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PROTECTIVE EFFECT OF SOME RENIN INHIBITORS IN ACUTE NEPHROTOXICITY INDUCED BY SOME ANTI-CARCINOGENIC DRUGS IN RATS

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ABSTRACT

Investigation was carried out to study protective effect of some renin inhibitors in acute nephrotoxicity on forty male Sprague Dawely rats weighting 200g to 250g which divided into four equal groups each group included 10 rats GroupI (Control group): was fed on normal ration for one month. While GroupII (cisplatin group) was injected i.p. by 7.5 mg\kg B.W of cisplatin for one month. GroupIII (captopril group) was injected i.p. by 60 mg\kgB.W of captopril for one month.GroupIV (captopril plus cisplatin group) there is injection of cisplatin (7.5mg/kg b .wt) i.p and within one hour it is proceeded by i.p injection of captopril (60 mg/kg b. wt) daily for one month. At the end of experiment the obtained results revealed that, administration of cisplatin and captopril caused a highly significant decrease in serum and kidney MDA ,serum creatinine concentration , serum blood urea nitrogen concentration, serum angiotensin II concentration and serum aldosterone level. whole blood and kidney p53 concentration compared to cisplatin treated rats .Also there was highly significant increase in whole blood GSH concentration, serum Glutathione peroxidase, serum catalase activity, serum superoxide dismutase activity and serum renin concentration compared to cisplatin treated group. Administration of cisplatin only revealed in increase in serum and kidney MDA ,serum creatinine concentration , serum blood urea nitrogen concentration, serum angiotensin II concentration serum aldosterone level, whole blood and kidney p53 concentration as compared to control group . There was a highly significant decrease in whole blood GSH concentration, serum Glutathione peroxidase, serum catalase activity, serum superoxide dismutase activity and serum renin concentration compared with control group. Administration of captopril only result in decrease in serum and kidney MDA ,serum creatinine concentration , serum blood urea nitrogen concentration, serum angiotensin II concentration serum aldosterone concentration, whole blood and kidney p53 concentration compared to control group also there was highly significant increase in whole blood GSH concentration, serum Glutathione peroxidase, serum catalase activity, serum superoxide dismutase activity and serum renin concentration when compared to control group. These results were supported by histopathological examination which revealed some alterations represented by that the tubule was dilated and shrinked or atrophied , the tubular cells was removed and lost and there is asignificant destruction of glomerular with penetration of leuococyte and intratubular bleeding. While administration of cisplatin and captopril result in regenerating glomeruli and tubules of kidney tissues produce by cisplatin administration.

INTRODUCTION

One of the features of Cislplatin is antitumor drug,so it isneeded for curing of several types of cancers **(Lebwohl and Canetta, 1998 and Alderden *et al.*, 2006)**. It is reported that several enzymes including catalase, superoxide dismutase, glutathione peroxidaseis lowered also there is lowering in the concentration of reduced glutathione. On the other hand, there is amarkedly increasing in nitric oxide and malondialdehyde therefore, cisplatin has the ability to enhance the concentration of blood urea nitrogen and with adepletion of glomerular filtration rate **(Cetin *et al.*, 2006)**. **Mai *et al.*, (1983)** indicated that

renin has both enzymatic and hormonal property, acute renal failure occurs through priciptation of cisplatin in the left and right kidneys which happens due to conversion of angiotensinogen into angiotensin I in the prescence of renin this accompanied by formation of angiotensin II which in turn has the ability to secrete aldosterone hormone **(Okui *et al.*, 2012)**.

Both of angiotensin converting enzyme and angiotensin II are elevated markedly by cisplatin in beagle dogs therefore, endothelial damage occurs due to high concentration of angiotensin II, **(Cubeddu *et al.,* 1990and Marvaala *et al.,* 2001)**. **Price *et al.,* (2004)**, generally, kidney failure and degeneration of tissue is mainly due to deposition and accumulation of p53 in kidney especially the outer medulla by cisplatin **(Wei *et al.,* 2007)**.

Due to involvement of p53 in renal failure induced by cisplatin so the kidneys protection occurs through suppression of p53 **(Gudkov and Komarova, 2005).**

Hypetension and left sided congestive heart failure are medicated by captopril which it is one of angiotensin converting enzyme inhibitor (**Akif *et al.,* 2010).**

Schoneich *et al.,* (1990) proved that oxidation reactions are prevented by captopril due to its role as antioxidant and free radical removal.

