Research Article

Nephroprotective Effects of Artichoke Extract against 5-Fluorouracil Induced Nephrotoxicity in Wister Rats: A comparative Study with Telmisartan

Safa Mustafa Najim[1], Mohammad Abdul Amir Ulaiwy[2], Intesar T. Numan[3], Maha N.Hamad[4], Alaa Radhi Khudhair[1]

[1] Department of Pharmacology and Toxicology, [2] Department of Pharmaceutical Chemistry, [4] Department of Pharmacognosy, College of Pharmacy, University of Baghdad, Baghdad, Iraq.

[3] Dean of College of Pharmacy, University of Al-Bian, Baghdad, Iraq.

***Corresponding author's E-mail:** alaa_z520@yahoo.com

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ABSTRACT

The present study was designed to evaluate the nephroprotective effects of methanol extract of Artichoke as a comparative study with telmisartan against 5-FU induced nephrotoxicity in Wister rats. Thirty Wister rats were randomly divided into five groups: I, negative control receiving normal saline (2 ml/kg) orally for 14 successive days; II, negative control receiving DMSO (2 ml/kg) orally for 14successive days; III, positive control receiving normal saline (2ml/kg/day) orally for 14 days, and subsequently received 5-Fluorouracil (5-FU) (150mg in 2ml normal saline per kg body weight)) single dose by intraperitoneal injection on the day 11; IV, receiving telmisartan (10mg/kg/day) for 14 successive days, and subsequently received 5-Fluorouracil (5-FU) (150mg in 2ml normal saline per kg body weight)) single dose by intraperitoneal injection on the day 11; V, receiving Artichoke extract (400mg/kg/day) by oral intubation for 14 days, and subsequently received 5-Fluorouracil (5-FU) (150mg in 2ml normal saline per kg body weight) single dose by intraperitoneal injection on the day 11. Prophylactic treatment of Artichoke extract and telmisartan significantly attenuates the serum creatinine and blood urea nitrogen (BUN) elevation caused by 5-FU-induced nephrotoxicity, also, the histopathological study show the nephroprotective effects of methanol extract of Artichoke and telmisartan against 5-FU induced nephrotoxicity in Wister rats. Results of the present finding suggest that methanol extract of Artichoke and telmisartan may be a useful modulator in mitigating 5-FU induced nephrotoxicity.

Keywords: Artichoke extract, 5-FU, Telmisartan, Nephroprotective.

INTRODUCTION

Kidney disease is frequently one of the complications of malignancy and its treatment. The spectrum of Kidney disease in this setting includes acute renal failure (ARF), chronic renal failure, and tubular disorders. [1]

5-Fluorouracil (5-FU) is still one of a widely used anticancer drug. Since 1957, it has played a crucial role in the treatment of colon cancer and is used for treatment of patients with breast and other cancers, like those of head and neck [2]. Due to the structure of 5-FU, it interferes with nucleoside metabolism and can incorporated into ribonucleic acid (RNA) and deoxyribonucleic acid (DNA), causing cytotoxicity and cell death[3, 4]. When used with radiation therapy, improved local control as survival rates has been reported in different malignancies, as compared to radiotherapy alone [5]. However, 5-FU has indiscriminate mechanism of action affect not only cancer cells, but all rapidly dividing cells in the body[6], so in addition to bone marrow depression, gastrointestinal tract reaction, or even leucopenia and thrombocytopenia[7]. 5-FU has many adverse effects such as cardiotoxicity, nephrotoxicity and hepatotoxicity which lead to restrict its wide clinical usage. 5-FU causes marked organ toxicity with increased oxidative stress and apoptosis [8, 9].

Part of angiotensin receptor blockers has a protective effect on kidney, one of which is telmisartan which is one of the angiotensin receptor blockers (ARBs) also; it acts as a partial agonist of peroxisome proliferator-activated receptor gamma (PPAR-γ) [10]. The biological activity of PPAR-γ is a wider and can involve in the processes of glucolipid metabolism in the body, inflammatory response, immunologic process and also the regulation of cell cycle as well as apoptosis [11]. PPAR-γ has extensive biological effect and is associated with the formation of atherosclerotic plaque and proliferation of vascular smooth muscle, so, PPAR-γ act a role in the progress of glomerulus and renal tubules lesions [12, 13].

