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Protective role of Ellagic acid against Ochratoxin A induced damage in kidney and Liver.

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Abstract

Production of.reactive oxygen;species in most.disease is consider to bethe most destructive process to human cell ,therfore antioxidant is need to overcome the effect of oxidative strees.In this work the impact of Ellagic acid on some parameters was determind in animals treated with ochratoxin A (QTA) , ochratoxin A +Ellagic acid and Ellagic Acid(EA) only .The results showed that Ochratoxin A treatment caused increased in creatine and urea level to 101mmol/L and 75.3mmol/L respectively while this treatment caused in reduced level of Glutathione Reductase (GR) and these data significantly different from animals treated with (EA) and Saline treated group that showed normal results for these paramters that were 37.3mmol/L,8.9mmol/L and 278 mmol/L for EA and Saline treated group were 36.1 mmol/L, 9mmol/L and 273 mmol/L for above parameters respectively.Animals treated with OTA +EA lead to decreased creatine level to 68.6mmol/L and 35.2 mmol/L for urea and 185 mmol/L.for GR.

***Key word* :**Ochratoxin A. Mycotoxins .Gs ,Urea ,Creatinine

INTRODUCTION

Ochratoxin A (OTA).A mycotoxin relased. From. *Aspergillus ochraceus*, *Aspergillus carbonarius*, and *Penicillium. verrucosum* inaproprate˜media ,it is one of the coomon. mycotoxin that contaminated˚ food .(Al-Anati and Petzinger 2006). It is also a common pollutant of water andwarming ˚ducts. (Richard , *et al*. 1999 , 1999; Polizzi *et al*., 2009) . Mycotoxosis ;can occur, through human feeding, of contaminated food products, chiefly polluted grainkand pork foodstuffs, as well as coffee, wine grapes, and dried grap.(O'Brien and Dietrich, 2005; Blesa ., *et al*. 2006 ; Pfohl-Leszkowicz. andManderville, 2007).

Reactive oxygen species (ROS). are relased; by all cells.during. normal .oxidative Process and, if left notcontrolled byantioxidant .systems, can lead to doungers damage to nucleic acid, proteinsand lipids. Intracellular, ROSare fundamentally released by. mitochondrial respiration,and,redox,enzymes, such,as,nitric,oxide synthase,cytochrom P-450,isoforms, and NADPH, oxidase subtypes (NOXs), in the form of superoxide. Alsothere were . many studies founded ,That,OTA had influence on enzymes in charge.of prohibition oxidative stress such as Glutathione reductase (GR) thatis an enzyme which in humans is, encoded through the GSR gene. GR stimulate the reducingof glutathione disulfide,,(GSSG) to the sulfhydryl form glutathione (GSH), ,,thatis a stringent molecule in combat, ,oxidative tension and preserving the reduction medium of the cell.(Staniek and Nohl,1999; Li and Shah, 2004; Stephens *et al*.,2010) .GR functions as dimeric disulfide oxidoreductase and used an FAD prosthetic group and NADPH for reducing one

molar of Glutathione disulfide to two molar of Glutathione , GR have important role in preserving basic function and prevent oxidative tension in body cells. So it had function as a scavenger for OH radicals, O-, and various electrophiles. Reducing of GR lead to generate the oxidized form of the glutathione peroxidase, which forether play role in reducing (H2O2), a hazardously reactive .species intracellular. SO, it had critical role in the cellular process and rescue of xenobiotics, works as a cofactor in clear detoxifying enzymes, take part 3 in transportand release antioxidants such Vitamins E and C to their active forms. The ratio of GSSG/GSH found in the cell is important factor in mantinace the oxidative balance of the cell, so that , it is essential that the cell preserving high amount of the reduced glutathione and a low level of the oxidized Glutathione disulfide. This narrow balance is preserved by glutathione reductase, that stimulate the reduction of Glutathione disulfide to Glutathione. (Deponte, 2013).

