Effect of Betaine on Hepatic and Renal Functions in Acrylamide Treated Rats.

*** Ramadhan, Sadiq jaffer and khudair, khalisa khadim**
Dept. of Physiology, biochemistry and Pharmacology/ College of Veterinary. Medicine. - University of Baghdad – Iraq
E-mail: alzmani@yahoo.com
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Summary

This study was designed to evaluate the ameliorative role of betaine on hepatic and renal dysfunction caused by acrylamide in female rats. Thirty two (32) adult female rats were randomly and equally divided into four groups (G1, G2, G3 and G4) and were treated for (65) days as following: Group G1 (Control group), G2: rats were intubated 250mg/kg B.W of betaine; animals in group G3 were intubated 1mg/kg B.W of acrylamide, in addition to acrylamide. 250mg/kg B.W of betaine were administered orally to rats in groups G4. Fasting (8-12 hrs.) blood samples were collected by cardio puncture technique at the end of the experiment, serum were collected for measuring the following parameters A: liver enzyme makers; serum activity of alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) B; renal function parameters including: serum creatinine, urea and uric acid concentration. The hepato and renal protective effect of betaine was clarified in groups (G2 and G4) manifested by significant decrease in serum, ALT, AST and ALP activity, as well as significant decrease in serum creatinine, urea and uric acid concentration comparing to acrylamide (G3) treated group. Such functional changes were accompanied with structural (histopathological) alteration in hepatic and renal tissue. In conclusion, the results of the current study documented the negative effect of acrylamide on liver and kidney function and documented hepatorenal protective effect of betaine.

Keywords: Acrylamide, AST, ALT, creatinine.

Introduction

Naturally betaine is found in common food, including vegetables, bran, seafood and wheat germ **(1).** Previous report indicates that the human being takes 1.0–2.5 grams of betaine per day from dietary intake and suggests there is no toxicity of betaine **(2).** The metabolism, betaine has two main functions, acting as main osmolyte in the brain and kidney to modulate cell volume **(3)** and as a methyl group donor for the methionine-homocysteine cycle **(4).** Besides the well-known cellular functions of betaine, previous studies have described that the exogenous betaine improves diets-induced fatty liver syndromes, cardiovascular diseases **(2** and **5)** and against chemicals-induced liver fibrosis **(6).** Previous studies that hepatoprotective role from free radical which produces from the oxidative stress which the main factor to liver injury **(7 - 9).** However, the information about the alleviating of liver fibrosis by betaine has yet to be clarified **.(10)**

Betaine has been demonstrated to suppress total cholesterol accumulation in the liver in a steatohepatitis model **(11).** Betaine is a potent agonist of adiponectin and has been demonstrated to prevent the hypoadiponectinmia that results from drinking **(12).** Betaine is a potential medical therapeutic for the alcohol-induced simple fatty liver **(13).** It possesses hypolipidemic and antioxidant effect in acrylamide treated rats **(14).** Acrylamide (ACR) is used in different scientific and industrial processes, such as water treatment, in cosmetics and gel electrophoresis **(15).** Direct exposure to AA usually is a result of consuming high-carbohydrate foods such as roasted cereals, chips, potato crisps, and breads. The packaging of food with polyacrylamide gives rise to indirect exposure to AA monomer sediment**.(16 -17)**

Acrylamide was conjugative with reduced glutathione (GSH). After that the resulting complex is metabolized by cytochrome P450 pathway to produced glycidamide **(18).** The

last metabolite is genotoxic leading to the finishing of hemoglobin and glycidamide-DNA adducts **(19).** It accumulates at higher levels in the blood than any other tissues following exposure via oral ingestion, inhalation, or via the dermis **(20).** Moreover, ACR caused a disruption of hematological parameters, a decrease in erythrocyte membrane resistance and retarded synthesis or destruction of Hb **(21 - 23).** More studies implicated that