In renal tissue, malondialdhyde levels are declined by Captopril **(Mansour *et al.,* 1999)**. Captopril intake suppress the elevation of both blood urea nitrogen and creatinine in the blood **(Krishan *et al.*, 1998)**. Renin concentration is increased due to stoppage of renin angiotensin system by captopril therapy **(Azizi *et al.*, 2004)**.

Morrissey et al., (1996) captopril inhibit proliferating cell nuclear antigen by suppressing the p53 gene expression.

The purpose of this study is aimed to find out the role of captopril in prevention of renal toxicity caused by cisplatin so as to lessen the harmful effect of aldosterone, angiotensinII, and other lipid peroxides.

MATERIAL AND METHOD

Experimental design:

Animals grouping:

Inorder to establish the aim of the work of this experiment forty male Sprague Dawely rats weighting(200g to 250g) were divided into four equal groups (each of 10 rats). GroupI (Control group): was supplied with normal control diet according to **NRC, (1995)** for one month. While GroupII (cisplatin group) was injected i.p. by 7.5 mg\kgB.W of cisplatin for one month.GroupIII (captopril group) was injected i.p. by 60 mg\kgB.W of captopril for one month.GroupIV (captopril plus cisplatin group) there is injection of cisplatin (7.5mg/kg b .wt) i.p and within one hour it is proceeded by i.p injection of captopril (60 mg/kg b. wt) daily for one month. Administration of 60mg/kg B.W of captopril i.p. according to **Mansour *et al.*, (1999).** Also cisplatin is administrated i.p. 7.5 mg/kgB.W according to **Uehara *et al.*, (2005); Mansour *et al.*, (2006)** .At the end of experiment, blood samples were collected from the heart of the rats. Thiopental sodium was used as anaesthetic agent for rats by adose 50 mg/kgB.W which was dissolved in 5ml distilled water and administrated intraperitoneally in rats according to the method of **Singh and Boyd, (1966).** Blood samples was collected for determination of reduced glutathione concentration in whole blood **(Beutler et al., 1963)**,serum Glutathione Peroxidase **(Pagliam and Valentine, 1967) ,** serum Catalase activity**(Aebi, 1984),** serum superoxide

dismutase activity**(Nishikimi et al., 1972),** Serum Malondialdehyde **(Draper and Hadley, 1990)**, Serum creatinine concentration**(Murry and Kaplan ,1984)**, serum blood urea nitrogen concentration **(Kaplan, 1984)** , Serum renin concentration was determined by ELIZA **(Müller and luft, 2006)**, serum angiotensin II concentration was determined by ELIZA **(Porstmann and Kiessig , 1992)** serum aldosterone concentration was determined by ELIZA **(Thomas, 2005)**,whole blood and kidney p53 gene was determined by semi quantitative real time PCR **(Miyajima *et al* ., 2001).** At the end of experiment rats were dissected to obtain kidney,wich then divided longitudinally into two equal parts . The First part of the kidney was kept in phosphate buffer saline and used for determination of kidney Malondialdehyde **(Yoshioka *et al*., 1982**). The second part was kept in 20% formalin for histopathology examination using Hematoxylin and Eosin **(Woods and Ellis, 1994).**

Statistical analyses were performed according to **Steel and Torrie, (1960).**

Table (1): Effect of captopril and cisplatin injection on whole blood and serum biochemical parameters and enzyme activities of rats. (Mean ±S.E) n=10

Groups	Reduced glutathione (mg/dl)	Glutathione peroxidase (mu/ml)	Catalase activity (U/L)	Superoxide Dismutase activity (U/ml)	MDA (nmol/L)	Kidney MDA (nmol/gram tissue)
Group I	54.85 ± 0.82^{b}	1424.43 ± 8.2^{b}	3.26 ± 0.08^{b}	820 ± 2.5^{b}	0.98 ± 0.03^{b}	2.12 ± 0.06^{c}
Group II	23.99 ± 0.78^{d}	330.61 ± 3.89^{d}	0.711 ± 0.02^{d}	448.7 ± 1.8^{d}	4.87 ± 0.08^{a}	10.74 ± 0.20^{a}
Group III	66.01 ± 0.99^{a}	1610.95 ± 4.84^{a}	4.06 ± 0.09^{a}	942 ± 4.5^{a}	0.68 ± 0.01^{b}	1.33 ± 0.04^{d}
Group IV	37.8 ± 0.97^{c}	844.65 ± 2.3^{c}	1.42 ± 0.07^{c}	597 ± 5.03^{c}	2.39 ± 0.07^{c}	6.19 ± 0.10^{b}

- Means carries the same superscript letter are considered non significant,while the means carries the different superscript letter are considered significant.