In addition that OTA cause pathophysiological effect on many physiological parameters such as GOT,GPT ,urea ,total protein ,Cholesterol, Sugar Creatine kinase ,ect. and lead to chronic diseases and renal failure.(Aydin etal.,2003). And in others hand there is no available treatment for diseases that generated from mycotoxins but many researcher indicates that some medical plants can prevent ,treat many diseases such as cancer ,heart diseases, kidney diseases and others diseases (Muntaha , 2016) The pomegranate plant extractor such as juice, seed and peel have been notify to display a powerful antioxidant action(Gil etal.,200). t the protective role of EA against mycotoxin toxicity was not studied in Iraq. Therfor the recent reserch had been designeded to discuss the protective role of EA against OTA toxicity in kidney and liver as attempt to application of EA as therapy in ochratoxicosis.

Material and methods

1-Ellagic acid

It was obtained from Akitin Nature connecting health (Aktin Chemicals, Inc)/china. as stock powder in concentration(5 g).One gram was diluted in 1ml Distale water and keep until using.

2-Ochratoxin A

One gram purified and crystalline OTA (Sigma chemical CO,Louis ,USA) was diluted in 1ml PBS and keep until using.

3-Experimental Design

In present study albino male rats were used ,weight (200-210)g ,and obtained from animals house in Education college/Biology department .The animals kept in room with temperature (25±2 C0) and light/dark cycle (12/12h)and provide with standard laboratory diet..30 animals were divided into 5 groups (6 animls for each group) as follow:

Group 1:Treated with OTA ,injection intrapertonealy at dose 250µg/kg body weight for seven day.

Group 2:Treated with OTA ,injection intrapertonealy at dose 250µg/kg body weight and EA at dose 10mg/kg body weight for seven day.

Group 3:Treated with EA ,injection intrapertonealy at dose 10mg/kg body weight for seven day.

Group 4:treated with saline , injection intrapertonealy at dose 10ml/kg body weight for seven day.

Blood were collected from all rats and serum separated and used for estimation of urea level,Creatine kinase leve and Glutothione reductase level and liver enzyme liver such as AST,ALT and ALP.as follow:

1- Assay of urea

By using Patton of crouch method for estimation of urea in serum by biomeriux which depending essentially on urea reaction with water to iberation of ammonium and by it reaction with salicylate and hypochlorite in alkaline medium to produce indophlrite and then measured the color intensity by spectrophotometer in wave length (580)nm as in procedure (Majdy etal.,2008).

2-Assay of CreatineKinase (CK)

This enzyme was determined by coloric method according to the Rendox method as the following reaction:

Creatine phosphate+ADP**___CK___** Creatine +ATP

Glucose +ATP**___HK_____**Glucose -6-phosphate +ADP

Glucose -6-phosphate +NADP+ **__G-6P-DH_____**Gluconate -6-p-NADPH

2NADPH +NBT**____Diaphorase_____** Diformazan +2NADP

The blue /Violate diformazan which has an absorption maximum around 560nm. (Allain etal. ,1973)

3-AssayofGlutathione reductase (GR)

Glutathione reductase was detected by Rendox method ,this enzyme catalyses the reaction of glutathione (GSSG) in the presence of NADPH which is oxidized to NADP+ .,the decreased in absorbance at 340nm is measured (Goldberg andSpooner ,1983) 6

NADPH +H+ +GSSG**___GR_____**NADP+ +2GSH

4-Assayof Alkaline.phosphate (ALP).activity

Depending on Belifield and Goldberg (1971) method by using colorimetric method to determined ALP activity which reaction scheme is as follow :

Phenylphosphate **____ Alkaline phosphate _____**Phenol+phosphate

And ALP activity calculation as follow :

$$\text{ALP activity} = \frac{\text{Abs.Assay-Abs.Specimen blank}}{\text{Abs.Standard}} \times 20$$

5-Assay of Aminotransferase. (ALT). activity

By using colorimetric method ,ALT activity were determined according to the following reaction :

Alanine +α-Ketoglutarate **___ALT___**Pyruvate+Glutarate

Number of ALT units/ml in serum were calculated by use standard curve . (Reitman and Frankel ,1957).

