmic reticulum stress and mitochondrial dysfunction) [19]. Anti-oxidative potential from plants used in traditional pharmacopoeia worldwide has shown beneficial effects on IR and has been tested. Abuta grandifolia promoted functional renoprotection and confirmed its antioxidant activity by reducing oxidative metabolites and increasing thiols, which reduced tubulointerstitial injury. Further investigations are needed to explore the mechanism of action of the extract against iAKI [20]. Urtica dioica would also inhibit apoptosis and inflammation [21].

4.10. Guierra Properties

Thus, antioxydatives and antiinflammatory qualities of *Guierra senegalensis* from Senegalese pharmacopeia have been investigated in the literature and these effects are probably related to its chemical compounds. Indeed the phytochemical analysis of *G. senegalensis* has revealed presence of various bioactive flavonoids (e.g., catechin, myricitrin, rutin and quercetin), alkaloids (e.g., harman and eleagnine), a naphthyl butenone (guieranone A) and also tannins (e.g., epicatechin, epigallocatechin gallate and galloylquinic acid. Of the identified tannins, radical scavenging and antioxidant activities of galloylquinic acid have been studied [22]-[24].

The triterpenoids are known for their therapeutic potentials as being immunomodulant. Among them, lupeol has shown in vivo and in vitro anti-inflammatory efficacies and was reported to decrease the ROS level and restore antioxidant enzyme activities in mouse liver after chemical-induced oxidative stress [25]. Finally, lupeol was found to exert anti-inflammatory and antioxidant effects in a renal IR model at the dosage of 100 mg/kg, thanks to its antioxidant properties [26].

Thus, all those compounds are potentially able to alleviate IR through the different pathways described previously *i.e.* oxidative stress, inflammatory response, and cell death.

In our study, we used doses of 250 mg/kg/day and no toxicity was found in guiera group. Safety of guierra on a toxicologic point of view has been assessed in a previous study with daily administration of *Guiera senegalensis* at 2 g/kg/day to Wistar male and female rats during six months [27].

This is a preliminary study and we would like to pursue the experiment by evaluating oxidative stress, apoptosis and inflammation response. We would like also to test higher dose of guiera to evaluate if we could have better effects without

toxicity.

5. Conclusion

In our study, *Guiera senegalensis* at the dosage of 250 mg/kg/day alleviated IR injury in Wistar albino rats. Thanks to its antioxidant and its anti-inflammatory properties, this plant appears to be a promising therapeutic means to inhibit IR. Further studies would allow us to specify the precise level of action of the plant in the IR process and propose new therapies.

Limitations

This is a preliminary study. A larger cohort will allow us to increase the precision of our statistical tests. The starting dose in our experiment was 250 mg/kg. Our results were conclusive in case of ischemia reperfusion. We therefore plan to continue the experiment with higher doses.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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