Protective effect of tomato against oxidative damage of liver induced by adenine in male rats

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Abstract
The aim of this research was to assess biochemical parameters; histological changes in the liver caused by oxidative stress, and the potential protective effect of tomato powder against damage that contains Lycopene. Lycopene has a high antioxidant activity, which helps to protect cells and tissues from oxidative stress caused by reactive oxygen species. Twenty-four male rats were used in the study, divided equally and randomly into four groups; the control group of control animals was fed with a regular diet and injected intraperitoneally with Dimethyl sulfoxide (DMSO). G1 group rats had been injected with adenine 50 mg/ kg B.W. suspended with DMSO, for 4 weeks induced liver damage, and fed with a standard diet, the G2 and G3 group rats had the same protocol used in the second group except they were fed with 10% and 20% Tomato Powder respectively. The results show the Tomato powder caused enhancement in antioxidant enzymes, liver function test, and histological liver section. In conclusion, induced oxidative damage to the liver by adenine leads to disorder in liver function tests (ALT and AST) and causes a harmful defect in the liver, the tomato powder contributed to the improvement of these parameters, especially at a dose of 20%.
Keywords: Tomato powder, Lycopene, Dimethyl sulfoxide, Adenine, liver damage, antioxidants.

Introduction

Tomatoes are common because of their taste and nutritional benefits. Carotenoids are important antioxidants that give fruits and vegetables their colors of yellow, orange, and red. Lycopene has the greatest antioxidant activity of all the carotenoids, which is due to the inclusion of the most double bonds in its composition. The most common carotenoid present in tomatoes is lycopene (Lycopersicon esculentum L.). The high radical scavenging and antioxidant potential of lycopene is responsible for its multiple health benefiting impact. Carotenoids' cancer chemopreventive effects have been extensively studied, with many epidemiological and laboratory trials supporting this (Tanaka, Shnimizu, and Moriwaki 2012; Imran M et al., 2020). In mice, studies performed in our lab have shown that lycopene enriched tomato extract (LycT) has a significant cancer chemopreventive effect against hepatic and skin cancer (Hasona et al., 2017; Nedamani, Nedamani, and Salimi 2019). Lycopene's protective properties against xenobiotic-induced toxicity have also been reported. We previously mentioned LycT's defensive effects in mice against doxorubicin nephrotoxicity (Hedayati et al., 2019; Koul et al., 2020). Antioxidant lycopene is well-known. It has the ability to preserve DNA, proteins, and lipids from oxidation. "Lycopene can act on other free radicals such as hydrogen peroxide, nitrogen dioxide, and hydroxyl radicals," according to Casaro et al. (2020).

Acute pancreatitis (AP) pathogenesis requires both oxidative stress and inflammation. In Wistar rats, lycopene (50 mg/kg) significantly reduced MPO activity, TNF-, and down-regulated iNOS gene expression while also lowering NO levels, raising pancreatic glutathione (GSH), and decreasing serum -amylase and lipase functions (El-Ashmawy et al., 2018). Fluorosis can cause oxidative stress by triggering MAPK cascade that can cause cell apoptosis. In rats, a mixture of vitamin E and lycopene blocked spermatogenic cell apoptosis caused by fluoride. Both reduced the expression of saved clustering and fluorosis-induced toxicity. In addition, (Tian et al., 2018) it decreased the increased JNK as well as phosphorylation of the ERK. Another research demonstrated the function of lycopene by inhibiting hepatocyte nuclear factor-1, improving LDL-receptor, and sterol regulatory element-binding protein-2, and downregulating the expression rate of the proprotein convertase subtilisin/kexin type-9 (PCSK-9) by inhibiting PCSK-9. Lycopene also decreases Apo-ability CIII's to bind with lipoprotein lipase (LPL). Lycopene also reduced LPS-induced oxidative stress by raising overall antioxidant and HDL-related PON-1 activity while also lowering plasma levels and inflammatory mediator expression (Alvi et al., 2017). Moreover, tomato powder has been shown to have a protective agent against alcohol-induced hepatic injury by inducing cytochrome p450 2E1 (Nedamani et al., 2019). The lycopene treatment considerably improved liver functioning in case of rats with bile duct ligation (BDL). It reduced NO and MDA levels and improved reduced enzymatic level (i.e., CAT, GSTs, GSH, and SOD) in the BDL rat. In addition, lycopene decreased DNA damage (Tokac et al., 2015; *Yu* et al., 2017).