6-Assay of Aminospartatetransferase (AST)activity

Also by using colorimetric method,AST activity was determined according to the following reaction:

L-Aspartate + α-Ketoglutarate **___AST__**Oxaloacetate+L-Glutamate.

Number of ALT units/ml in serum were calculated by use standard curve

(Reitman and Frankel ,1957).

General histopathological preparations

The specimens of liversand kidneys were fixed by 10% buffered formalin solution still the preparation of histological sections. Tissues were embedded in paraffin and several tissue sections were prepared for histopathological sections were stained with Hematoxylin-Eosin (H and E) according to Bancroft and Stevens (1982).

Statistical analysis

ANOVA and T student test were used to analyze the data .Value of P≤0.05 were regarded as significant.so Mean and SEM was used for analyze data.

Results and Disscution

The results summarized in table (1) showed that Ochratoxin A treatment caused increased in creatine and urea level to 101mmol/L and 75.3mmol/L respectively while this treatment caused in reduced level of Glutathione Reductase (GR) and these data significantly different from animals treated with (EA) and Saline treated group that showed normal results for these paramters that were 37.3mmol/L,8.9mmol/L and 278 mmol/L for EA and Saline treated group were 36.1 mmol/L, 9mmol/L and 273 mmol/L for above parameters respectively.Animals treated with OTA +EA lead to decreased creatine level to 68.6mmol/L and 35.2 mmol/L for urea and 185 mmol/L.for GR. So data in table 2 showed effect of OTA on liver enzmes where this toxin caused increased level of AST ,ALT and ALP enzymes to reach into (56,120 and 128)U/L respectively and these data different significantly(P≤0.05) in saline and EA treated group which were (18.3,65 and 70)U/L respectively for saline treated group and (19.1,66 and73)U/L respectively for EA treated group.So data in the same table showed the effect of pretreatment of animals with EA that lead to reduction of AST ,ALT and ALP level to (30,69 and 80)U/L respectively Compared with animals treated with OTA only as showed above.

Table (1) Effect of Ellagic acid on OTA-induced defect in Creatine Kinase ,Urea and GR parameters in rats .

GR NmolNADPH oxidized /min/mg protein	Urea mmol/L	Creatine Kinase mmol/L	Treated Animals
132±3.4a	75.3±4.4a	101±5.3a	OTA(µg/kg b.w)
185±4.8b	35.2±3.2b	68.6±4.3b	OTA(µg/kg b.w) + EA(10mg/kg b.w)
278±4.6b	8.9±2b	37±4.5b	EA(10mg/kg b.w)
273±6.3b	9±2.1b	36.1±3.1b	Saline(10ml/kg b.w)

Value Mean± SEM .a P≤0.05 signficantly different from saline trated group.bP≤0.05 signficantly different from OTA trated group.OTA =Ochratoxin A. E.A=Ellagic Acid .GR=Glutathione Reductase.

Table (2)Effect of Ellagic acid on OTA-induced defect in Liver enzymes activity (AST,ALT and ALP) in rats .

Alkaline phosphatase (U/L)	Alanine transaminase (U/L)	Aspartate transaminase (U/L)	Treated Animals
128±2.4a	120±1.7a	56±1.2a	OTA(µg/kg b.w)
80±4.6b	69±1.8b	30±1.3b	OTA(µg/kg b.w) + EA(10mg/kg b.w)
73±1.6b	66±2.1b	19.1±4.5b	EA(10mg/kg b.w)
70±3.3b	65.3±1.1b	18.3±2.1b	Saline(10ml/kg b.w)

Value Mean± SEM .a P≤0.05 signficantly differ from saline trated group.bP≤0.05 signficantly differ from OTA trated group.OTA =Ochratoxin A. E.A=Ellagic Acid . U/L =Unit/Litter .