Artichoke (Cynara scolymus L.) is one of the oldest medicinal plants of 2000 y history. It belongs to the family of (Asteraceae) [14]. Originally it's from the Mediterranean region and North Africa and then cultivated in the world. Artichoke was used as a food (as a digestive aid) and as a medicine by ancient Egyptians, Greeks, as well as Romans [14]. It grows to a height of about 2 m and gives a large, violet-green flower head. The flower petals as the fleshy flower bottoms were eaten as a vegetable through the world, which has led to its commercial cultivation in variant parts of South and North America (chiefly California) as in Europe [14]. Artichoke is widely distributed in Iraq and located in the outer lines of the fields, humid watery soil and water lines. The plant flourishes in winter and is usually harvested in February and March. Because of the plant durability, it is hardy temperature below

freezing [15]. Cynara scolymus L. is not just a good food, as known to have a pleasant bitter taste, but also an interesting and as widespread herbal medicine [16]. Artichoke leaves contain 2% phenolic acids, mostly 3-caffeoylquinic acid (chlorogenic acid), plus 1.3-di-O-caffeoylquinic acid (cynarin), and caffeic acid; 0.4% bitter sesquiterpene lactones of which 47-83% is cynaropicrin; 0.11.0% flavonoids including the glycosides luteolin-7-β-rutinoside (scolymoside), luteolin-7-β-Dglucoside and luteolin-4-β-D-glucoside; phytosterols (taraxasterol); sugars; inulin; enzymes; and also a volatile oil consisting mostly of the sesquiterpenes β-selinene and caryophyllene [17]. Artichoke leaf extract have been used as a hepatoprotective [18], antimicrobial [19] and also as a cholesterol reducer [20]. Also it found to attenuate the production of reactive oxygen species, as well as the oxidation of low-density lipoproteins [21], lipid peroxidation [18], and protein oxidation and increase the activity of glutathione peroxidase [22]. The present study was designed to evaluate the protective effects of methanol extract of Artichoke and telmisartan against 5-FU induced Nephrotoxicity in Wister rats.

MATERIALS AND METHODS

Chemicals and drugs

5-fluorouracil obtained from Flakon, Turky, Telmisartan obtained from Boehringer Ingelheim, Germany and (DMSO) from Sigma, USA.

Plant material

The plant collected from the garden of the medicinal plants at Department of Pharmacognosy and medicinal plants/college of pharmacy/University of Baghdad. The leaves of the plant dried in the shade at room temperature, and then crashed into a fine powder using an electrical mill. Extraction of the plant: 750 g of the powdered leaves extracted by soxhlet, using 3000 ml of each of methanol as solvent, the extract were filtered and evaporated until dryness under reduced pressure using rotary evaporator, and then the collected amount weighted. Preparation of extracts for injection: A known weights from the dried methanol artichoke extracts was dissolved in (DSMO) to get a concentration of 40 mg/ml.

Animals and treatment

Thirty Wister albino rats weighing 180-250 gm. were brought from the animal house of the College of Pharmacy/University of Baghdad. The animals were maintained on normal conditions of temperature, humidity and light/dark cycle. They were fed standard rodent pellet diet and they have free access to water. The local Research Ethics Committee in College of Pharmacy, University of Baghdad, approved the research protocol. The animals used in this study were classified into five groups six rat of each group as follow: Group I; received single oral daily dose of distilled water (2 ml/kg) for 14 successive days given by oral gavage. Group II; received single oral daily dose of DMSO (2ml/kg body weight/day) orally for 14 days. Group III; first received normal saline (2ml/kg b.w./day) orally for 14 days, and subsequently received 5-FU (150mg in 2ml normal saline per kg b.w.) single dose by intraperitoneal injection on the day 11. Group IV; received oral dose of telmisartan (10mg/kg/day) given daily by oral gavage for 14 successive days, and subsequently received 5-FU (150mg in 2ml normal saline per kg b.w.) single dose by intraperitoneal injection on day 11. Group V; received oral dose of Artichoke extract (400mg /kg/day) given daily by oral gavage for 14 days, and subsequently received 5-FU (150mg in 2ml normal saline per kg b.w.) single dose by intraperitoneal injection on day 11. All the animals were sacrificed under diethyl ether anesthesia 24 hours later, blood sample were collected from each rat withdrawn from carotid artery at the neck in to labeled centrifuging tubes and allowed to clot for 20 min at room temperature.

