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Herbal Extract Diminishes Diclofenac-Induced Nephrotoxicity

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Abstract. *Nonsteroidal Anti-Inflammatory Medications (NSAIDs) are essential of the most frequently recommended painkillers, and their renal toxicity effects are predictable. Numerous studies have shown a link between the development of advanced stage chronic kidney disease (CKD) and high doses of NSAID exposure. Frequently prescribed medications that make up 5–10% of all prescriptions written in the US. Diclofenac (DFC) is widly administered as an analgesic and anti-inflammatory drug. The medical plant is a new strategy to reduce the adverse effect of other medications. Artemisinin has a rapid onset of action, which is crucial for treating severe malaria and for reducing mortality rates.Combination Therapy: To combat resistance, artemisinin is often used in combination with other antimalarial drugs (ACTs - Artemisinin-based Combination Therapies). This strategy helps to enhance efficacy and reduce the likelihood of developing resistance. This study aimed to examine the capability of Artemisinin to reduce (DFC) and stimulate hepatic's and kidney toxicity in a rat model.DFC was injected intramuscularly twice daily for seven days, and Artemisinin was administrated by oral gavage for the same time. Hematological with biochemical profiles were analyzed. Tissue damages were assessed under microscopy and histopathological reporting. DFC administration produced renal and hepatic function test defects and diminished hematocrit and hemoglobin points but augmented WBC and platelet calculations. Histopathological outcomes displayed renal tubular injury, hepatocyte injuries, and amplified fibrosis in the DFC rats group. Artemisinin administration, besides DFC treatment, reduced hematological test irregularities and DFC, which brought renal functional damage as verified by expressively bringing back serum creatinine and uremia levels. These outcomes show Artemisinin which might improve hepatic and renal toxicity due to severe DFC treatment.*

Keywords: *Artemisinin, Diclofenac, Hepatic toxicity,Renal toxicity*

INTRODUCTION

Kidneys are extraordinary tissues since they make numerous roles necessary for a healthy life, including controlling body fluids contrasted with blood pressure, eliminating leftover products, and synthesizing erythrocytes [1]. Normal kidneys obtain roughly 25% of cardiac output and consume roughly 7% of everyday energy spent to sustain their various functions. Kidney disorders posture global health issues, leading to insignificant morbidity and mortality rates [2]. The inequality between the substances mechanisms that manage oxidative stress, responses to infection, protection, and necrosis are important reasons for either acute kidney injury (AKI) or chronic kidney diseases (CKD) [3]. NSAIDs can prompt numerous types of kidney damage, counting hemodynamically facilitated acute kidney injury [4]. This

medication is recognized to originate renal damage on their repeated usage and extraordinary amount. Diclofenac is one of the NSAIDs that is used as a pain killer and for arthritis [5].

Evidence confirmed that normal substances are alternative materials for remedying kidney infections based on straight experience and multi-target features [6]. Artemisinin is an active component with a high molecular weight of 282, initially obtained from an old Chinese medication called Artemisia annua L, founded by Chinese researchers in 1972. Artemisinin has a chemical structure, sesquiterpene lactone, and a peroxide link has been verified to employ an exceptional antimalarial consequence [7]. Artemisinin selectively kills Plasmodium-infected erythrocytes while sparing healthy cells, making it an effective treatment for malaria [8]. Artemisinin has a quick start of the act and may be swiftly fascinated by the digestive system after oral uptakes, with half-live extending from 2 - 5 hours. It is mainly circulated in the accessory organ of the digestive system, including the liver, kidney, and bile, and roughly 80% of the Artemisinin was defecated via the urine and feces after one day of uptaken [9]. In addition to remarkable improvement alongside malaria, investigations have proved a variation of other pharmacological properties of Artemisinin, such as anti-cancer and immunosuppressive impacts [10]. However, the therapeutic effect of kidney disease Artemisinin has not been fully investigated. This study targets research on Artemisinin therapeutic applications for kidney disorders by assessing therapeutic characteristics and possible molecular mechanisms.

MATERIAL AND METHODS

Preparation of Artemisinin : Most plant divisions, including leaves, branches, central stem, and roots, were harvested, air-dried, and crushed by a mechanical crusher to a fine powder. Then, 100 mg of this powder was positioned into an extraction protector. The extraction process started with 170 mL of solvent (n-hexane, acetone, and methanol) by boiling the soxhlet abstraction technique for 5-6 hours and was completed in a water bath. The over left material was vaporized in a vacuum device and resuspension in 5 mL methanol. Ten μL of extraction test liquid were taken for quantification.