From above results we showed there were increasing in Creatine Kinase and Urea level when animlas treated with OTA this explains the damage that occurs in kidney in this group and mechanism of nephrotoxicity induced by OTA in animals that lead to above results. So above treatment caused decresing in GR level in serum that may be due to effect of OTA on kidney that made it loss it function which caused the increase in renal extraction of CR and increasing in glomerular filtration rate that lead to exit of GR with urine and decreasing level in serum,decreasing GR level lead to increases sensevity of organs to oxidative and chemical injury and infected body by many diseases. SOthis treatment had high effect on liver enzymes activity and caused high incrasing in both AST,ALT and ALP level in serum , The liver consider important target of OchratoxinA biotransformation. though, some studies about effect of OTA on liver, used high doses of Ocratoxin A and showed marked damage in liver (**Aydin etal.,2003; Ferrante *et al,*. 2006**). low concentration of Ochratoxin A did not appear significant pathological effect (**Kamp *et al.* 2005; Rached*et al.* 2007; Palabiyik *et al,*. (2012)**. More studies had been focused on effect of OTA on kidney, less studies effect of this toxin on liver. On the other hand , it is yet unclear how O chratoxin A effects on the liver which is consider the largest detoxification organ in the body. This effect may be due to Effect of OTA on hepatocytes that lead to relase these enzymes into blood and increase it level.

In another side treated animals with EA cause decrease in urea, creatine kinase,AST,ALT and ALP level and increase GR to normal level ,this mean EA protect OTA-inducing disorderds in treated animals and act as

scavenging initial radical such as OH_0that generated by OTA in animals body.

With regard to the results of this study that listed in table (1) ,It agreement with results of (Mahgoub.and Sfaa 2010) but he was used pomegranate peel extract in his study.So **Halvorsen etal.,(2002)** found in their study the EA were shown to have high antioxidant activity in vitro models and **Reasner (2008)** reffered to EA can offer wide protective role against cardiovascular diseases.SO our results listed in table (2) is agreement with **(Young etal.2012)** study whom found the activities of AST,ALT in animals feed diets contain OTA alone were significantly higher than control groupbut when added Mycotoxin deactivator lead to increase of avove enzyme level.

For all above there were no study about protective effect of Ellagic Acid for OTA-induced kidney and liver to compared our study with it.

