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ORIGINAL ARTICLE

The study of Protective effects of Chlorogenic acid on Kidney toxicity caused by Arsenic trioxide in mice

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ABSTRACT

The protective effects of chlorogenic acid were studied on the kidney toxicity induced by arsenic trioxide. Inorganic arsenic compounds like arsenic trioxide are carcinogen for human. Studies have shown that chronic exposure to inorganic arsenics may lead to many cancer types, like lung, skin, liver, kidney, and urinary bladder. Chlorogenic acid is a plant chemical compound that is as ester between caffeic acid and quinic acid molecules. Chlorogenic acid is a powerful antioxidant that is in foods. Kidney damage was studied by assessing the changes of blood biochemical parameters, including Blood urea nitrogen (BUN), and creatinine. The serum levels of BUN and creatinine have significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the groups of control and negative control. The serum levels of BUN, and creatinine have significantly decreased ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg) when compared to the positive control group. These results conclude that chlorogenic acid has protected the kidney from arsenic trioxide induced toxicity.

Keywords: *Chlorogenic acid, Arsenic trioxide, Blood urea nitrogen, Creatinine*

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INTRODUCTION

Arsenic is in both organic and inorganic forms in nature and is as a potent threat to the environment, human health, and animals [1,2]. Arsenic can lead to acute and chronic poisoning. The features of severe poisoning with arsenic include digestive disorders, convulsion, diarrhea, shock, bloody urine, vomiting, coma and death. The chronic effects of arsenic have impact on various body systems like respiratory, blood, liver, kidney, nervous, cardiovascular, and endocrine [3]. Exposure to inorganic arsenic occurs through various factors such as drinking water, air, food, fuel and pesticides [4, 5]. The trivalent arsenic compounds like arsenic trioxide, sodium arsenite, and arsenic trichloride are more toxic than the pentavalent arsenic compounds like arsenic pentoxide, arsenic acid, and calcium arsenates [6]. The kidney and liver are as the most sensitive organs for metals because those are contain a lot of the metallothionein binding toxic metals [7]. The kidney is the major source for regulation of water and electrolytes, waste and chemical compounds. Many studies have shown that the risk of kidney cancer in patients with severe renal failure is 5 to 20 higher than healthy people [8]. The effect of arsenic on kidney function have done by assessing serum levels of blood urea nitrogen, creatinine, uric acid [9, 10]. It has been proven that oxidative stress and inflammation play an important role in liver and kidney damages [11]. Free radicals can lead to a wide range of toxic oxidative reactions like peroxidation of membrane

lipids, inhibition of mitochondrial respiratory chain enzymes, DNA damage, enzymes damage, and proteins damage [12]. Antioxidants prevent damages caused by free radicals. Antioxidants can greatly reduce damages caused by free radicals with naturalize those [13]. Chlorogenic acid is a polyphenolic compound that is in various foods like coffee, potato, and apple. Chlorogenic acid is as ester between caffeic acid and quinic acid molecules. Studies have shown that chlorogenic acid has many medicinal properties like anti-bacterial, anti-inflammatory, and anti-cancer [14, 15]. Phenolic compounds have antioxidant properties that play an important role in protection of body cells and organs against oxidative stress [16]. The present study evaluates the protective effects of chlorogenic acid on the kidney toxicity caused by arsenic trioxide in vitro.

MATERIALS AND METHODS

Animals

42 male mice (27 ± 2 g) procured from the animal house of the Mazandaran University of Medical Sciences, Sari, Iran. They were maintained in a controlled environment (12 h light/dark cycles) and temperature (28 ± 2°C). The mice were fed with drinking water and standard diet.

Chemicals

Chlorogenic acid was obtained from Sigma-Aldrich Company (USA). Arsenic trioxide was purchased from Merck Company (Germany).

Treatment groups

Mice were divided in 7 groups and 6 mice in each group. In these experiments, the effects of intraperitoneal administration of different doses of chlorogenic acid on the biochemical parameters of the kidney were investigated. The first group was administered with normal saline (0.9%) (10 mg/kg) as control, the second group was administered with arsenic trioxide (10 mg/kg) as positive control, the third group was administered with chlorogenic acid (100mg/kg) as a negative control, and the fourth to the seventh groups were administered with different doses of chlorogenic acid (5, 10, 50, 100 mg/kg), then after 2 hours the fourth to the seventh groups were administered with arsenic trioxide (10 mg/kg) [17].

