Egypt. J. Chem. **Vol. 64,** No. 4 pp. 2067 - 2074 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Aescin Ameliorates Acute Kidney Injury Induced by Potassium Dichromate in Rat: Involvement of TLR 4/ TNF-α Pathway

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Abstract

Acute kidney injury (AKI) exhibited more than 1 million deaths every year worldwide; inflammation has a vital role in AKI development and considered as a risk factor in its progression. Aescin is a natural compound with anti-inflammatory vasoconstrictor and vasoprotective effects. The current study aimed to assess Aescin's possible renal protective and therapeutic effect on potassium dichromate (PD)-induced AKI in rats. Single injection of PD was causing AKI (15 mg/kg; s.c). Rats were divided randomly into four groups. Group I: Normal control. Group II: Rats injected with PD and served as AKI group. Group III: Rats received a daily injection of Aescin for 2 weeks (3.6 mg/Kg; orally), prior PD injection and group IV after PD injection. Kidney functions, kidney contents of inflammatory and proliferative markers as toll-like receptor4 (TLR4), tumour necrosis factor-alpha (TNF-α), heat shock protein-70 (HSP-70) and insulin growth factor-1 (IGF-1) were estimated. In addition, histopathological examination was performed. Aescin improves kidney functions, alleviated inflammatory and proliferative markers and ameliorated hyaline materials in the Bowman's space and necrosis of proximal convoluted tubules that induced by PD. The present study confirmed the effectiveness of use of Aescin in AKI protection or treatment.

Keywords: Aescin; TNF-α; TLR 4; HSP-70; IGF-1.

1. Introduction

Acute kidney injury (AKI) is diagnostic by a complex pathophysiological process based on serum creatinine level elevation or urine output reduction [1]. It is a complication of heart failure, chronic hypertension, kidney ischemia, surgical procedures or nephrotoxic drugs administration [2]. AKI found in 16% of the world 's population and triggered chronic kidney disease affecting up to 1.2 million died from chronic kidney disease, globally in 2017, with diabetic nephropathy [3] and 25.3 million cardiovascular disease were associated with impaired kidney function [4]. In Egypt, Deaths from Kidney Disease reached 3.98% of total deaths, according to WHO, in 2017.

Renal cells and some immune cells mediate inflammation response and expressed pro-inflammatory cytokines; TNF-α and IL-6 which disrupt the biological function and cellular structure of the renal cells to facilitate kidney injury [5] and promote cell death [6]. Serum TNF-α levels can be useful as an early biomarker for evaluating AKI severity [3]**.** In addition, Toll-like receptors (TLRs) are genes controlling an innate immune response and monocytes, polymorph nuclear leucocytes (PMN) and macrophages activation [7]**.** TLRs were implicated as important mediators in acute and chronic renal failure[8]**.** TLR4 with TNF-α and IL-1β have varied effects in regulating endothelial changes [9]**,** and glomerular filtration rate (GFR) [10].

Heat shock protein (HSP70) is a protein normally expressed in renal tissue [11]**.** HSP70 is recognized as one of the significant biomarker for AKI [12]**.** During infection, the HSP70 level elevated inducing inflammatory signalling pathways, such as NF-κB pathway [13].

Chromium is a heavy metal. Its hexavalent states is used in stainless steel manufacturing, leather tanning,

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Receive Date: 12 January 2021, Revise Date: 20 January 2021, Accept Date: 01 February 2021

DOI: 10.21608/EJCHEM.2021.57553.3237

and wood preservation and can found in drinking water[14]**.** Chromium nephrotoxicity is mainly due to the increased chromium excretion through the kidney[15]. Potassium dichromate (PD)-induced AKI is mediated by inflammatory pathway including the elevation of TNF-α cytokine [16]**.**

Aescin, a pent acyclic triterpene, is a major active component of horse chestnut seeds [17]**.** It has been used after trauma to avoid inflammatory oedema, used as an antioxidant, analgesic, antiseptic, antipyretic, and anti-haemorrhoid agent [18]. Therefore, the present study investigates the protective and therapeutic effect of Aescin against PD-induced AKI in rats. Additionally, our research focused on the inhibition of TLR4/TNF-α pathway to be a potential target to reverse AKI.