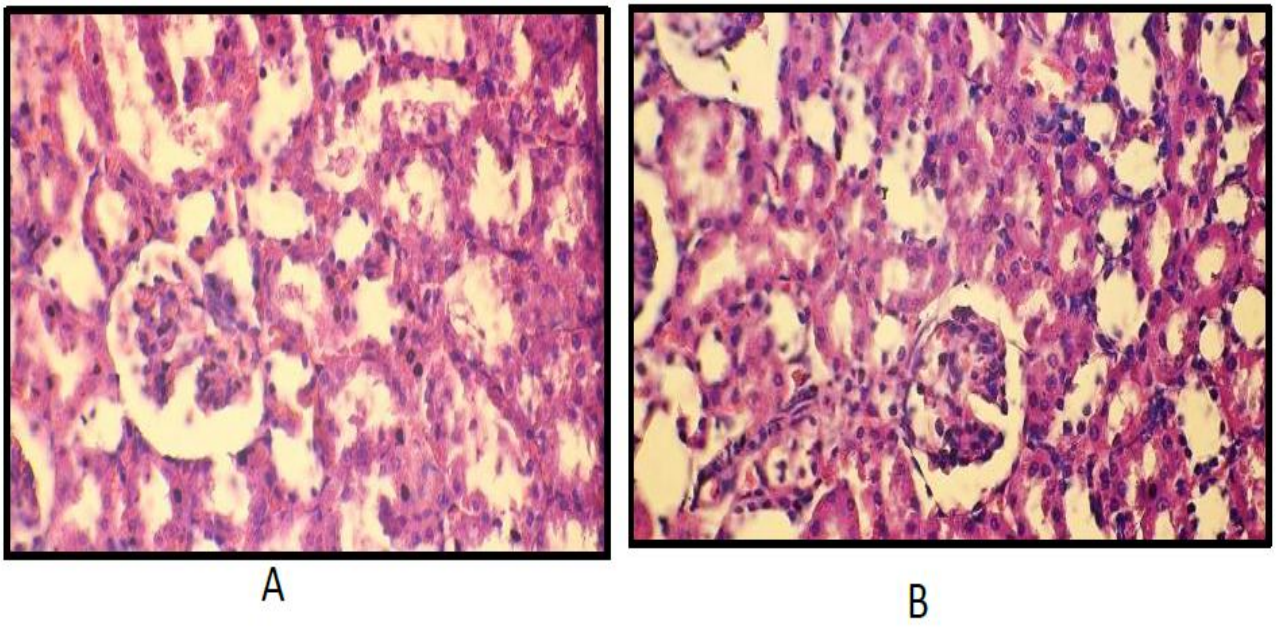
The oxidative tension considered important mechanism for the effects that occur by Ochratoxin A,this toxin lead to relase of Reactive Oxygen Species (ROS) in addition to those relased by redox reactions that normally occur in different activity of cell .ROS if not controlled on it can offensive all active molecules in body for example Nucleicacid ,Lipids ,Enzymes and Proteins ,therefore Reactive oxygen species are involved in many serouis diseses e,g. diabetes , Alzheimer's , Parkinson's ,cancer and other diseses **(Halliwelland Gutteridge ,1986**).

Microscopically results of kidney and Liver tissue sections male white rat that treated with OTA at dose250µg/kg body weight for seven day several pathological changes ,in kidney tissue this changes include :vascular congestion , dystrophy and the disappearance of the glomerulus in addition to cell necrosis of glomerulus. (Picture2)

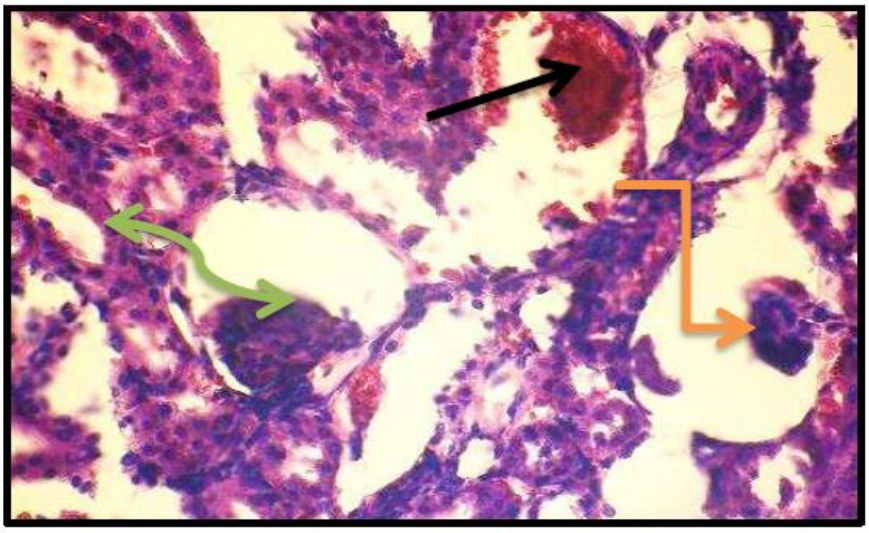
In liver tissue histopathological changes include :cell necrosis , vascular congestion and loss of normal structure of liver (Picture 5) While treated animals with Ellagic acid at dose10mg/kg body weight for seven day and saline at dose10ml/kg body weight for seven day any pathological changes (Picture1,4) .Treated animals with Ellagic acid mix with OTA showing little histopathological changes in liver and kidney include vascular congestion in liver and congestion of blood vessels between renal tubules (Picture3,6) This confirms the safety role of Ellagic acid and have capacity to OTA toxicity reduction or OTA or decompose products have lost effectiveness toxic for biological systems in treated animals. (**Alina etal.,2012**) emphasized that treated rats with OTA lead to liver carcinomas ,and cause of these effect may be belong to ability of OTA on Because starting a cancer by interfering with DNA molecule or via triggered abnormal growth of cells in this case called carcinogenic agents and perhaps cancer originates because of genetic mutations in