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Material and Method

Experimental animals

Rats were housed in an animal house for two weeks to acclimate to laboratory conditions before being used in the experiment; 24 stable adult male rats weighing 200-250 gm were used in the experiment. The animals were housed in the animal house of the University of Kerbala's College of Veterinary Medicine, where they were held in a normal setting with a temperature of 22-25 degrees Celsius and a 12-hour light-dark period. In this experiment, Twenty four adult male rats were used inthis experiment, and divided into four groups; each group consisted of 6 rats as the follows:

Control group : Rats were injected DMSO by intraperitoneally (as control) for four weeks, G1: Rats were injected with Adenine suspended withDMSO intraperitoneally at dose (50 mg/kg) for four weeks according to the method reported by (Al Za'abi *et al.*, 2015), G2: Rats were injected with Adenine dissolved by DMSOintraperitoneally at dose 50 mg/kg BW for four weeks, and then given 10% Tomato powder mixed with diet at the same time for four weeks according to the method reported by (Campbell *et al.*, 2007), G3: Rats were injected with Adenine suspended withDMSO intraperitoneally at dose 50 mg/kg BW for four weeks, and then given 20% Tomato powder mixed with diet at the same time for four weeks according to the method reported by (Suganuma and Inakuma, 1999).

Preparation of adenine: Adenine was obtained from Sigma Aldrich Company (USA). Preparation of tomato powder Fresh, mature, and ripe tomatoes (*Lycopersicon esculentum*) were purchased from local market (approximately 60 KG). A sharp stainless steel knife was used to cut the tomatoes into slices of roughly 10.0 + 0.1 mm thickness in a direction perpendicular to the vertical axis (Arslan and Oscan, 2011). In November, tomato slices were evenly spread as a thin layer onto stainless steel trays and dried in direct sunlight at temperatures ranging from 20 to 30 degrees Celsius (Balladin and Headley, 1999).

Collection of blood and tissue sample

At the end of experiment the rats before sacrifice were anaesthetized by placing them in a closed jar containing cotton sucked with chloroform anesthesia, then Puncture of heart was done by using a 5 ml disposable syringe and 6 ml of blood was drawn slowly and gently. Then part of the blood placed in the test tube that holds a gel at room temperature for thirty minutes, and is used for serum by centrifuge at 3000 rpm to separate the serum for fifteen minutes, and is put into Eppendorf tubes, which are freezer-positioned in –20C° and Biochemical parameters are estimated including serum Aspartate aminotransferase activities (AST) concentration, Serum Alanine aminotransferase activity ALT is determined by using a special kit (SPECTRUM AST – kit, Egypt- IFUFCC22) by using device (Spectrophotometer Sesil, England), Estimation of Antioxidant enzyme including serum Glutathione-S-transferase (GST) and serum Superoxide dismutase (SOD) concentration; the procedure was done according to the instructions of the manufacture of ELIZA Kit -Elabscience biotechnology/ china. The abdominal cavity was opened and the liver removed after punching and blood gathering, and formalin (10 percent) was placed as a fixative for histologic preparation.

Statistical Analysis

Data were analyzed using the software package SPSS version 23.00 where one way (ANOVA) was used. The data were expressed as mean ± standard Error (SE), p-value >0.05 was considered significant.