Experimental design (Animal groups): This study was considered to inspect Artemisinin's renoprotective outcome in the Diclofenac (DFC) rat, which stimulates acute renal failure and gastrointestinal ulceration. 25 male Wistar rats were separated into four groups of 5 males each as monitors: a control group that received propylene glycol by oral administration gavage for seven days and treatment groups that received (100 mg/kg.) for seven days (100mg/kg) were intragastric intake to each rat DFC, DFC retrieval, DFC followed by Artemisinin, Artemisinin only and Artemisinin plus DFC for the same period of other groups.

Histopathological Consideration: Hepatic and renal tissues were dissected and fixed in 10% formalin. Then, the typical histological procedure was applied with dipping in sequential arising dilution of ethanol. Afterward, the tissue samples were fixed in paraffin. The achieved paraffin blocks were split at four μm width, and then the slides were stained with hematoxylin and eosin (H&E), as confirmed by Bancroft and Layton [11].

Ethical Matters: The research tracked the views of the statement of veterinary medicine; knowledgeable permission was achieved, and the ethical team of the Kerbala University of Veterinary Medicine permitted the research. Statistical Analysis: Outcomes were stated equally means ± standard error of the mean (SEM). Statistical differences were assessed using two-way analysis of variance (ANOVA) followed by Tukey's post hoc test. The equal significance was regular at $P < 0.05$.

RESULTS

Clinical signs: DFC-treated rats model showed laziness, infection, and anorexia. However, their urine confined considerable protein, glucose, and ketone bodies.

Laboratory tests: Hematological besides biochemical profiles were analyzed. Diclofenac (DFC)intramuscular effects on diet intake, liquid intake, urine productivity, protein levels, glucose concentrations, ketone bodies, and electrolytes were considerably diminished in animals treated with DFC. It showed a crucial escalation in urea and creatinine stages and malondialdehyde levels within a marked decrease in catalase processing and reduced glutathione level, as stated in (Table 1).

Table 1: Renal activity parameters of the control group(group 1) and animals with mild group 4 (Artemisinin + DEC), moderate group 3(DEC followed by Artemisinin), and severe uremia group 2 (DEC Only).

Renal function parameters (at 7 days)				
Parameters	**Control(group1)**	**Group 4**	**Group 3**	**Group 2**
Serum Na^+ (mEq/l)	140.2±2.1	145.0±2.3	150.8± 2.1[a]	161.2± 2.8[a]
Serum K^+ (mEq/l)	4.2±0.13	4.6±0.4	5.4±0.5[a]	6.2±0.5[a,b]
Urine Na^+ (mEq/l)	283.8± 27.1	238.3± 31.2	181.3± 23.1[a]	140.3± 12.2[a,b]
Urine K^+ (mEq/l)	213.4± 32.3	196.0±24.2	156.8± 22.4[a]	118.2± 16.1[a,b]
Serum urea (mEq/l)	34.5±2.4	65.2±3.6[a]	172.2± 8.1[a,b]	210.2± 11.3[a,b]
Serum creatinine(mg/dl)	1.1±0.1	1.7±0.5[a]	5.7±1.1[a,b]	7.3±1.2[a,b]
Creatinine clearance (mL/min)	0.41±0.05	0.3±0.02[a]	0.14± 0.03[a,b]	0.07± 0.02[a,b]
Microalbuminuria (mg/day)	0.41±0.03	10.4±0.7[a]	45.7±3.6[a,b]	76.6± 4.3[a,b]

The results proposed that Artemisinin improved DFC-promote renal damage in Wistar rats by diminishing kidney oxidative injury and reinstatement of kidney PGE2 return to normal levels. DEC prompted toxicity in the liver in the rats model (Table2).

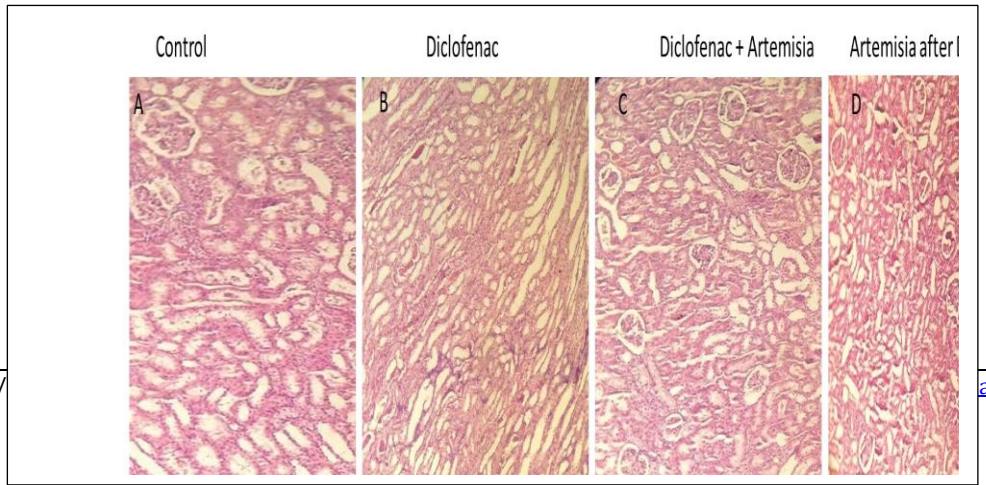
Table 2: Data through the column are stated as mean ± SEM. (*p < .05)is significantly