Table (2): Effect of captopril and cisplatin injection Serum creatinine,urea,angiotensin and aldosterone level of rats. (Mean ±S.E) n=10

Groups	creatinine (mol/L)	blood urea nitrogen (mg/dl)	renin concentration (pg/mL)	angiotensin II concentration (ng/ml)	aldosterone concentration (pg/mL)
Group I	0.67 ± 0.04^{c}	25 ± 0.93^{c}	27.08 ± 0.30^{b}	476.5 ± 3.5^{c}	140 ± 0.85^{d}
Group II	3.17 ± 0.09^{a}	71 ± 0.80^{a}	17.57 ± 1.32^{d}	548.8 ± 3.8^{a}	574 ± 10^{a}
Group III	0.65 ± 0.03^{c}	25 ± 0.85^{c}	32.7 ± 0.64^{a}	427.2 ± 2.9^{d}	106 ± 1.3^{b}
Group IV	2.2 ± 0.08^{b}	55 ± 0.81^{b}	20.5 ± 0.36^{c}	513 ± 2.9^{b}	316 ± 13.8^{c}

Table (3): Effect of captopril and cisplatin injection on whole blood and kidney p53

whole blood p53	kidney p53
0.004 ± 0.001^{a}	0.01 ± 0.001^{a}
0.042 ± 0.0036^{b}	0.1 ± 0.01^{b}
0.001 ± 0.0004^{d}	0.005 ± 0.0004^{d}
0.014 ± 0.002^{c}	0.04 ± 0.003^{c}