Results

1. Effect of adenine and tomato powder on some serum biochemical parameters:

Alanine Transferase concentration: there were statistically significant increases (p≤0. 05) in ALT activity in adenine group compared with control groups and groups that are supplemented with tomato powder (10% and 20%). The groups treated with tomato powder (10% and 20) show significant reduction (p≤ 0.05) in the activity of ALT in comparison withadenine group but no significant (p <0.05) between the group tomato 10% and 20% as shown in table 1. Aspartate amino transferase concentration: the AST activity showed significant increase (P ≤ 0.05) in adenine group compared with control group. Tomato powder 10% was decrease significantly (P ≤0.05) in compression with adenine group. The high dose of tomato (20%) show significant reduce (P ≤0.05) in AST activity compare with adenine group but no significant (P <0.05) when compare with control group (Table 1).

Table 1. Effect of adenine alone and in combination with tomato powder (10% and 20%) on Some Serum Biochemical Parameters in male rats.

Parameter Group	ALT U/ml	AST U/ml
Control	51.47 ± 3.69 C	133.31 ± 3.61 C
Adenine	105.32 ± 6.22 A	318.21 ±15.44 A
Adenine+Tomoto10 %	76.21 ± 3.99 B	191.93 ± 6.42 B
Adenine+Tomato20 %	70.30 ± 2.45 B	131.74 ±5.90 C

-Values = Mean ± SE
-Different letters represent significant (P ≤0.05) differences between groups
-Number of rats in each group = 6

2. Effect of adenine and tomato powder on some serum Antioxidant parameters.

Superoxide dismutase concentration: SOD significantly decrease (P ≤0.05) in adenine group in comparison with control group as shown in table 2. The group treated with tomato 20% shows significant elevation (P ≤ 0.05) in SOD compared with control group, adenine and 10% tomato groups.The treatment with 10% tomato leads to elevated but don't reach to the result shown in tomato powder 20%. GST (Glutathione S- transferase) concentration: Adenine group shows significant decrease (P ≤ 0.05) in GST comparison with control group. The adenine + 20% tomato lead to elevat the value of GST compare with the treated group tomato 10%, adenine and control. Tomato 10% significantly increases (P ≤ 0.05) the level of GST compare with adenine and control groups (Table 2).

Table 2: Effect of adenine alone and in combination with tomato powder(10% and 20%) on some antioxidant parameters in male rats

Z	SOD ng/ml	GST ng/ml
Control	6.44 ± 0.38 C	13.30 ± 0.43 C
Adenine	4.76 ± 0.42 D	11.98 ± 0.47 D
Adenine+Tomoto10%	10.51 ±0.72 B	20.16± 0.83 B
Adenine+Tomato20%	15.75 ± 0.81 A	22.98 ± 0.76 A

-Values = Mean ± SE
-Different letters represent significant (P ≤ 0.05) differences between groups
-Number of rats in each group = 6

Discussion

AST and ALT are two enzymes of the most reliable markers of hepatocellular injury or necrosis. Their levels are elevated in a variety of hepatic disorders. Of the two, ALT is thought to be more specific for hepatic injury because it is present mainly in liver cytosole and in low concentration elsewhere (Giboney, 2005). The results revealed significant elevation (P ≤ 0.05) in AST and ALT activities, in male rats treated by adenine (50 mg/kg/BW) intraperitoneally compare with control group table 1. These results were matched with results obtained by (Al Za'abi *et al.*, 2015) who induced CRD in rats.

In the group treated with tomato powder at 10% and 20% dosage, the concentration of AST and ALT is significantly lower than in adenine groups and the current finding is consistent (entirely, 2016). There is good evidence (Eze et al., 2016) that lycopene (main component of tomato in higher doses provided for (4 weeks) is capable of lowering serum ALT and AST, Baymaroglu et al. (2013) published similar findings. Superoxide dismutase (SOD) is the cell's first detoxification enzyme and the most effective antioxidant. It is regarded as an essential endogenous antioxidant enzyme that serves as the first line of protection in the system against reactive oxygen species (ROS) (Dringen et al., 2005; Kaur and Chugh, 2021). Concentration of SOD and GST in plasma is significantly decreased (P≤ 0.05) in adenine group in comparison to control group as shown in table 2.