DNA .Our results agreed with **(Horvath etal.,2002**) that referred to OTA lead to cause pathological effect in animals liver such as hepatocytes necrosis and vascular congestion, this may be because of OTA highly toxic compound have toxic effect on liver and kidney and that appear through inhibition of enzymes like Glutathione reductase enzymes and AST, ALT, ALP and these enzymes are important in the expulsion of toxic free radicals in the body and inhibited it may lead to increased accumulation of free radicals and the inability of the liver to be removed .

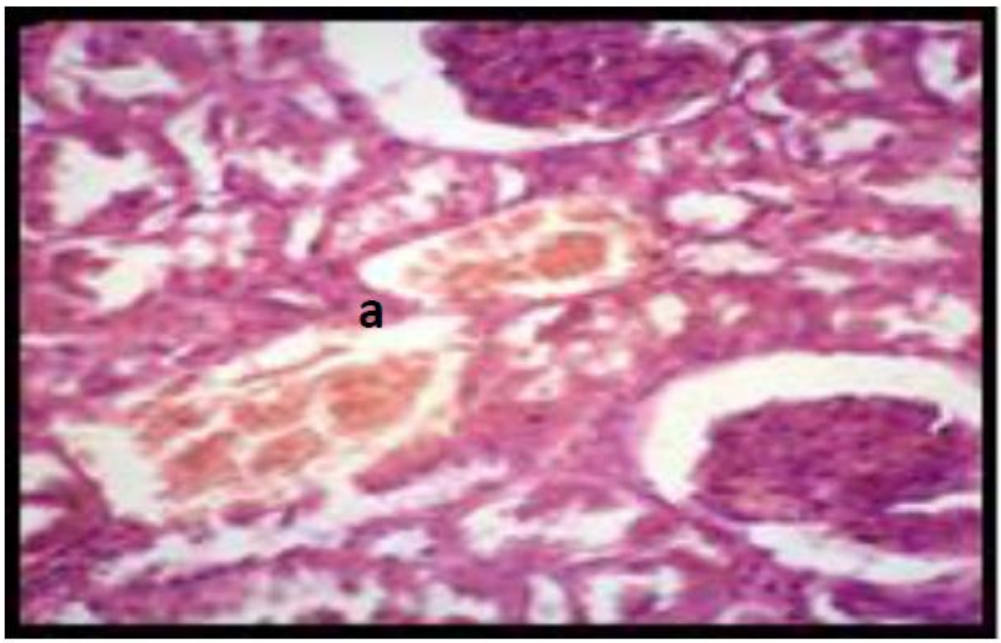
Researchers (**Horvath etal.,2002**) refereed to OTA have ability to induce pathological effects in Kidney such as renal cell necrosis and Gaps in Proximalconvoluted tubule and OTA lead to Inhibition of Glomerular filtration process that occur by Glomerulus in kidney through loss of glomerulus function .