2. Materials and Methods

1.1.Animals

Adult male Wister albino rats weighing 120 – 140g purchased from the animal house colony of the National Research Centre (Dokki, Giza, Egypt) and were kept in the animal house under conventional laboratory conditions. Experiments were performed according to National Research Centre Animal Care, Egypt and The Animal Research: Reporting of *in Vivo* Experiments (ARRIVE) guidelines and in compliance with the guiding principles for animal experimentation as enunciated by the US guidelines (NIH publication #85-23, revised in 1985).

1.2.Chemicals and Kits

Potassium dichromate (PD) was obtained from National Research Centre (Dokki, Cairo, Egypt). Aescin was purchased from Sigma–Aldrich (St. Louis, MO, USA). Creatinine and blood urea nitrogen (BUN) were purchased from Bio diagnostic, Egypt. Tumor necrosis factor –alpha (TNF-α), Toll-like receptor 4 (TLR4), heat shock protein70 (HSP70) and insulin growth factor-1 (IGF-1) Elisa kits were obtained from NOVA, Beijing, China.

1.2.Experimental design

AKI was induced by a single injection of PD (15 mg/kg, subcutaneously) [19]**.** Rats were assigned randomly into four groups. Group I: Normal control group injected s.c with saline. Group II: Rats were injected s.c with PD and served as AKI group. Group III: Rats received Aescin (3.6 mg / kg; orally) daily for 2 weeks before PD injection [20]. Group IV: Rats received Aescin (3.6 mg / kg; orally), daily for 2 weeks after PD injection.

1.3.Assessment of kidney functions

Blood samples were taken, 24 h following the last treatment, from the abdominal aorta under light anaesthesia with pentobarbital sodium. Collected blood samples were allowed to stand for 10 min at room temperature then centrifuged at 4 ºC using cooling centrifuge (Laborezentrifugen, 2k15, Sigma, Germany) at 3000 r.p.m for 15 min [21] and used for determination of creatinine and BUN

1.3.Assessment of inflammatory and proliferative mediators

The animals were sacrificed by cervical dislocation, and one kidney from each rat was immediately dissected out, washed with ice-cooled physiological saline and homogenized in 0.15M KCl solution [22] using a tissue homogenizer (MPW−120, Bit-Lab Medical instruments, Poland) to prepare the 20% homogenate. Homogenized tissues were centrifuged at 4000 rpm/min for 5 min at 4ºC using a cooling centrifuge (Laboratory Centrifuge, 2 K15, Sigma Co., Germany) [23]. The supernatant was collected and stored at −80 °C for determination of kidney contents of TNF-α, TLR 4, HSP70 and IGF-1 using commercially available ELISA kits.

1.4.Histopathological examination of kidney

Kidney was immediately removed and washing in saline solution. The kidney was fixed in 10% phosphate buffered formalin. Following an overnight fixation, slices (3–4mm) of kidney tissue were dehydrated in ascending grades of alcohol, cleared in xylene and embedded in paraffin wax (58-60°C). Blocks were made and sectioned of 5 μm thickness with microtome. The tissue sections were stained with haematoxylin and eosin and observed under the light microscope. The slides were observed for histopathological changes and microphotographs were taken using a microscope system (Olympus, Japan).

1.5.Data analysis

All the values are presented as means ± standard error of the means (SE). Comparisons between different groups were carried out using one-way analysis of variance (ANOVA) followed by Tukey´s HSD test for multiple comparisons. Difference was considered significant when $p < 0.05$. Graph Pad prism® software (version 5) was used to carry out these statistical tests.

3.Results

3.1.Effect of Aescin on kidney functions

Serum creatinine and BUN levels were elevated after induction of AKI by PD by 76% and 87%, respectively, as compared with normal control group. Whereas pre-treatment with Aescin

significantly reduced serum creatinine and BUN levels by 32% and 31%, respectively, moreover, post-treatment with Aescin significantly reduced serum creatinine and BUN levels by 28% and 10%, respectively, as compared with PD group (Table 1).

3.2. Effect of Aescin on renal contents of inflammatory mediators

Induction of AKI by PD significantly elevated TNF-α, TLR4 and HSP70 renal contents by 1.5 fold, 1.9 fold and 2.3 fold, as compared with normal control group. While pre-treatment with Aescin significantly reduced renal TNF-α, TLR4 and HSP70 contents by 55%, 60% and 62%, respectively, also, post-treatment with Aescin significantly reduced renal TNF-α, TLR4 and HSP70 contents by 47%, 45% and 41%, respectively, as compared with PD group (Figure 1-3).