AA can be known as a strong neurotoxic agent **(24** and **25).** Incurs to acrylamide was really related with kidney, and breast cancers in postmenopausal women **(26).** Also**(27)** Noticed a positive relation between AA in the food and renal cell cancer whereas there are no positive relations with bladder and prostate cancer risk. Male and female Reproductive toxicity of acrylamide was documented **(28** and **29).** With elevation in AA concentration, glutathione S-transferase (GST) and Superoxide dismutase (SOD) activity is elevation and the GSH count is depleted **(30).** Also, it has been shown that AA can create apoptosis as a result of oxidative stress **(24).** Low level expose of human to AA along like high different food source, smoking and environment exposure increase its hazard effect on human health accordingly, this study was designed to investigate the protective action of betaine towards AA caused hepatic and renal damage. Oral intubation of 1mg/kg B.W ACR exaggerates metabolic syndrome parameters including dyslipidemia and hyperuricemia **(31),** as well as hypercholesterolemia and central obesity **(32).**

Materials and methods

Albino Wistar rats (aged 8-9 weeks and weighted 200±10g) were used in this study, rats in all stages of the experiment were put in plastic cages in conditioned room (22-25°C) for the period from January 2018 to march 2018 providing daily light of twelve hours (7.00 to 19.00) and twelve hours night cycle. They were left for ten days for adaptation with the experimental conditions. Rats had free access to water and standard pellet diet along the experiment. Thirty two (32) female rats were divided randomly into four equal and treated daily for (65) days as below: Group G1 inoculated distilled water, 250mg/kg B.W of betaine, 1mg/kg B.W. of AA, combination of some compositions of betaine and AA for groups G2, G3 and G4, respectively **.**

Fasting blood sample (8-12 hrs.), were inoculated at the end of the experiment by cardiac puncture technique, rats anesthetized by I/M injection of Ketamine-HCL 90mg/Kg body W. and Xylazine 40mg/kg body w. Serum were isolated and frozen at -20°C till analysis for measuring the following parameters. Determination of liver function include alanine aminotransferase (ALT) and aspartate aminotransferase (AST) activity using ALT and AST kit (Redox, united kingdom) and alkaline phosphatase (ALP) activity using ALP kit (Bio system, Spain). Also, the renal function tests included creatinine, urea and uric acid using enzymatic kit (bio system, Spain). Statistical analysis of data was performed on the basis of one-Way Analysis of Variance (ANOVA) using a significant level of ($P<0.05$). Specific group differences were determined using least significant differences (LSD) as described **(33).** Histopathological picture was done according to **(34).**

Results and Discussion

Effect of Betaine, Acrylamide and / or Combination of both Administrations on Serum Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST) and Alkaline Phosphatase (ALP) Activity in Experimental Adult Female Rats**:**Significant increase ($P<0.05$) in serum activities of liver enzymes ALT, AST and ALP were observed in Acrylamide treated groups (G3) compared to groups G1, G2 and G4, (Fig.1-3), whereas betaine administration alone or in combination with AA caused significant decrease ($P<0.05$) in liver enzymes when compared with G2 and the value Normalized that of control.

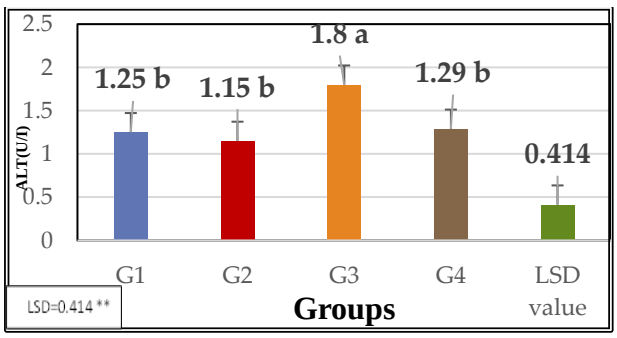
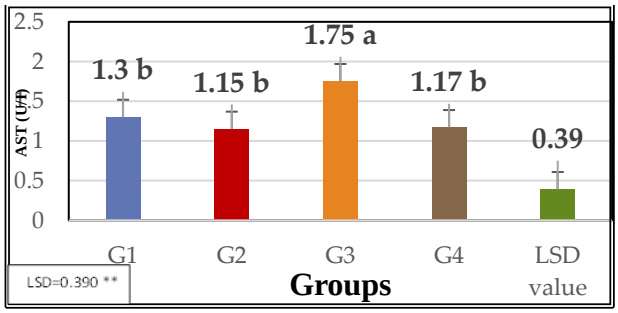