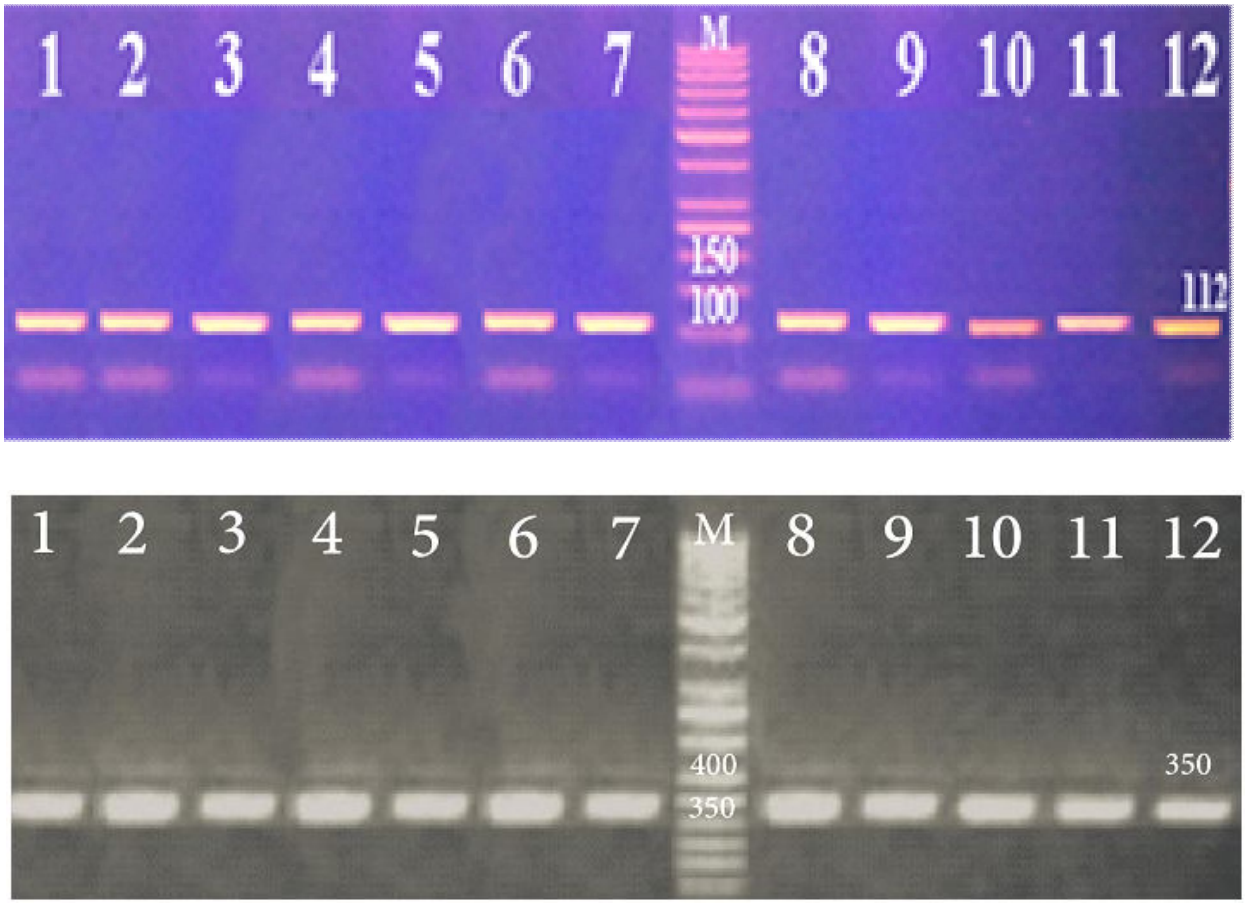

Fig.(1): Semiquantitative RT-PCR of blood tumor protein p53 against β actin as housekeeping gene, where the amplified segement of blood tumor protein p53 gene expression was at 112bp, while the amplified segment of β actin gene expression was at 350 bp against DNA ladder (M) ranged from 50 bp to 1500 bp. Lan (1, 2&3) represented Group I. Lane (4, 5, 6) represented Group II. Lane (7, 8&9) represented Group III. Lane (10, 11, and 12) represented Group IV.