3.3. Effect of Aescin on proliferative mediator (insulin growth factor-1; IGF-1)

IGF-1 renal content was elevated after injection of PD by 81%, as compared with normal control group. Whereas pre-treatment with Aescin significantly reduced IGF-1 renal content by 264%, moreover, post-treatment with Aescin significantly reduced its content by 55%, as compared with PD group (Figure 4).

3.4. Results of Histopathological Examination

Photomicrograph of the kidney, in the normal control group, the main architecture of the renal tissue is within normal limit. While in PD group, the renal corpuscle showing hyper cellularity, pyknotic and accumulation of hyaline materials in the Bowman´s space (yellow star), the proximal convoluted tubules showing dilatation, degeneration and necrosis of the epithelial lining cells and hyaline casts were detected in the lumen of other tubules (red star). In Aescin (pre-treatment) group, the renal corpuscles are within normal limit, the proximal convoluted tubules showing dilatation, degeneration. In Aescin (post-treatment) group, the renal corpuscle showing accumulation of less hyaline materials in the Bowman's space (yellow star), the proximal convoluted tubules showing less necrosis of the epithelial lining cells (arrow) (H&E.X 400) (Figure 5).

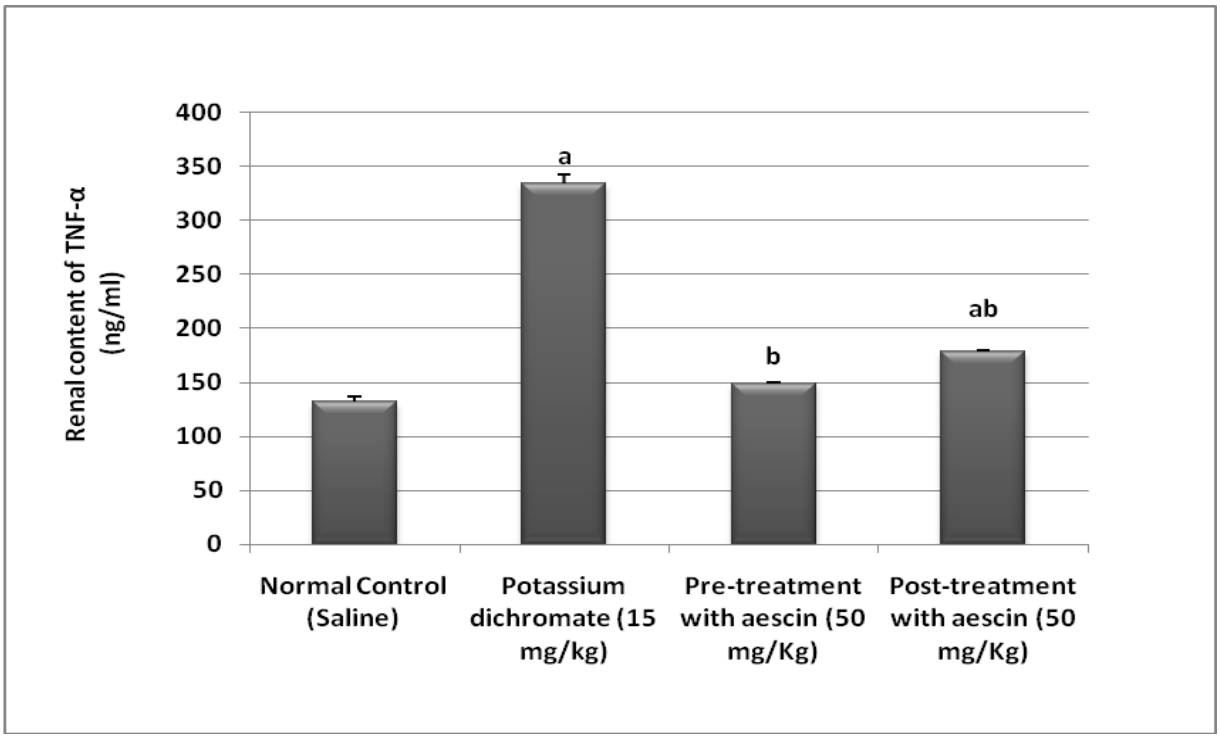

Figure 1: Effect of aescin on renal TNF-α content

Data were expressed as mean ± SE.
Statistical analysis was carried out by one-way ANOVA followed by Tukey´s test.
[a] Significantly different from normal control (Saline) at *P<0.05*.
[b] Significantly different from renal injury group (PD) at *P<0.05*.