Biochemical assessment

The serum was separated by centrifugation at 3000 rpm for 20 min and stored into eppendorff tubes at–20 °C to be used for determination and assessment of biochemical parameters: Rat Serum creatinine and blood urea nitrogen (BUN).

Renal histological analysis

The kidneys from the rats of each group was removed and embedded in paraffin to prepare 4-mm tissue slices. The tissue slices were stained with periodic acid-Schiff (PAS) for histological evaluation.

Statistical Analysis

Data were expressed as mean ± standard deviation (SD). The Statistical significance of the differences between various groups was determined by student t-test. Differences were considered statically significant for p-value< 0.05.

RESULTS

5-FU (Group III) significantly ($P<0.05$) increases serum parameters of creatinine (Fig. 1) and blood urea nitrogen (BUN) (Fig. 2) with respect to Group I and Group II. Administration of telmisartan in association with 5-FU at a doses of 10mg/kg body weight (Group IV) significantly ($P<0.05$) decreases the elevation of serum creatinine (Fig. 1) and significantly ($P<0.05$) decreases the elevation of blood urea nitrogen (BUN) (Fig. 2) with respect to Group III, also administration of Artichoke extract in association with 5-FU at a doses of 400mg/kg body weight (Group V) significantly ($P<0.05$) decreases the elevation of serum creatinine (Fig. 1) and significantly ($P<0.05$) decreases the elevation of blood urea nitrogen (BUN) (Fig. 2) with respect to Group III.

Also Group IV and V significantly different ($P<0.05$) in serum creatinine and blood urea nitrogen (BUN) with respect to Group I and II respectively as shown in Fig.1 and 2.

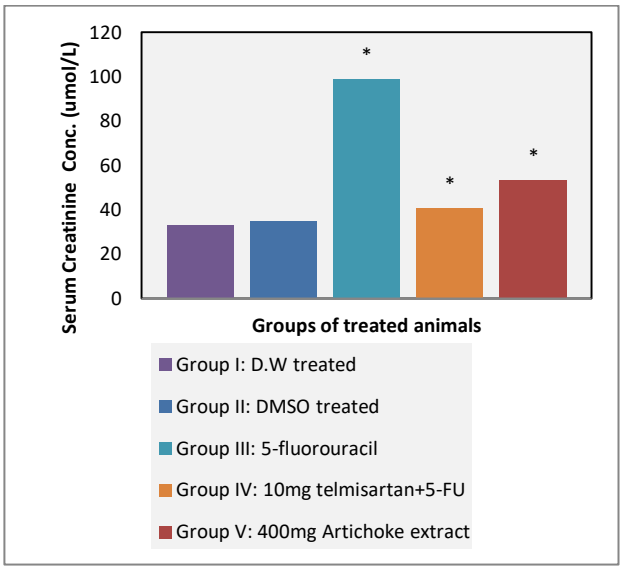

Figure 1: The effects of telmisartan (10mg) and Artichoke extract (400mg) on 5-FU induced nephrotoxicity on serum creatinine.

Data are expressed as Mean±SD, n =6, *p<0.05.