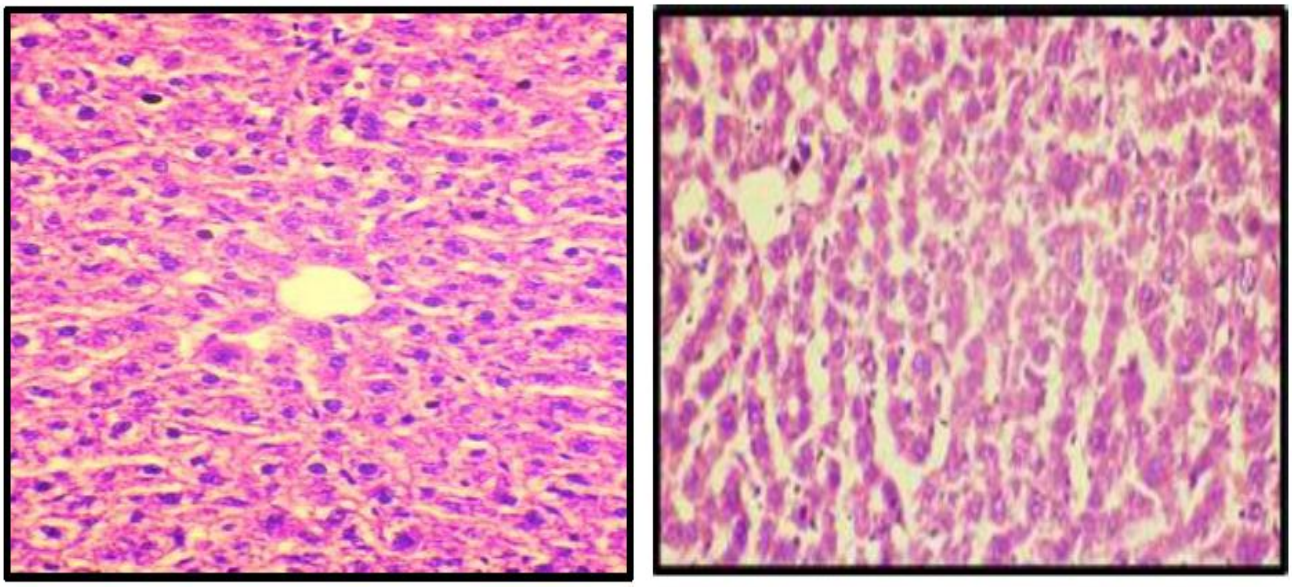
Picture (1) Histological section of control group Kidney.A=treated with EA at dose 10mg/kg b.w B = treated with slaine at dose 10ml/kg b.w (H and E stain 40X)
Picture



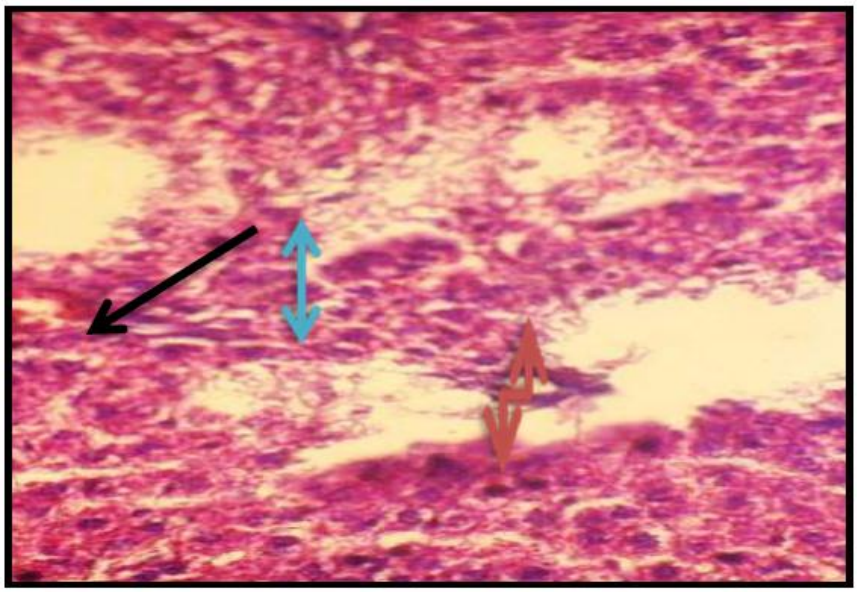
Picture (2): Histopathological section of Kidney for rat after 7 days of treatment with OTA at dose 250µg/kg b.w. shows → = vascular congestion, ↴ =dystrophy, ↜ =cell necrosis of glomerulus (H and E stain 40X).