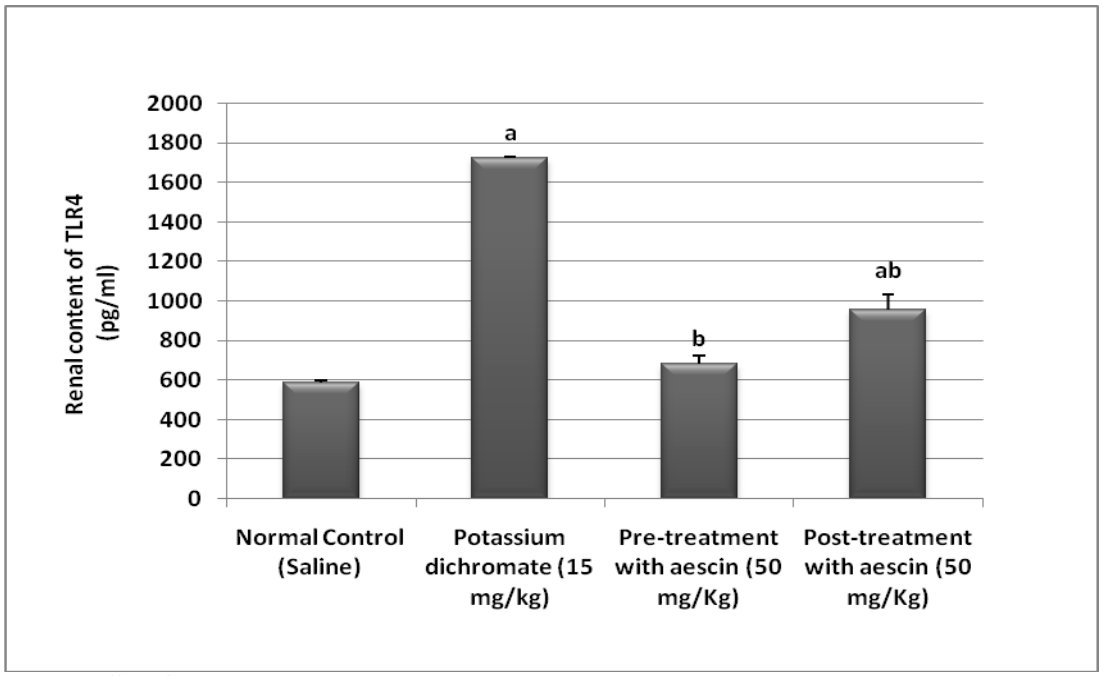

Figure 2: Effect of aescin on renal TLR4 content

Data were expressed as mean ± SE.
Statistical analysis was carried out by one-way ANOVA followed by Tukey´s test.
[a] Significantly different from normal control (Saline) at *P<0.05*.
[b] Significantly different from renal injury group (PD) at *P<0.05*.