Adenine and its metabolite, 2,8-dihydroxyadenine (DHA), have low solubility (Nasir *et al.*, 2012). The increase in the oxidative derivative of deoxyguanosine, 8-OHdG, which is one of the major DNA oxidative products, in the adenine treated groups, It also indicates oxidative stress inside the cells. These oxidative biomarkers on time ,as told before previously, can have potential systemic toxicity leading to damage of some other organs such as liver and heart (Lacour *et al.*, 2005 and Imarah, 2017).

Superoxide (O2.-), singlet oxygen (1O2), peroxyl radical (ROO.), nitric oxide (NO.), hydrogen peroxide (H2O2), and dimethylarsinic peroxyl radicals [(CH3)2AsOO.] are among the ROS generated (Elvira-Torales et al., 2019; Abdullah A. Mohammed et al., 2020), Such compounds can, by binding to their sulfhydryl (–SH) groups, inhibit antioxidants, in particular GSH-driven enzymes such as glutathione-S-transferases (GSTs), glutathione peroxidase (GSH-Px), and GSH reductase (**Alaa Hashim Alqatab, Ayyed Hameed Hassan** 2019; Hasanuzzaman et al., 2020).

Toxic elements trigger a rise in lipid peroxidation (Przybylska S 2020) and a substantial decrease in tissue SOD activity (Yu L et al., 2017), so adenine, as a toxic agent, could cause the same case. As a result of this research, it was discovered that there was a rise in SOD and GST concentration in the treatment group at doses of 10% and 20% tomato powder by diet when opposed to the control group, as seen in table 2. This study agrees with Moreira et al., (2005) and Kulczyski et al., (2005) studies (2017).

Lycopene enhances GSH, which plays an essential role in the preservation of the high levels of GSH-Px and GST operations, as seen by Imran M et al. (2020). The effects on lycopene contribute to oxidative stress prevention and an improvement in anti-oxidant body potential, maintaining the cell membrane's permeability (Yilmaz et al., 2018). The effects do not only minimize oxidation of DNA in significant proportions, they can also avoid the LPO mechanism (lipid peroxidation) (Yilmaz *et al.*, 2006; Nowfel AJ and Al-Okaily BN 2017).

Histopathological study of liver

Liver tissue from the control groups (figure 1) stained with (H&E) shows normal parenchymal tissue with no

lobular inflammation and portal areas show either no inflammatory infiltrates. The liver tissue treated with adenine shows infiltration of the liver tissue with inflammatory cells (lobular inflammation), The portal areas show mild to moderate round cell inflammatory infiltrate (Figure 2). Histopathological sections in groups that induced liver damage (treated with tomato powder) 10% and 20% (figure 3 and 4). It has shown normal architecture of center vein, normal hepatocyte surrounded the central vein but in the group of tomato powder.

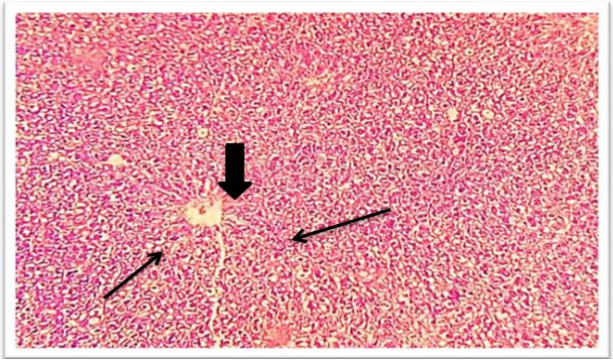

Figure 1: Liver in male rats of control group shows normal central vein (thick arrow) and normal hepatocytes (thin arrow) arranged in an irradiation manner.(Stain H&E).(X10).