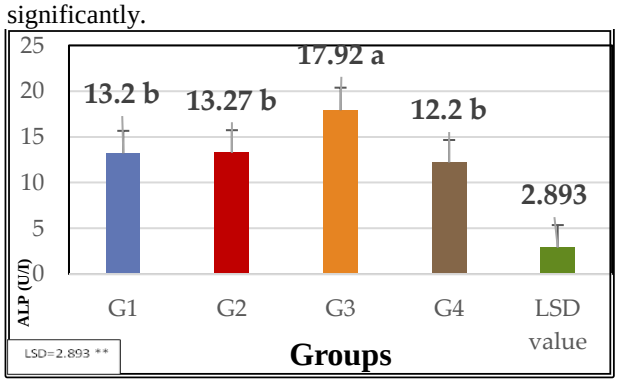
Figure 1: Effect of betaine intubation on serum Alanine Aminotransferase (ALT) Activity in experimental group.

Values are expresses as mean ± SE. n= 8 / each groups. G1: Control Group, G2: Rats Inoculated 250mg/kg B.W Betaine for 65 day. G3: Rats Inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats Inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W of Betaine for 65 day. Different small letters in same row differed significantly.



Figure, 2: Effect of Betaine intubation on Aspartate Aminotransferase (AST) Activity in experimental group.

G1: Control Group, G2: Rats Inoculated 250mg/kg B.W Betaine for 65 day. G3: Rats Inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats Inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W. of Betaine for 65 day. Different small letters in same row differed significantly.

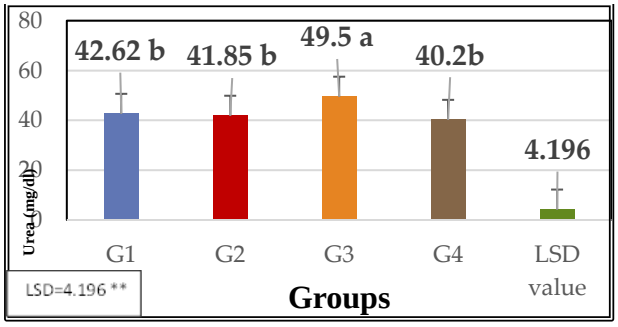


Figure, 3: Effect of Betaine intubation on alkaline phosphatase (ALP) Activity in experimental group.

G1: Control Group, G2: Rats Inoculated 250mg/kg B.W. Betaine for 65 day. G3: Rats Inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats Inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W. Betaine for 65 day. Different small letters in same row differed significantly.

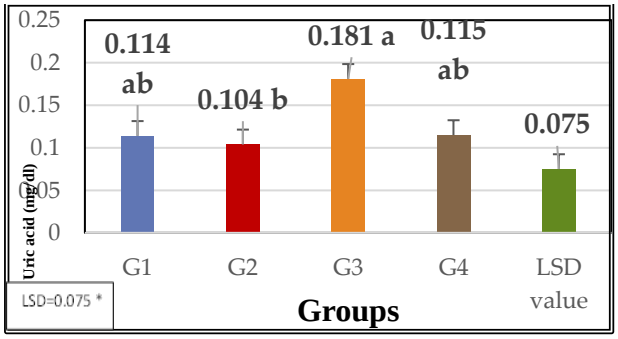
Effect of Betaine, Acrylamide and / or Combination of both Intubations on Creatinine, Urea and Uric Acid Concentration in Experimental Adult Female Rats**:**

Significant increase (P<0.05) in serum Urea concentration was absent in Acrylamide (G3) group as compared to the value in the control (G1), Betaine (G2) and combination of both Betaine plus AA (G4) group, the results also showed that Betaine intubation alone or in combination of both Betaine plus Acrylamide caused significant decrease (P<0.05) in this parameters comparing to G3 group (figure 4 - 6). The figure also pointed to significant decrease (P<0.05) in serum Uric acid concentration after Betaine intubation for (65) day comparing to the value in (G3). Besides combination of Betaine and Acrylamide, normalized the value near that of the control, Significant decrease (P<0.05) in serum creatinine was observed after Betaine intubation comparing to the value in Acrylamide (G3) and (G4) treated groups