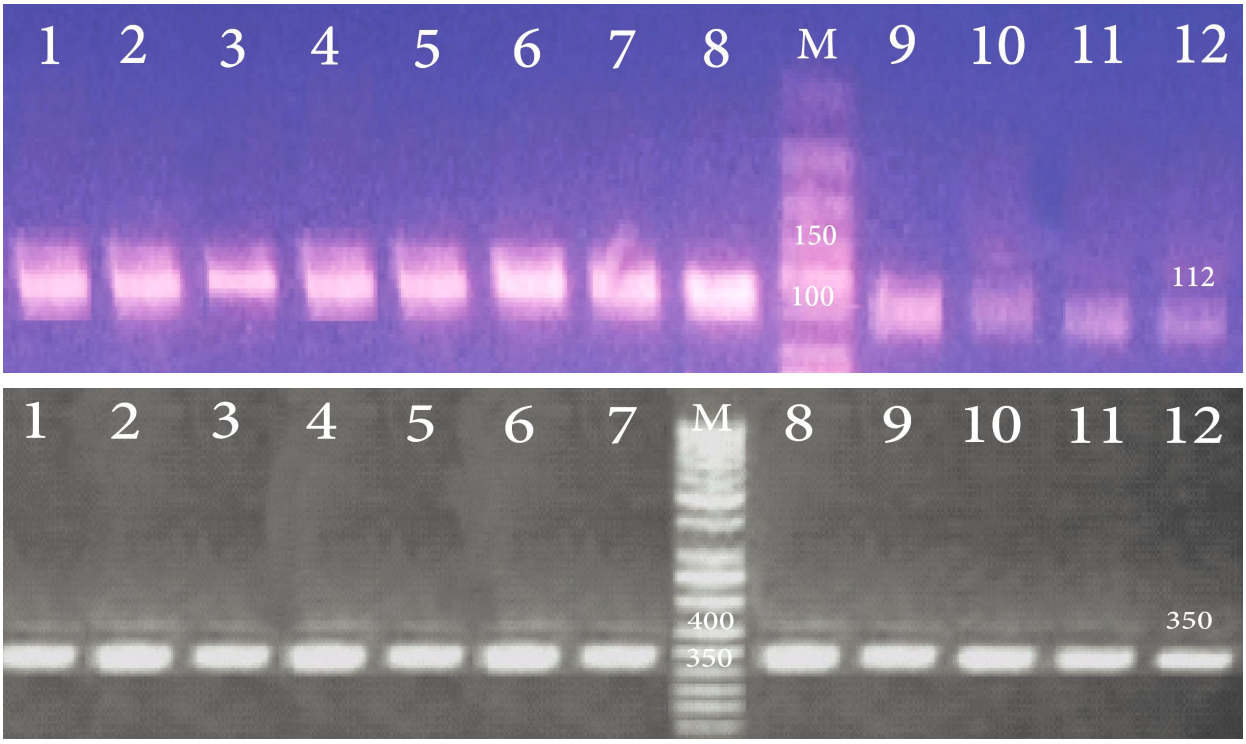

Fig. (2): Semi-quantitative RT-PCR of kidney tumor protein p53 against kidney β actin as housekeeping gene, where the amplified segement of kidney tumor protein p53 gene expression was at 112bp, while the amplified segment of kidney β actin gene expression was at 350 bp against DNA ladder (M) ranged from 50 bp to 1500 bp. Lan (1, 2&3) represented Group I. Lane (4, 5, 6) represented Group II. Lane (7, 8&9) represented Group III. Lane (10, 11, 12) represented Group IV.

Histopathological examination of kidney

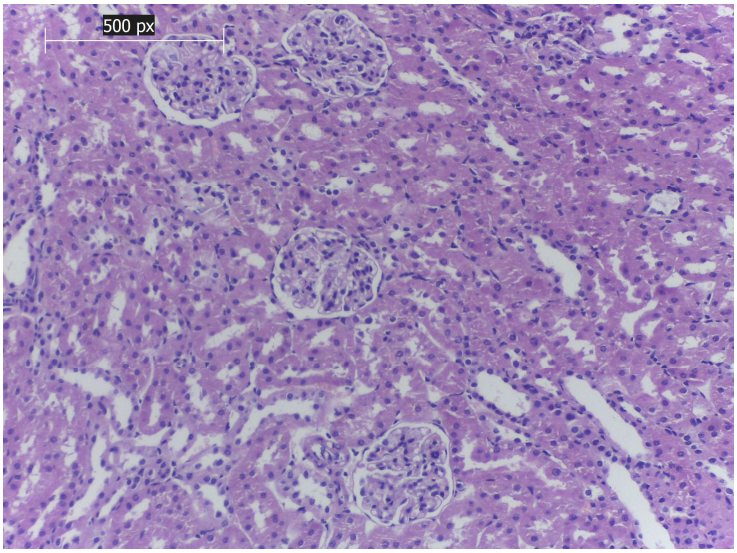

Fig.(3): Control group, showing normal structure of the glomerulus, Bowman's capsule, proximal tubules and distal tubules. (10x, H&E).

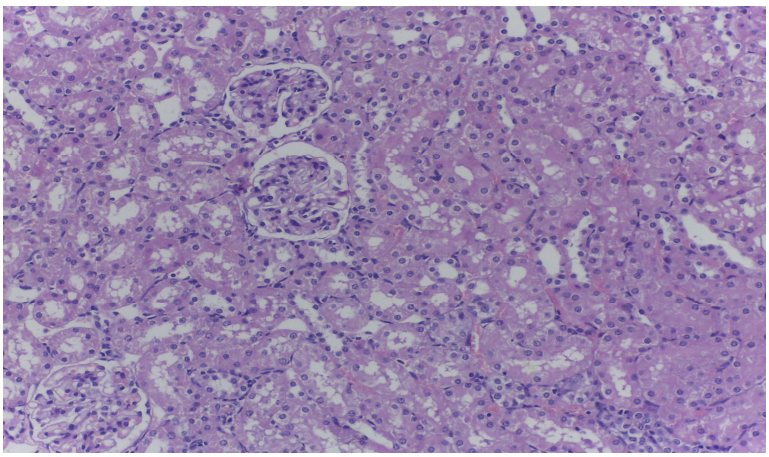

Fig.(4): Captopril group, showing normal structure of the glomerulus, Bowman's capsule, proximal tubules and distal tubules. (10x, H&E).