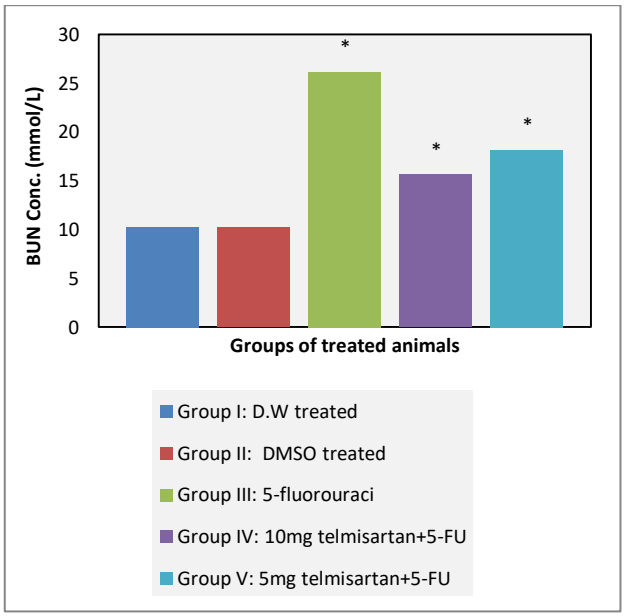

Figure 2: The effects of telmisartan (10mg) and Artichoke extract (400mg) on 5-FU induced nephrotoxicity on BUN.

Data are expressed as Mean±SD, n =6, *p<0.05.

Histopathological changes of the kidney of each group

The Histopathology of the kidney in rats of group I and group II was Normal glomeruli without inflammatory cell infiltration and the renal tubules in rats of group III were obvious kidney focal necrosis with inflammatory cell infiltration. The glomerulus and renal tubules in rats of group IV and group V were normal glomeruli without inflammatory cell infiltration (Figure 3).

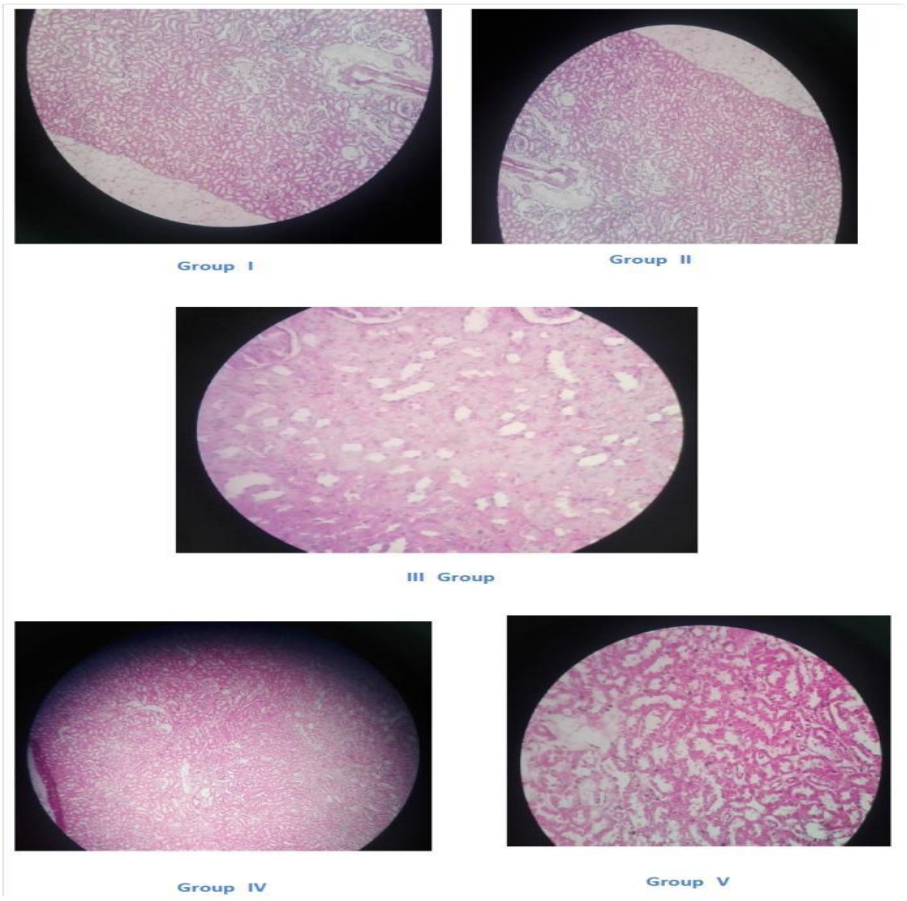

Figure 3: Histopathology of kidney in each group.