associated with group 1 (control); #p < .05 is significantly more associated with group 2 (DEC only); ap < .05 is significantly more with group 3 (DEC followed by Artemisinin vs. group 4(Artemisinin + DEF). Diclofenac sodium (DEC) administration increased platelet-lymphocyte ratio (PLR) and neutrophil-lymphocyte ratio (NLR), indicating hepatic toxicity in the rat model.

Groups	**PLAT (%)**	**NEUT (%)**	**LYMPH (%)**	**PLR**	**NLR**
Control(group1)	192.21 ± 1.78	11.19 ± 0.89	90.87 ± 0.75	2.19 ± 0.02	0.12 ± 0.03
DEC Only(group2)	214.68 ± 1.27*	32.23 ± 2.12 *	71.73 ± 2.13 *	3.08 ± 0.05*	0.48 ± 0.03 *
Artemisinin and then DEC(group3)	149.32 ± 3.54*#	14.38 ± 0.84 #	85.35 ± 0.81 #	1.73 ± 0.06* #	0.18 ± 0.02 #
Artemisinin + DEC(group4)	202.86 ± 4.72a	12.04 ± 0.24 #	89.18 ± 2.06 #	2.40 ± 0.10# a	0.13 ± 0.00 #

Histopathological examination :Histopathology showed significant acute tubular necrosis in their kidneys. Plasma creatinine, urea, sodium, chloride, and potassium ion levels were all markedly elevated by DFC treatment. Additionally, renal tissue activities of superoxide dismutase and catalase, and level of malondialdehyde, and hydrogen peroxide were elevated. The increasing was indicates a compensatory response. Furthermore, the groups treated with DFC showed a substantial decrease in renal tissue levels of prostaglandin E2 (PGE2) and reduced glutathione, as well as in the fractional excretion of potassium sodium. However, administering artemisinin considerably lessened the harmful effects of DFC on PGE2 release, creatinine, urea, glucose, and electrolyte plasma levels, and it also greatly reduced oxidative and renal tubular damage.

Figure 1. Histopathologically, DEC made fatty modifications, and eosinophilic casts were distinguished in the renal tubules; those were diminished by oral uptake of Artemisinin after Diclofenac. (A) Control rat: display regular renal construction with healthy glomerulus and renal tubule arrangement. (B) Showed congestion of the renal blood vessels with mononuclear cell infiltration and noticeable dilation of the renal tubules. (C) Showed no harmful impact of DEC on the renal structure and no significant difference between A image and C. (D) Presented a few thrombotic effects of DEC on a few nephrons.



DISCUSSION AND CONCLUSION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most commonly prescribed medications worldwide, including in Thailand, for the treatment of pain and inflammatory conditions such as osteoarthritis [12], [13]. However, it has remarkable adverse properties [14]. The renal toxicity of the effect of Diclofenac was earlier confirmed in varied investigational models using together *in vitro* and *in vivo* examination [15] in a rat model [16] and mice model.

Artemisinin is a selective medical plant used to treat Rheumatoid arthritis [17]. This study aimed to combine Artemisinin and Diclofenac as a new strategy to obtain better results without side effects. This study's histological results corresponded to the biochemical and hematological outcomes. Comparative to the standard control group, there was a significant ($p < .05$) intensification in platelet count in the DFC control group (Table 2), Which agreed with [18] but disagreed with others [19]. However, a significant reduction was documented in groups 3 and 4 ((Table 2).

This set of data arguments diclofenac as a possible stimulator of renal failure and hepatotoxicity increases concern about the ecological influence of DFC consumption despite its medical efficiency. It is also remarkable to the declaration that DFC is associated with a chain of not simple side effects apart from renal and hepatic injury. Some medical plants can reduce the Some medicinal plants may mitigate the adverse effects of DFC. Artemisia plant acts as a protective and therapeutic impact.

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Conflict of Interest Statement:*The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.*