Biochemical assay

Blood samples were collected by cardiac puncture with the aid of syringe, transferred into centrifuge tubes, and centrifuged at 2000 rpm for 10 minutes until the serum was partitioned from blood cells. According to usual methods of measuring urea, Diacetyl derived from the hydrolysis of diacetyl monoxime was combined with urea and yellow color was created. Measure absorbance of solutions done at 475 nm with spectrophotometry. The orange color derived from the combined of creatinine and picric acid was measured at 500 nm with spectrophotometry [18].

Statistical analysis

The data were analyzed with SPSS 16 software. Statistical analysis of data was carried out with one way analysis of variance and Tukey test. The differences were considered significant at $p < 0.05$.

RESULTS

In this study, the serum level of BUN has significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the control group (normal saline, 10 mg/kg) (Figure 1).

The serum level of BUN has significantly decreased ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg) when compared to the positive control group (arsenic trioxide, 10 mg/kg) but didn't show significant difference in dose of 5 mg/kg (Figure 2). The serum level of BUN has significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the negative control group (chlorogenic acid, 100 mg/kg) (Figure 3). The serum level of creatinine has significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the control group (normal saline, 10 mg/kg) (Figure 4). The serum level of creatinine has significantly decreased ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg) when compared to the positive control group (arsenic trioxide, 10 mg/kg) but didn't show significant difference in dose of 5 mg/kg (Figure 5). The serum level of creatinine has significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the negative control group (chlorogenic acid, 100 mg/kg) (Figure 6).

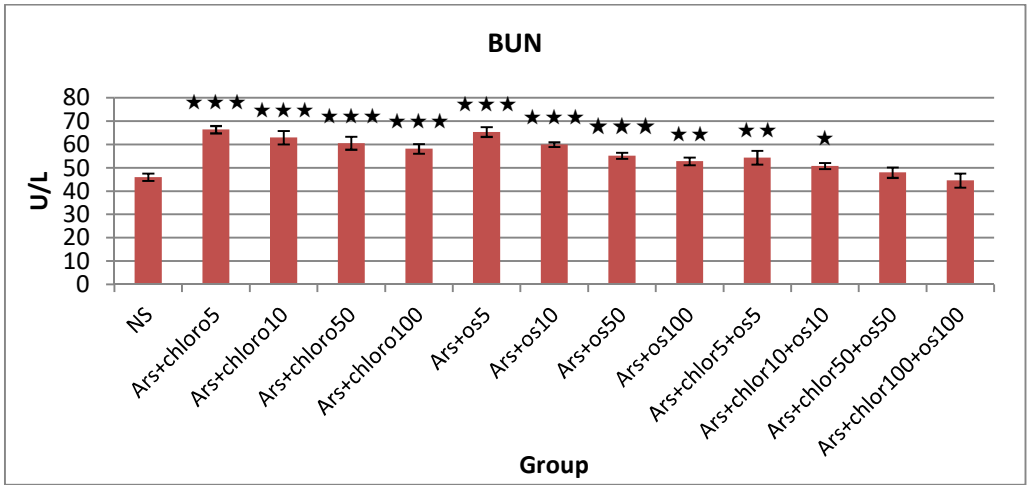

Figure 1: Serum level of BUN has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg).