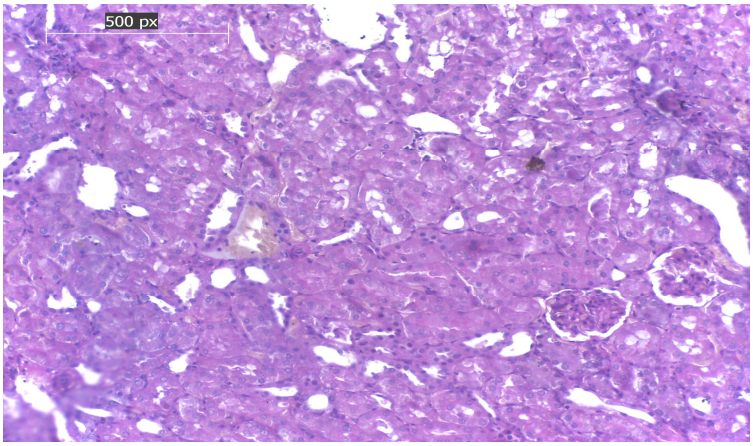

Fig.(5):Cisplatin group, showing glomerular degeneration with tubular dilation and atrophy with sheded tubular cells, intratubular hemorrhage and leuococytic infiltration.

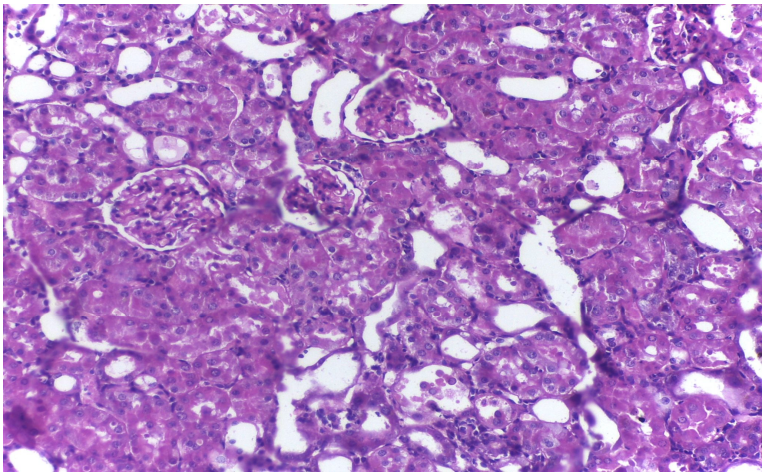

Fig.(6): Mixed group, exhibit that there was regenerating glomeruli and tubules.

RESULTS AND DISCUSSION

In Table(1), Injection of cisplatin (7.5 mg /kg B.W) interperitoneally in normal rats caused a significant decrease in whole blood reduced Glutathione , serum Glutathione peroxidase,serum catalase and serum superoxide dismutase and a significant increase in serum and kidney MDA when compared with control group. These results agree with the findings of **Silva *et al*., (2001)** who recorded a significant depletion in renal GSH level after interperitoneal administration of cisplatin (7.5mg/kgB.Wt). It has been indicated that cisplatin is able to inhibit the activity of antioxidant enzymes such as CAT, SOD, GPx and generate reactive oxygen species in renal tissue **(Noori and Mahboobc, 2010)**. Cisplatin has the ability to induce nephrotoxicity, this usually occur through reducing activities of enzymatic antioxidants including SOD and catalase (**El-Beshbishy *et al*., 2011)**. Cisplatin administration in rats caused a reduction in serum reduced glutathione levels and an elevation in the concentrations of serum and tissue MDA **(Chirino and Pedraza-Chaverri , 2009)**.

Administration of captopril (60 mg/kg) interperitoneally induced a significant increase in whole blood reduced Glutathione , serum Glutathione peroxidase, serum catalase and serum superoxide dismutase and a significant decrease in serum and kidney MDA compared to control group. While in cisplatin and captopril-treated rats,the tested drugs caused a highly significant increase in whole blood reduced Glutathione, serum Glutathione peroxidase, serum catalase and serum superoxide dismutase and a significant decrease in serum and kidney MDA compared to cisplatin treated group, It is indicated that when animals were treated with captopril before cisplatin administration, the GSH is significantly increased. In erythrocytes and brain, captopril has been found to increase GSH content **(DeCavanagh et *al*., 2000)**. It is reported that the antioxidant effects of captopril against cisplatin-induced nephrotoxicity are in agreement with those of **Kalia *et al*., (2007)**. Enalapril and captopril treatments have the ability to increase both the activities of SOD and Se-GPx **(Groner *et al*., 1992)**. Captopril was found to decrease MDA levels and increase the GSH levels, this followed by induction of angiotensin II which has the ability through the membrane bound NADH / NADPH oxidase to increase the generation of ROS, so, the level of angiotensin II is decrease by ACEIs followed by a significant decreasing the ROS production which finally produces a decrease in MDA production and decrease in GSH activity (**Uzunova *et al*., 2005)**.