DISCUSSION

5-Fluorouracil (5-FU) a potent antineoplastic agent mainly used for the management of various malignancies [23]. 5-FU was found to produce a significant kidney injury biochemically manifested through a significant increase in serum urea, creatinine, uric acid, cortisol and potassium and also by a significant decrease in the sodium and magnesium. Additionally, there was a significant increase in malondialdehyde and a significant reduction in glutathione concentrations in the renal tissues after treatment with 5-FU. These results are agreed with previous studies that reported by investigators that 5-FU-induced nephrotoxicity in normal rats [24].

The mechanism of 5-FU induced renal toxicity is possibly the induction of oxidative stress; activation of apoptotic pathway through the up regulation of p53, bax, caspase-3 and the down regulation of Bcl-2 [23].

Other histomorphological and biochemical studies indicate a much direct drug-mediated cytotoxic action [24].

The present study confirms the nephrotoxicity of 5-FU, as evidenced by the significantly ($P<0.05$) increases in serum creatinine and blood urea nitrogen (BUN).

Telmisartan, belonging to ARB drugs, which control blood pressure by inhibiting renin-angiotensin-aldosterone system, which is used in the treatment of hypertension [11]. The structure of telmisartan was found to have differences with other ARB drugs, that it has the activity of PPAR-γ agonist [25].

The PPAR-γ was reported to inhibit glomerular sclerosis, renal interstitial inflammatory cell infiltration and fibrosis by lowering the genes expression in the glomerular, such as PAI, TGF and Type IV collagen, so relieving renal lesion[26].

The present study shown that telmisartan (10mg/kg/day) decreases the 5-FU-induced elevation in serum creatinine and blood urea nitrogen (BUN) in rats. And according to the results of the present study, the activity of telmisartan may not attributed to the Ag II receptor blockade only, and other mechanisms may be involved including PPAR-γ agonist activity. Further studies are highly suggested to compare the effects of different ARB analogues as in this model.

Artichoke is a potentially a good source of antioxidant activity because it contains a large amounts of caffeic acids [27, 28]. Caffeic acid derivatives are the most phenolic compounds in artichoke heads, and with a wide range of caffeoylquinic acid derivatives as (cynarin) [29] with chlorogenic acid (5-Ocaffeoylquinicacid) as the main important of these derivatives [30]. Other phenolics constituents such as the flavonoids apigenin and luteolin (both glucosides and rutinosides) [31] as a different cyanidin caffeoylglucoside derivatives [32] also have been identified.

The other effects of artichoke extracts have also been investigated for activity against oxidative stress through studies using human leucocytes [33]. The extracts demonstrated a concentration-dependent attenuation of oxidative stress induced by many agents, such as hydrogen peroxide, who generates reactive oxygen species. The constituents; cynarin, caffeic acid, chlorogenic acid and luteolin also showed concentration-dependent oxidative stress attenuation activity [33]. In addition, the artichoke extracts has a marked protective effects against oxidative stress induced through the inflammatory mediators and also by oxidize-LDL in a cultured endothelial cells and monocytes [34]. In vivo, administration of an edible artichoke to the rats has shown to raise the level of glutathione peroxidase activity in the erythrocyte and reduced the level of 2-Aminoadipic semialdehyde (a protein oxidation biomarker) [35]. Many studies were suggested that flavonoids exhibit a biological activity, including anti allergenic, antiviral, anti-inflammatory, vasodilation effects. These pharmacological actions are linked to the antioxidant properties of flavonoids. Flavonoids could express these properties by: (1) decreasing the ROS formation by inhibiting some enzymes or chelating trace elements involved in the free radical production, (2) scavenging free radical species and mainly the ROS, and/or (3) up-regulation or protecting the antioxidant defense [34].

The present study was shown that the artichoke extracts (400mg/kg/day) attenuates 5-FU-induced elevation in serum creatinine and blood urea nitrogen (BUN) in rats.

CONCLUSION

Our results suggest that telmisartan and methanol extracts of artichoke have protective effects against 5-FU-induced nephrotoxicity in albino rats. However, before a conclusive statement can be made about the potential use of telmisartan or artichoke extracts as an adjunct to 5-FU therapy, there is a need for further long-term chronic studies.

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