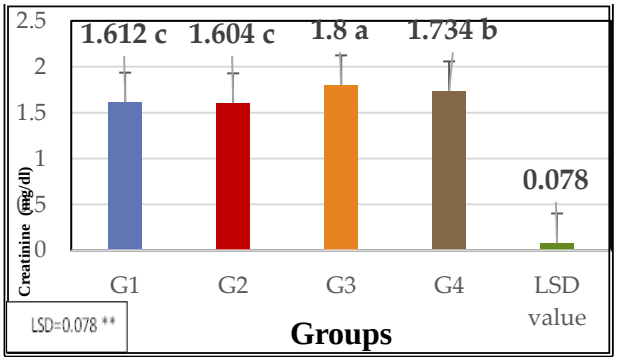
Figure, 4: Effect of Betaine intubation on Urea (mg/dl) concentration in experimental group.

G1: Control Group, G2: Rats Inoculated 250mg/kg B.W Betaine for 65 day. G3: Rats Inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats Inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W. of Betaine for 65 day. Different small letters in same row differed significantly.



Figure, 5: Effect of Betaine intubation on Uric acid concentration in experimental group.

G1: Control Group, G2: Rats Inoculated 250mg/kg B.W. Betaine for 65 day. G3: Rats Inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats Inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W. of Betaine for 65 day. Different small letters in same row differed significantly.



Figure, 6: Effect of Betaine intubation on Creatinine (mg/dl) concentration in experimental group.

G1: Control Group, G2: Rats inoculated 250mg/kg B.W. Betaine for 65 day. G3: Rats inoculated 1mg/kg B.W. of Acrylamide for 65 day. G4: Rats inoculated 1mg/kg B.W. of Acrylamide and 250mg/kg B.W. of Betaine for 65 day. Different small letters in same row differed significantly.

Effect of betaine, Acrylamide and combination of both in rat on hepatic function: Hepatoprotective effects of betaine was documented by **(35** and **36)** in human patient and rats (37). In an ongoing study, the treatment of betaine attenuated ALT level and get better stage of steatosis, inflammation, and fibrosis (38) in NASH patient. Animals and human subjects, high-fat diet, ethanol as well as high sucrose induced hepatic lipid accumulation and liver injury, and these changes could be reversed by the intubation of Betaine (37). Betaine treatment significantly decreased GOT levels. Previous studies indicated that Betaine triggers hepatoprotective effect mostly through alleviating impairment of sulphur-amino acid metabolism and oxidative stress (39).

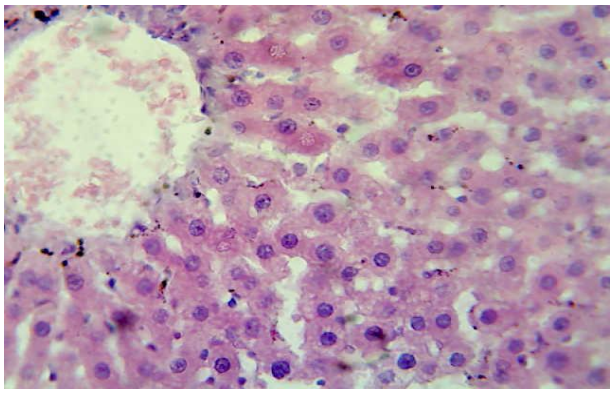
The hepatic disease diagnosis is depending on ALT and AST enzymes are more sensitive biomarkers (40). The liver cell damage different enzymes naturally found in the cytosol released in the blood and there are useful sign to damage of hepatocyte (41). In conjunction with previous reports (42 - 45), investigation results showed significant increment in serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and alkaline phosphatase (ALP) activities following AA rats as compared to their corresponding controls. An elevation in liver enzyme activity after AA exposure could be attributed to the bipolar nature of ACR, where the CH2=CH has hydrophobic interactions since the CONH2 part has ability to form hydrogen bonds with the cellular compounds. This property may enhance its ability to change the structure of cell membrane and make the parenchymal cell membrane of hepatic more permeable and thus active retention of enzyme in the extracellular space and then in the blood. These changes were confirmed by histopathological findings (46). The study results recorded that betaine intake alleviated renal damage induced by acrylamide indicating its renoprotective effect (28, 47, and 48). The protection effects of betaine against the nephrotoxic of carbon tetrachloride in rats (49), and also can reduce post methionine homocysteine concentrations in renal failure cases (50). The roles that documented of betaine are observed in the kidney, in order to adapt the rise of extracellular osmolarity, betaine consider as the suitable osmolytes that are gathering by the cells of renal medulla (51, 52). Also betaine prevents the up-regulation of hear shock protein-70 (53). Osmolyte accumulation is necessary for the viability of cells of renal medulla, this is because renal medulla is exposed to diverse ionic and osmotic compositions in their environment, which may result in reactive oxygen species production (54) and thus renal damage. In conjunction with the reports of (55 and 56), the present study showed that, intubation of AA induced some alterations in the serum creatinine, urea and uric acid concentration as compared with other treated rats **.**