In Table (2), administration of cisplatin (7.5 mg /kg B.W) interperitoneally in rats caused a significant increase in serum creatinine , blood urea nitrogen, angiotensin and aldosterone levels and a significant decrease in serum renin when compared with control group. These results agree with the findings of **Ugur *et al*., (2015)** high concentration of creatinine and urea in serum induced by cisplatin. Both of angiotensin converting enzyme and angiotensin II are elevated markedly by cisplatin in beagle dogs therefore endothelial damage occurs due to high concentration of angiotensin II **(Taskin *et***

***al*., 2014)**. Priciptation of cisplatin in the left and right kidneys due to conversion of angiotensinogen into angiotensin I in the prescence of renin this accompanied by formation of angiotensin II which in turn has the ability to secrete aldosterone hormone leading to acute renal failure **(Okui *et al*., 2012)**. The increased release of angiotensin II due to increase the renin level than AngII reacts with AT1 receptors in the CJG. leads to the inhibition of renin secretion occur through these binding which is known as short feedback loop **(Chan *et al*.; 2000)**.

Administration of captopril 60 mg/kg interperitoneally evoked a significant decrease in serum creatinine, blood urea nitrogen, angiotensin and aldosterone levels and a significant increase in serum renin when compared to control group. While in cisplatin and captopril-treated rats induced a highly significant decrease in serum creatinine, blood urea nitrogen, angiotensin and aldosterone levels and a significant increase in serum renin compared to control group. These results agree with the findings of **Deng *et al*. (2001)** who indicated that attenuation of oxidative stress, ROS-NO interaction and NO production by captopril, occur through decreasing of angiotensin II which lead to a signficant decrease in aldosterone. Treatment of hyper tension due to stimulation of renin release by both renin and ACE inhibitors. **(Duncan et al., 2009)**. ACE and renin inhibitors suppress the activity of AT1 receptor that lead to blocking the negative feedback of renin release which accompanied by increasing the blood renin concentration **Staessen *et al*., 2006)**.

In Table (3), administration of cisplatin at 7.5 mg /kg B.W interperitoneally in rats caused a significant increase in whole blood and kidney tissue p53 gene expression when compared with control group. These results agree with the findings of **Wei *et al*.,(2007)** who found that cisplatin treatment activates p53 in kidney in vivo and p53 phosphorylation and accumulation is induced by cisplatin mainly in the outer medulla of the kidneys and cell nuclei of cortex, resulting in renal dysfunction and tissue damage in mice . **Price *et al*., (2004)**, reported that in response to cisplatin treatment, there is a rapid nuclear deposition of p53 in the outer medulla of the kidney.

Administration of captopril 60 mg/kg interperitoneally caused a significant decrease in whole blood and kidney tissue p53 gene expression compared to normal rats. While in cisplatin and captopril-treated rats caused a highly significant decrease in whole blood and kidney tissue p53 gene expression when compared to control group. It was reported that captopril and other ACE inhibitors inhibit the expression of p53**(Ziori *et al*., 2006)**. On the other hand **Kossmehl *et al*., (2006)**, ACE inhibitors inhibit proliferating cell nuclear antigen by suppressing the elevation of p53 gene expression.

Histopathological examination of kidney showing In Control group**,** showing normal structure of the glomerulus, Bowman's capsule, proximal tubules and distal tubules. (10x, H&E). while in captopril group , Administration of captopril 60 mg/kg interperitoneally showing normal structure of the glomerulus, Bowman's capsule, proximal and distal tubules. (10x, H&E). therefore in