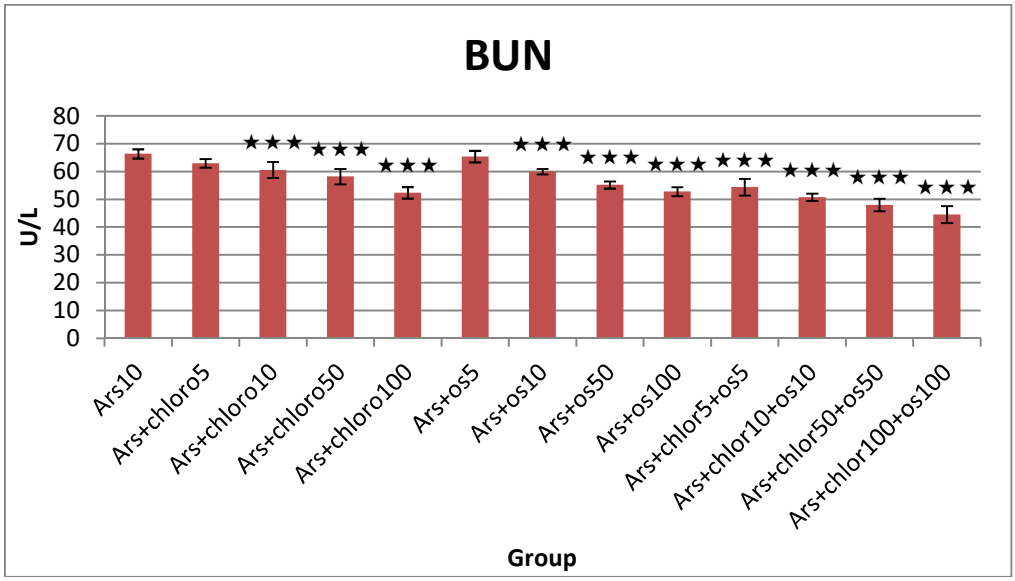

Figure 2: Serum level of BUN has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg).

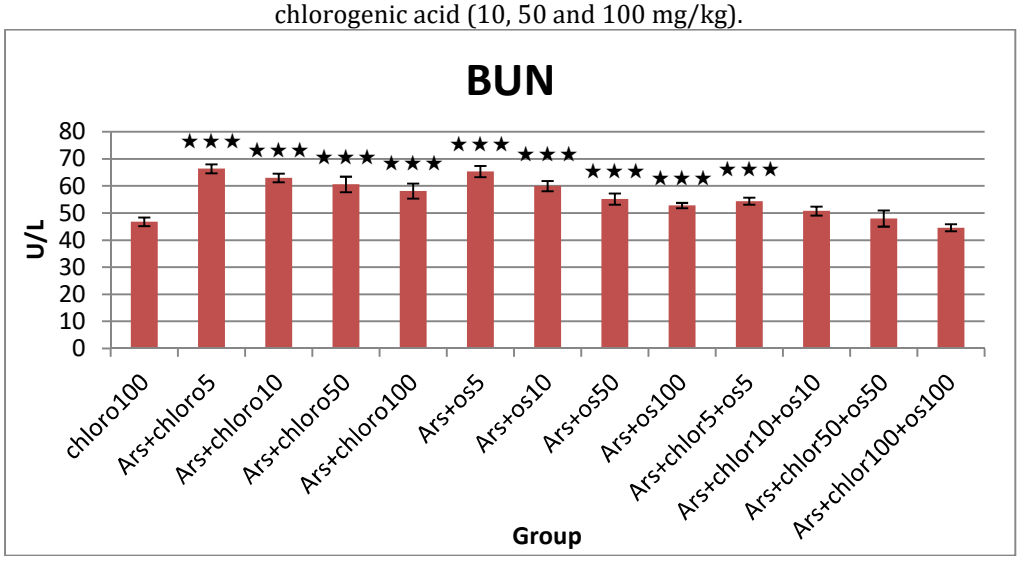

Figure 3: Serum level of BUN has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg).