The current data regarding the effect of AA on uric acid level in serum (Hyperuricemia) is in accordance with other previous studies (57 and 58). A case of dyslipidemia referred to hyper cholesterolemia, elevation in serum TAG and reduction in HDL-C concentration was found to be correlated with hyperuricemia and metabolic syndrome by some investigators (32 and 58). In our previous study, serum lipid profile was similarly affected by AA which may explain its mechanism in hyperuricemia (14). Besides, significant elevation reactive oxygen species release and lipid per oxidation, inducing oxidative stress by AA accompanied by depletion in the antioxidant level of kidney (59 and 60), could impair renal function leading to hyperuricemia. Hyperurecemia

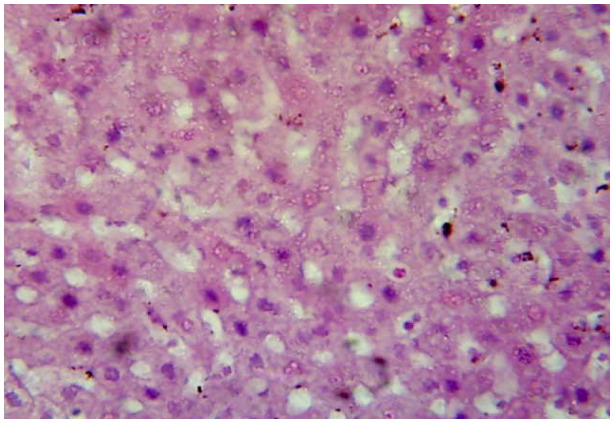
observed in the current study was accompanied with moderate histopathological changes in the kidney, attributed to the fact indicating that the kidney was the way for excrete of AA and their metabolites and hence transient impairment in renal function.

Histopathological Finding Comparing to liver section in normal rats (control group), which showed normal structure (Fig 7), animal inoculated 250mg/kg B.W of betaine for 65 day (group G2), showed no lesion (Fig 8), in section of histopathology in liver of animal inoculated 1mg/kg B.W of acrylamide (G3 group), showed necrosis (Fig 9), fatty changes (Fig 10), Other section in liver of animal inoculated betaine and acrylamide (group G4), showed no clear lesion (Fig 11)**.**

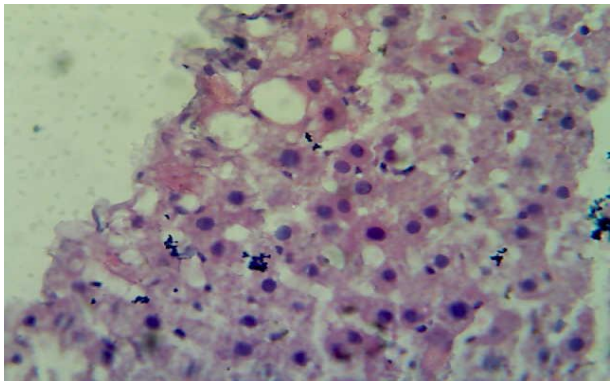
In section of histopathology of kidney of rats inoculated acrylamide (group G3), showed acute cellular degeneration with disappearance or atrophy of glomerular tubules (Fig 14), comparing to the section in (Fig 12) of control and (Fig 13) in betaine (G2) groups and in (G4) group (Fig 15) which showed no clear lesion.