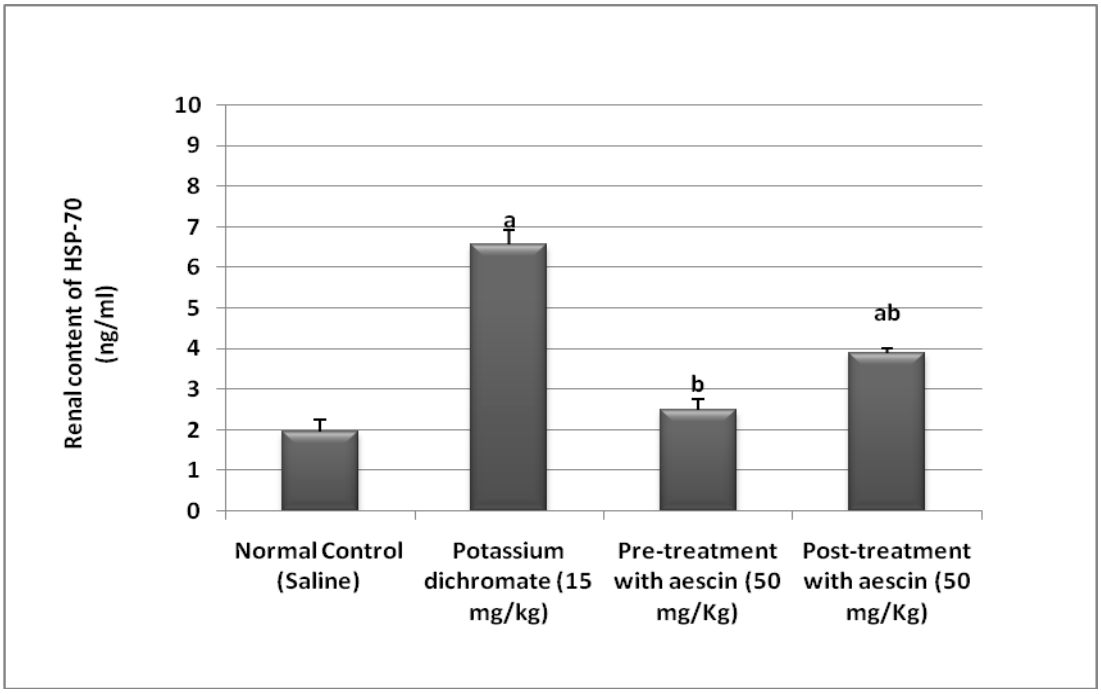

Figure 3: Effect of aescin on renal HSP70 content

Data were expressed as mean ± SE.
Statistical analysis was carried out by one-way ANOVA followed by Tukey´s test.
[a] Significantly different from normal control (Saline) at *P<0.05*.
[b] Significantly different from renal injury group (PD) at *P<0.05*.

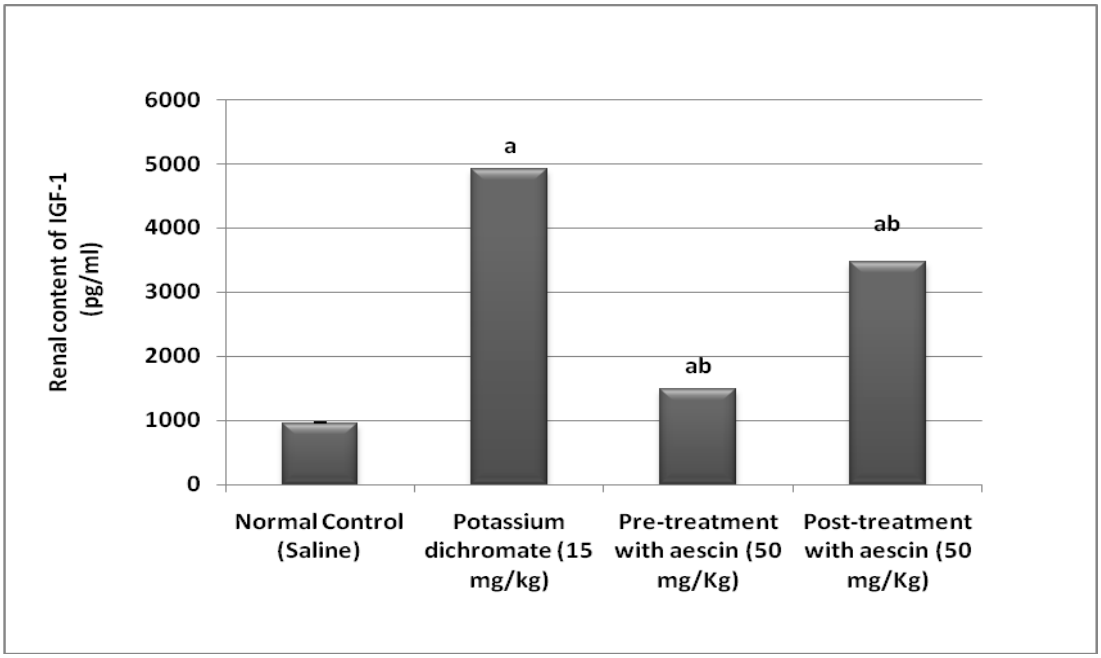

Figure 4: Effect of aescin on renal IGF-1 content

Data were expressed as mean ± SE.
Statistical analysis was carried out by one-way ANOVA followed by Tukey´s test.
[a] Significantly different from normal control (Saline) at $P<0.05$.
[b] Significantly different from renal injury group (PD) at $P<0.05$.