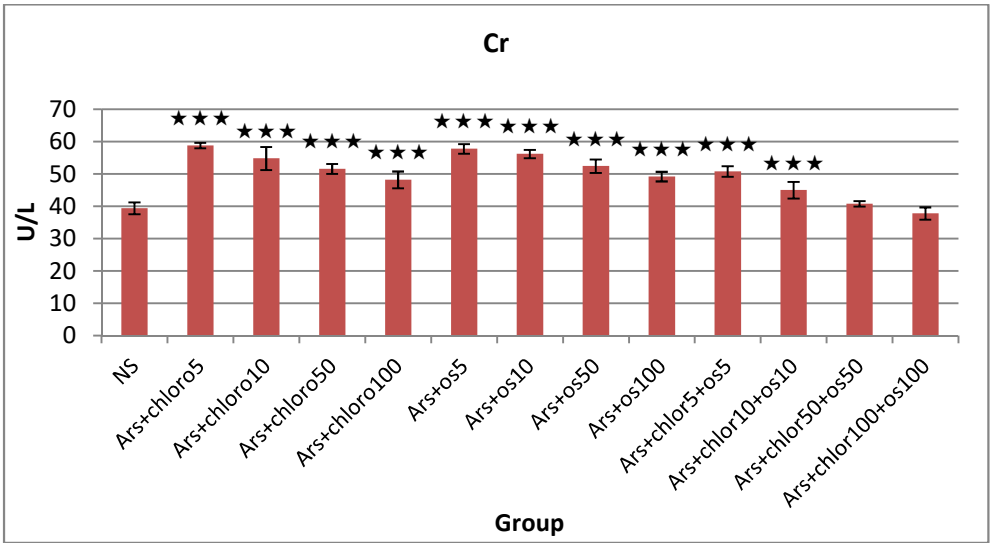

Figure 4: Serum level of creatinine has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg).

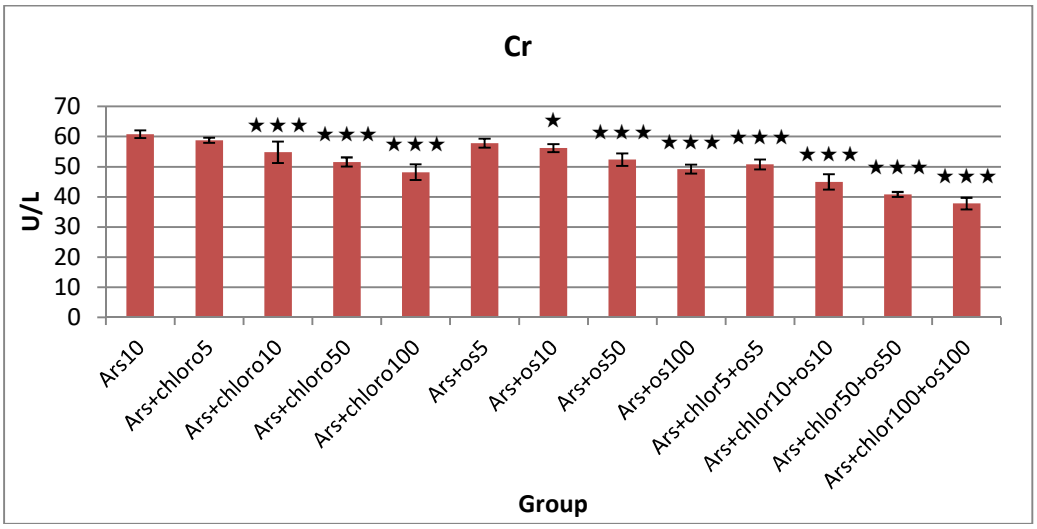

Figure 5: Serum level of creatinine has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg).

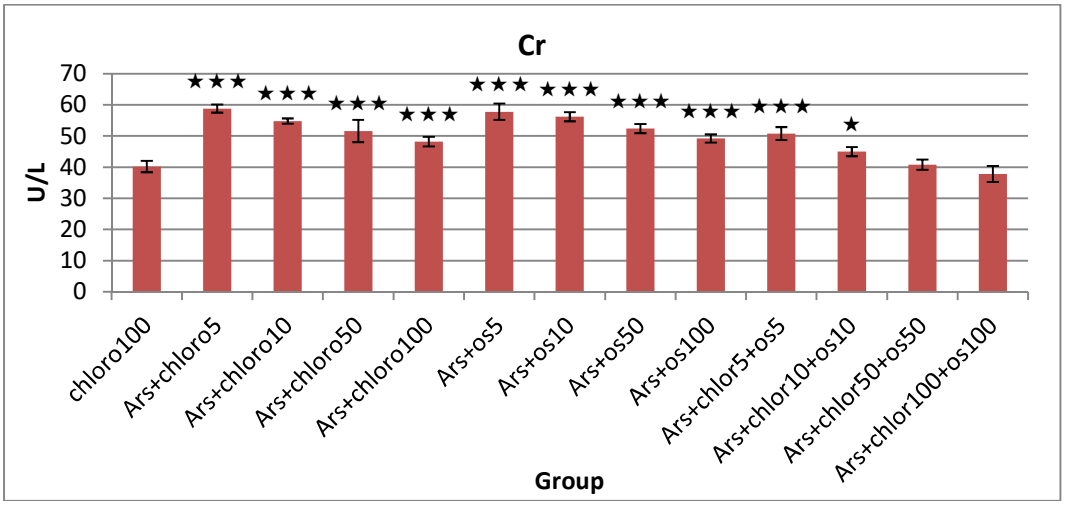

Figure 6: Serum level of creatinine has significantly difference ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg).