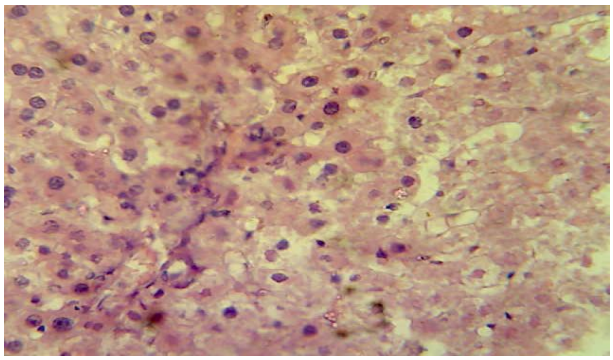
Figure,7. In section of histopathology in the liver of rat (control) in G1group at day 65: showed normal structure of hepatocyte (H.& E.stain 400X).



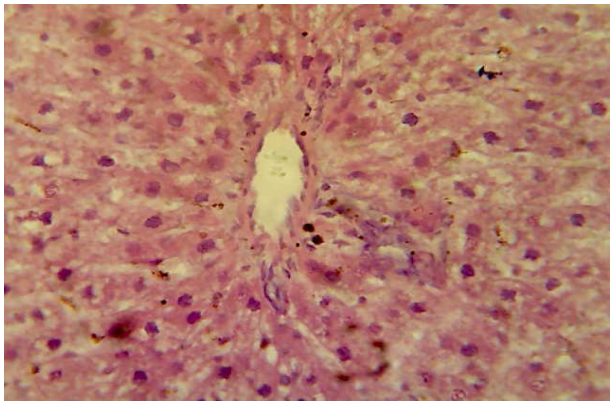
Figure, 8. In section of histopathology in the liver of rat receiving 250mg/kg B.W. of betaine for 65 days in (G2 group): showed normal structure (H.& E.stain 400X).



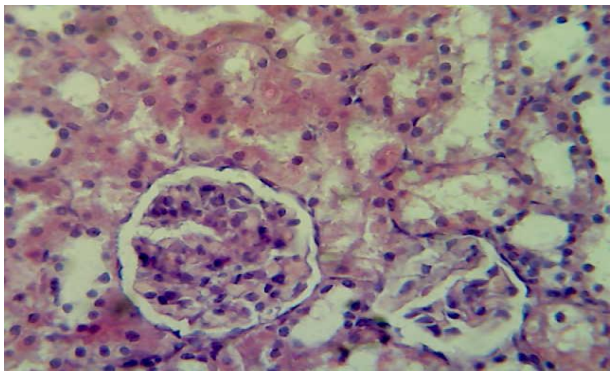
Figure, 9. In section of histopathology in the liver of rat receiving 1mg/kg B.W of acrylamide for 65 days (G3 group): showed fatty changes (H.& E.stain 400X).



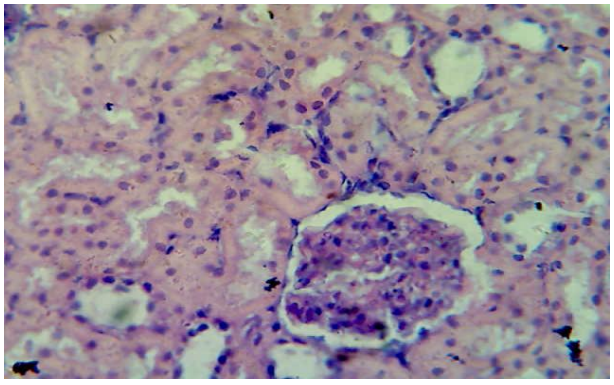
Figure, 10. In section of histopathology in the liver of rat receiving 1mg/kg B.W of acrylamide for 65 days in (G3 group): showed Coagulative necrosis of hepatocytes separated from normal tissue by inflammatory reaction (H.& E.stain 400X).



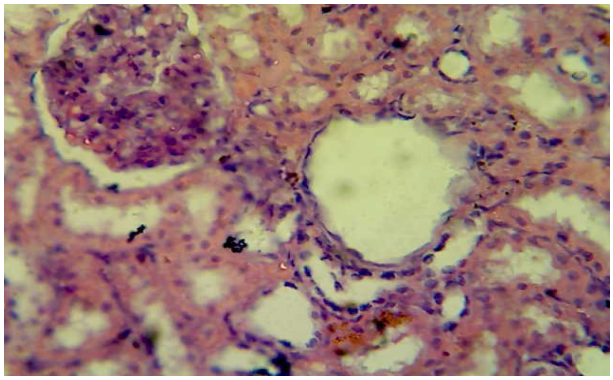
Figure, 11. In section of histopathology in the liver of animal receiving 1mg/kg B.W. of acrylamide and 250mg/kg B.W betaine for 65 days in (G4 group): showed normal structure (H.& E.stain 400X).