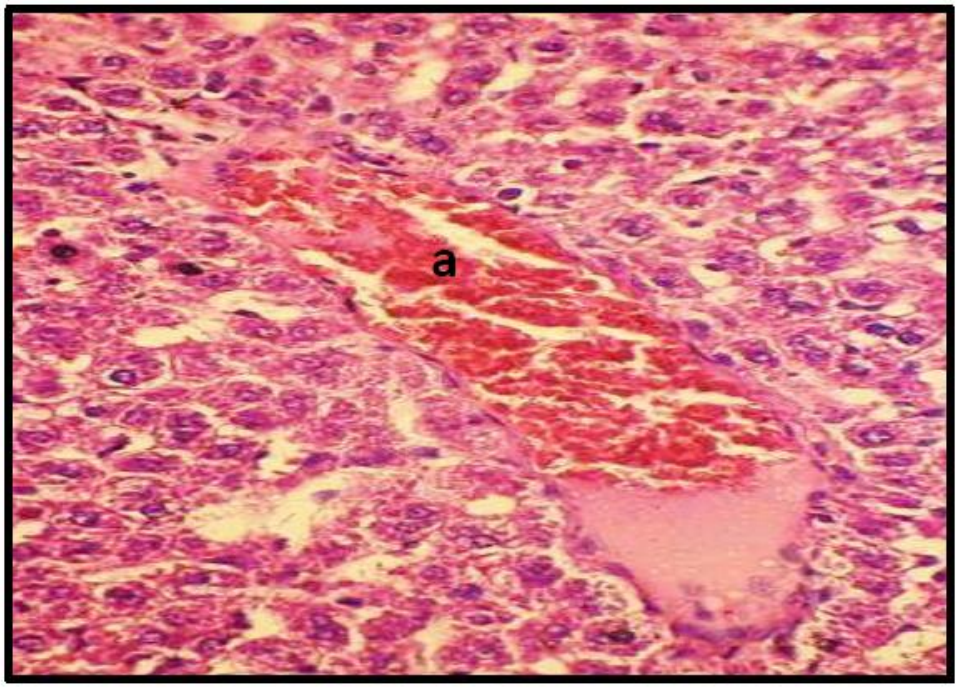
picture (3): Histopathological section of Kidney for rat after 7 days of treatment with OTA at dose 250µg/kg b.w. +Ellagic acid at dose 10mg/kg b.w. shows a= congestion of blood vessels between renal tubules . (H and E stain 40X)



Picture (4):Histological section of control group liver .A=treated with EA at dose 10mg/kg b.w B = treated with slaine at dose 10ml/kg b.w(H and E stain 40X)



Picture (5): Histopathological section of liver for rat after 7 days of treatment with OTA at dose 250µg/kg b.w. shows → = vascular congestion, ↔ =cell necrosis , ↕ =loss of normal structure of liver (H&E stain 40X)



Picture (6): Histopathological section of Kidney for rat after 7 days of treatment with OTA at dose 250µg/kg b.w. +Ellagic acid at dose 10mg/kg b.w. shows a= Vacular congestion . (H and E stain 40X)

Plants,leaves ,seeds and fruits used in traditional medicine and by anthopharmacology folk healers for treatment of many medical condiation have been passable recently as one of the important sources for chemoprotective drug detection and expantion ,more of these plant play important role in protective body from ROS and mutagenic compounds effects **(Ayrton etal.,1992).**

In conclusion, EA have a protective role toward Ochratoxin A effects through an suppression of the oxidative injury and catalyze of GR activity and play important role as antioxidant and free radical scavenger characters and act as nephroprotective and hepatoprotective agent ,Furthur studies is required for determine the mechanism involved in the nephroprotective and hepatoprotective role of EA,hence clinical implementation of EA as treatment must be belived in condition of ochratoxicosis.

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