cisplatin group, administration of cisplatin at 7.5 mg /kg B.W interperitoneally in rats that the tubule was dilated and shrinked or atrophied , the tubular cells was removed and lost and there is asignificant destruction of glomerular with penetration of leuococyte and intratubular bleeding. These in agree with**(Antunes *et al*., 2000)** that , after CP injection in rats there is a significant increase in BUN and creatinine in serum and histopathological changes including protein casts vacuolation and necrosis were observed in proximal renal tubules on the second day. Also there is a significantly elevation in urea and plasma creatinine values, therefore there is extreme tubular damage in renal failure rats **(Zhou *et al*., 2006)**. It is reported that the DNA damage is induced by p53 as degeneration of DNA has been identified as the major cause of cell injury and death during cisplatin chemotherapy **(Megyesi *et al*., 1996 andCepeda *et al*., 2007).** whrease in mixed group,administration of captopril 60 mg/kg interperitoneally and administration of cisplatin at 7.5 mg /kg B.W interperitoneally in rats exhibit that there was regenerating glomeruli and tubules.this agree with **(El-Sayed *et al*., 2008)** who discuss that nephrotoxicity caused by cisplatin is treated by captopril because it has the ability to erase the free radical and has antioxidant activity. captopril inhibite the concentration of angiotensin II in rats with high blood pressure, so the oxidant stress reduce the abbility of captopril in lowering the blood pressure **(Bolterman *et al*., 2005)**. Furthermore, the expression of p53 is suppressed by ACE inhibitors **(Ziori *et al*., 2006)**.

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الملخص العربى

التأثير الوقائى لبعض مثبطات الرينين فى التسمم الكلوى الحاد الناتج عن بعض الادوية المضادة للسرطان فى الجرذان

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تهدف هذه الدراسة الى استبيان تأثير دواء الكابتوبريل على بعض الدلالات الكيميائية فى مصل الدم فى الفئران الطبيعية ونموذج الفئران المصابة بالتسمم الكلوى الحاد المستحدث بواسطة دواء السيسبلاتين وذلك من خلال البيانات المستمدة من الدراسات العلمية المتعددة . لذا أجريت هذة الدراسة على عدد ٤٠ من الجرذان والتي تم تقسيمها الى ٤ مجموعات متساوية. المجموعة الأولى (الضابطة) وتتكون من ١٠ جرذان وتم تغذيتها على عليقة تحتوى على الاحتياجات الاساسية للجرذان. المجموعة الثانية وتتكون من ١٠ جرذان وتم تغذيتها على عليقة المجموعة الضابطة مع اعطاء الفئران دواء السيسبلاتين بنسبة ٥ و٧مجم/كجم من وزن الجسم عن طريق الحقن داخل الغشاء البريتونى.المجموعة الثالثة وتتكون من ١٠ جرذان وتم تغذيتها على عليقة المجموعة الضابطة مع اعطاء دواء الكابتوبريل بمعدل ٦٠ مجم/كجم من وزن الجسم عن طريق الحقن داخل الغشاء البريتونى .المجموعة الرابعة اشتملت علي ١٠ جرذان وتم تغذيتها على عليقة المجموعة الضابطة مع الحقن بدواء الكابتوبريل بمعدل ٦٠ مجم/كجم من وزن الجسم عن طريق الحقن داخل الغشاء البريتونى ثم خلال ساعة يتم حقن الفئران بدواء السيسبلاتين بنسبة ٥ و٧مجم/كجم من وزن الجسم عن طريق الحقن داخل الغشاء البريتونى لمدة شهر كامل وفى النهاية أتضح أن تناول دواء الكابتوبريل في الجرذان المعالجة بالسيسبلاتين أدى الى علاج التسمم الكلوى الحاد مما يتضح دور دواء الكابتوبريل (مثبطات الرينين) فى تقليل تأثير السيسبلاتين على الكلى. كما أن تناول دواء الكابتوبريل أحدث انخفاضا كبيرة في مكونات المصل مثل أنجيوتنسين وهرمون ألدوستيرون و المالون داى ألدهيد فى المصل و أنسجة الكلى وبروتين ٥٣ فى الدم و أنسجة الكلى. وكذلك انخفاض غير ملحوظ فى مصل الكرياتينين و نتروجين يوريا الدَّم. كما تسبب تناول دواء الكابتوبريل الى زيادة كبيرة في نشاط انزيم الجلوتاثيون المختزل فى الدم و انزيم السوبر أكسيد ديسميوتاز و أنزيم كتاليزو انزيم الجلوتاثيون بروكسيديز. وتم تأكيد تلك النتائج بالفحص المهجرى للانسجة حيث وجد أن تناول دواء الكابتوبريل فى الفئران المعالجة بالسيسبلاتين أدى الى تقليل الاثر المدمر الذى أحدثة السيسبلاتين فى الانسجة .