DISCUSSION

Arsenic trioxide is used as ingredient compounds like insecticides, herbicides, fungicides, glass, and ceramic [19]. Arsenic trioxide is a carcinogen. Strong epidemiological evidence of cancer is in people exposed to arsenic trioxide, like cancers of lung, bladder, kidney, prostate, liver, breast, skin, and colon [20]. Trivalent arsenic in the liver converted to non-toxic compounds. Arsenic trioxide after ingestion during the methylation reaction as dimethylarsenic acid (50%), methylarsonic acid (14%), pentavalent arsenic (8%) and trivalent arsenic (8%) excreted in urine. The majority of these compounds excreted through the kidneys and a little excreted in feces [21, 22]. Inorganic arsenic with the production of reactive oxygen species can damage to kidneys. Arsenic with accumulation in the kidney tissue cause increase oxidative stress, reduce of kidney function, increase of blood urea nitrogen, lipid peroxidation and reduce glutathione [23]. Blood urea nitrogen and creatinine are waste productions in the blood that removed by the kidney. The serum level of creatinine and blood urea nitrogen are used for assessing kidney function [24,25]. Kidney function was evaluated by determining the serum level of BUN and creatinine. Based on the results of this study, the serum levels of BUN and creatinine have significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the control group (normal saline, 10 mg/kg). Creatinine is a breakdown, production of creatine phosphate in the muscle. Conversion of creatine to creatinine is a non-enzymatic irreversible process. Arsenic causes the release of creatine phosphokinase from muscle cells. This enzyme is responsible the conversion of phosphocreatine to creatine [7]. The kidney is the major site for excretion of arsenic that is as significant place for conversion arsenic pentavalent to arsenic trivalent. Arsenic damages to capillaries, tubules, and glomeruli in the kidney [26]. Arsenic damages to proximal tubular cells that lead to proteinuria and oliguria in the kidney, but sever poisoning with arsenic is caused shock and dehydration that is a real risk for kidney failure [26,27]. The toxic effects of acute exposure to arsenic trioxide are because of its ability for binding to sulfhydryl groups in proteins. It inhibits the production of energy needed to function of tissues and reduce of glutathione, which reduce the detoxification of arsenic [28,29]. In this study, the serum levels of BUN and creatinine have significantly decreased ($p<0.05$) in the groups administered with of chlorogenic acid (10, 50 and 100 mg/kg) when compared to the positive control group (arsenic trioxide, 10 mg/kg). Chlorogenic acid is an antioxidant polyphenolic compounds that have been shown effects in cultured human endothelial cells and ischemia – perfusion injury to the liver in vitro [30,31]. Chlorogenic acid has an important role in the prevention of many diseases related to oxidative stress like cancer, cardiovascular, neurological, and aging [16,31]. Phenolic compounds are in many foods that have beneficial effects on health and are attractive for nutrition specialists. Phenolic compounds after consumption exposed reactions methylation, sulfation, and glucuronidation in small intestine, large intestine, and liver cells [32, 33]. In this study, the serum levels of BUN and creatinine have significantly increased ($p<0.05$) in the groups administered with of chlorogenic acid (5, 10, 50 and 100 mg/kg) when compared to the negative control group (chlorogenic acid, 100 mg/kg). Phenolic compounds combined with free radicals that converted those to non-radical forms. These non-radical forms regulated glomerular filtration rate in kidney and to be maintained the normal serum levels of nitrogenous waste products [7,34]. According to what was said, the antioxidant property of chlorogenic acid could be important in decrease the serum levels of BUN and creatinine where arsenic trioxide plays a great role.

COMPETING INTEREST

The authors have declared that no competing interest exists.

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