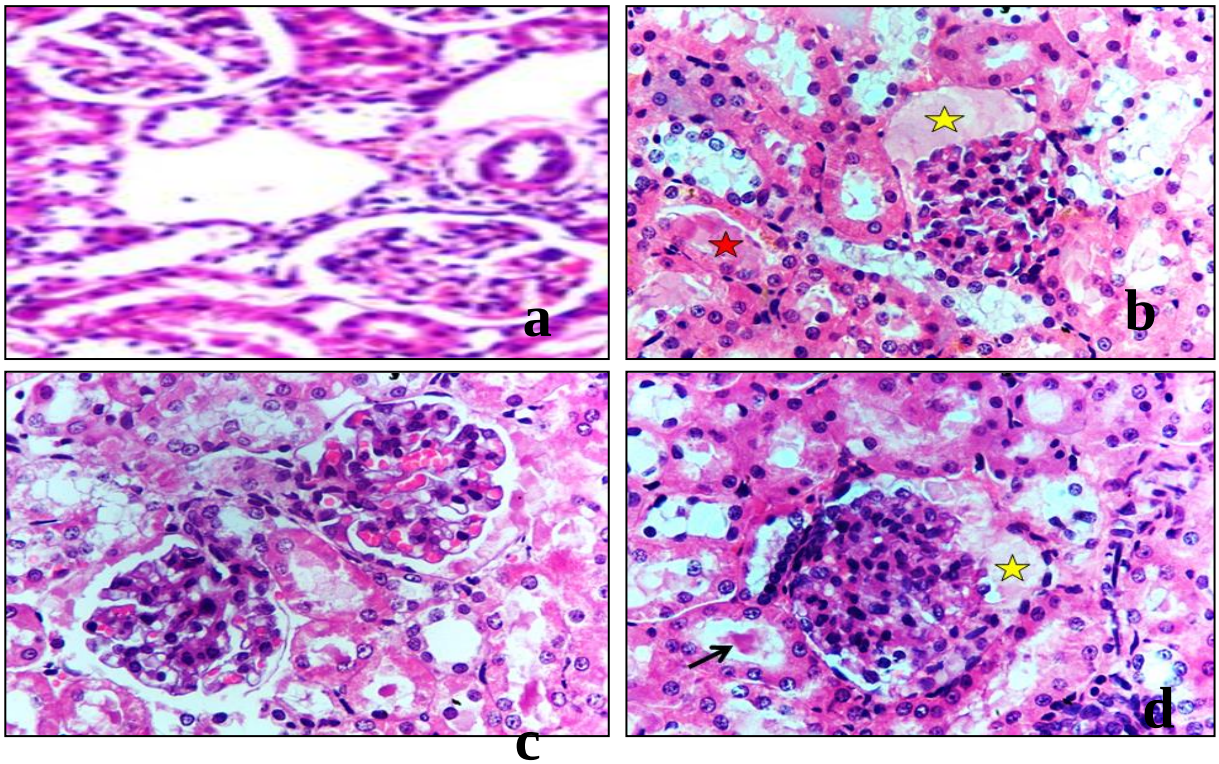

Figure 5: Photomicrograph of the kidney
a) the control group: the main architecture of the renal tissue are within normal limit (H&E.X 400). b) PD group: the renal corpuscle showing hyper cellularity, pyknotic and accumulation of hyaline materials in the Bowman<s space (yellow star), the proximal convoluted tubules showing dilatation, degeneration and necrosis of the epithelial lining cells and hyaline casts were detected in the lumen of other tubules(red star). (H&E.X 400). C) Aescin (pre-treatment): The renal corpuscles are within normal limit, the proximal convoluted tubules showing dilatation, degeneration. (H&E.X 400).d) Aescin (post-treatment): The renal corpuscle showing accumulation of less hyaline materials in the Bowman's space (yellow star), the proximal convoluted tubules showing less necrosis of the epithelial lining cells (arrow). (H&E.X 400).

Table 1: Effect of aescin on serum creatinine and blood urea nitrogen (BUN)

	Normal Control (Saline)	Potassium dichromate (15 mg/kg)	Pre-treatment with aescin (50 mg/Kg)	Post-treatment with aescin (50 mg/Kg)
Creatinine (mg/dl)	1.57±0.06	2.78±0.06 [a]	1.90±0.01 [ab]	1.99±0.01 [ab]
BUN (mg/dl)	2.50±0.07	4.68±0.07 [a]	3.24±0.13 [ab]	4.22±0.06 [ab]

Data were expressed as mean ± SE.
Statistical analysis was carried out by one-way ANOVA followed by Tukey´s test.
[a] Significantly different from normal control (Saline) at *P<0.05*.
[b] Significantly different from renal injury group (PD) at *P<0.05*.