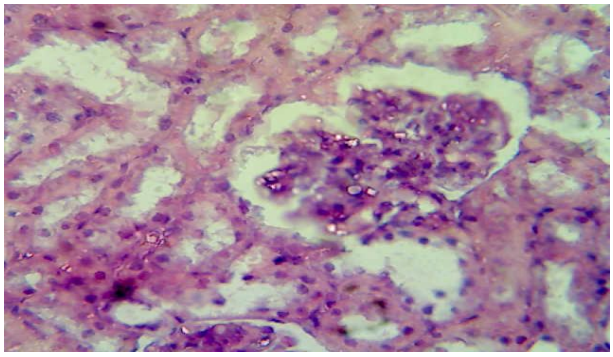
Figure, 12. In section of histopathology in the kidney of rat (G1 group) for 65 day: showed normal structure (H. & E.stain 400X).



Figure, 13. In section of histopathology in the kidney of rat receiving 250mg/kg B.W. of betaine for 65 days in (G2 group): showed normal structure (H. & E. stain 400X).



Figure, 14. In section of histopathology in the kidney of rat receiving 1mg/kg B.W. of acrylamide for 65 days in (G3 group): showed acute cellular degeneration, disappear of glomerular tufts left dilated Bowman space (H.& E.stain 400X).



Figure, 15. In section of histopathology in the kidney of rat receiving 1mg/kg B.W. of acrylamide and 250mg/kg B.W. of betaine for 65 days in (G4 group): showed no clear lesions (H. & E.stain 400X).

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(المبحث الثاني) على وظائف الكبد والكلية في الجرذان المعاملة بالاكريلامايد (betaine) تأثير البيتين

***صادق جعفر رمضان** ***خالصة كاظم خضير**

فرع الفسلجة والكيمياء الحياتية والادوية / كلية الطب البيطري / جامعة بغداد

E-mail: alzmani@yahoo.com

الخلاصة

صممت هذه الدراسة لتقييم الدور الملطف للبيتين (betaine) على الخلل الوظيفي للكبد والكلية المستحدث بأستخدام الاكريلامايد (acrylamide) في أناث الجرذان. تم تقسيم (32) من أناث الجرذان البالغة عشوائيا" وبالتساوي الى أربع مجاميع (G1, G2, G3 و G4) وعوملت كالأتي لمدة (65) يوم: مجموعة السيطرة (G1)، مجموعة (G2) جرعت فمويا" البيتين 250 ملغم/كغم من وزن الجسم، في حين جرعت حيوانات المجموعة الثالثة (G3) الاكريلامايد فمويا" 1 ملغم/كغم من وزن الجسم، وجرعت حيوانات المجموعة الرابعة (G4) فمويا" البيتين والاكريلامايد بنفس الجرعة المذكوره اعلاه. تم جمع عينات الدم في نهاية التجربة بطريقة الوخز القلبي وتم جمع مصل الدم الأجراء الفحوصات الاتية : فعالية انزيمات الكبد متمثلة بانزيم الناقل للألنين ALT والناقل للأسبارتيت AST والفوسفاتيز القاعدية ALP بالأضافة الى قياس تركيز الكرياتنبين واليوريا وحامض البوليك في مصل الدم. اوضحت النتائج التأثير الوقائي للبيتين لوظيفتي الكبد والكلية في مجموعتين G2 و G4 تمثلت بحدوث إنخفاض معنوي في فعالية ALT و AST و ALP وانخفاض في تركيز الكرياتينين واليوريا وحامض البوليك مقارنة مع مجموعة الثالثة (G3) المعطاه الاكريلامايد وصاحب هذه التغيرات الوظيفية تغيرات نسيجية في الكبد والكلية. تؤكد التجربة التأثير السلبي للاكريلامايد على الكبد والكلية والتأثير الوقائي للبيتين.

الكلمات المفتاحية: الاكريلامايد ، انزيمالاسبارتيت ، انزيم ناقل الانين ، كرياتينين .