4.Discussion

AKI is recognized as the main cause of death in cases exposed to chrome due to its systemically absorption through kidneys [24] and its accumulation in proximal convoluted tubules for a long time[25]. Injection of PD, in the present study, caused glomerulus dysfunction, and alteration of kidney function serum levels as creatinine and BUN with hyaline materials in the Bowman's space and necrosis of proximal convoluted tubules. PD was used to induce renal injury elevating kidney functions and oxidative kidney damage [26]. Aescin reduced creatinine and BUN serum levels as well as decreased accumulation of hyaline materials in the Bowman's space and necrosis of proximal convoluted tubules, compared to PD group. The anti-inflammatory of Aescin is mainly responsible for kidney functions lowering effect.

Inflammation plays important role in AKI. Inflammation is associated with macrophages and neutrophil mobilization and combined with cytokine expression in damaged renal tissue that in turn mediates the immune response. However, continuous inflammation generates progressive renal disease [27] and fibrosis, kidney has ability to regenerate or recover fully depending on the form of kidney lesion [28]. Many types of renal cells such as tubular cells and mesangial cells provoke inflammation response, and tubular cells also release numerous cytokines to initiate kidney injury. It has been reported that the progression of renal diseases includes pro-inflammatory cytokines; TNF-α and IL-6 [5]. T cell-derived TNF-α treated mice from nephritis and fibrosis [29]. Additionally, TLRs are receptors positioned as a first line of innate response, expressed on leukocyte subsets and regulated innate and adaptive immune defenses by recognizing tissue injury signals. Upon stimulation, tubular epithelial cells express TLR4 that stimulate inflammatory cytokines inducing tubule interstitial injury. Acute renal failure induced by endotoxin is dependent on TLR4 signaling. Also, cisplatin and endotoxin renal toxicity is TLR4-dependent [30]. In the current study, for the first time, TLR4 is responsible for the nephrotoxic effect of PD which produced inflammatory process and elevated the renal TNF-α and TLR4 levels after its injection. Previously PD injection exhibited TNF-α elevation and recruitment of mononuclear histopathologic cells [31], macrophages, neutrophils, and lymphocytic cells [32].

Extracellular HSP is considered as a dangerous signal and expressed in kidney during pathological stress stimulating the immune system through antigen presenting cell (APC) that recognized HSP via TLR. APC activated inflammatory cytokines and stimulated adaptive immune system [33]. The present results revealed that AKI induced by PD elevated TLR4 which in turn facilitated HSP70 recognition by APC, while, Aescin decreased TLR4 and HSP70 renal contents. Aescin has in vitro impact on the inflammatory reaction of periodontal ligament cells [34] as blocked TLR2 expression and reduced lipopolysaccharide -induced pro-inflammatory cytokines interleukin-1β (IL-1β), TNF-α, and IL-6. These results are in agreement with our findings that Aescin has a powerful protective effect by inhibiting the inflammatory response by reducing the TNF-α, TLR4 and HSP70 contents as compared to PD group.
Another important factor expressed in proximal tubules is insulin like growth factor-1 (IGF-1) which is a factor involved in multifunctional cells, such as development, proliferation and regeneration of the kidneys. It exhibits pathogenic role following AKI [35]. AKI induced by PD, in this study, elevated IGF-1 renal content while, Aescin reduced its content in kidney. This result suggests ant proliferative effect of Aescin.

5.Conclusion

As a response to renal injury induced by PD, inflammatory pathway (TLR4/TNF-α) is initiated, kidney dysfunction occurred and hyaline materials in the Bowman's space and necrosis of proximal convoluted tubules were observed. Renal protective and therapeutic activity of Aescin is mainly its diagnosed with its ability to reduce the elevated renal functions and its anti-inflammatory effect via

regulation of TNF-α/TLR4/HSP70 pathway. In addition, Aescin modulated proliferative mediator; IGF-1 and reduced accumulation of hyaline materials in the Bowman's space and necrosis of proximal convoluted tubules.

6.Conflict of interest

The authors declare that they have no conflicts of interest.

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