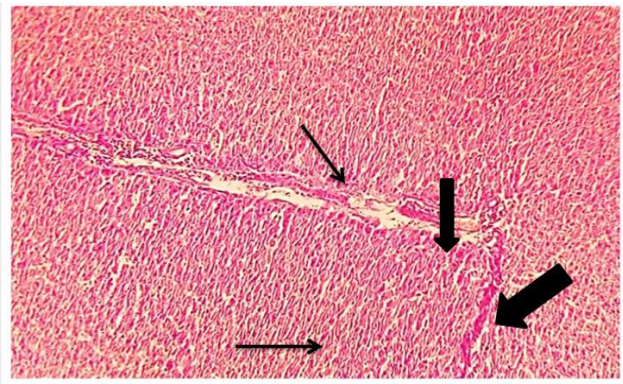

Figure 2: Liver in male rats treated with adenine shows infiltration of inflammatory cells in bile canculai hemorrhage and congestion (thick arrow), shows coagulated degeneration of hepatocyte loss irradiation architecture(thin arrow).(stain H&E).(X10).

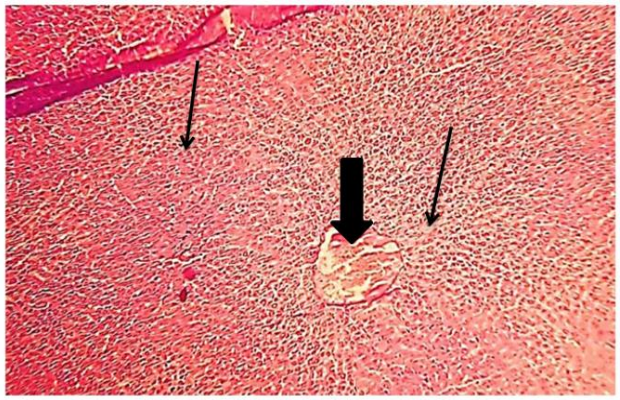

Figure 3: Liver in male rats. Treated with adenine and tomato powder 10%. Shows central vein still enlargement and hemorrhage (thick arrow). The improvement in hepatocyte surrounded the central vein hasn't reached that of 20% (thin arrow).(Stain H&E).(X10).

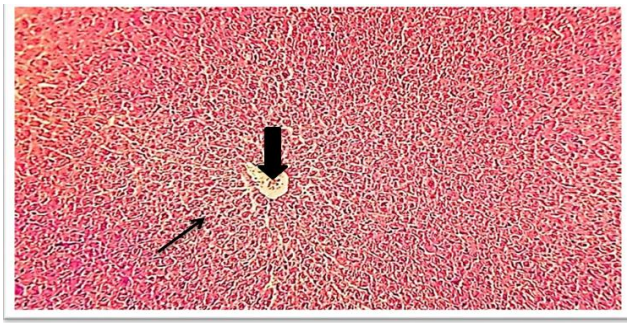

Figure 4: Liver in male rats injected adenine and tomato powder 20%. Shows normal architecture of center vein (thick arrow), normal hepatocyte surrounded the central vein (thin arrow). (Stain H & E). (X10).

Histopathological section from liver of rats treated by adenine which is stained by (H and E stain) infiltration of the liver tissue with inflammatory cells (lobular inflammation), The portal areasshow mild to moderate round cell inflammatory infiltrates (Figure 2) comparison to the control group that show normal architecture andhistology (figure 1).This probably indicates some tissue damage in the liver in adenine treated rats, which is at variance severity with results obtained by (Feere *et al.*, 2015). In addition, our hepatichistology showed inflammatory infiltration of the portal and hepatic area suggesting some degree of tissue damage. However, we are not certain whether the degree and the extent of this damage explain the discrepancy in our results agreement with (Feere *et al.*, 2015). This change in liver may be due to indirectly chronic renal failure or directly by toxic effect of adenine on hepatic cell, Our finding is support by elevation in the activity of liver enzyme as mention in table 1.

The effect of tomato content 10% and 20% on group was effect antioxidant by prevented the chemical-induced changes in antioxidant enzyme activities and this agree with (Koul *et al.*, 2010; Yu L et al., 2017), they proved changes inantioxidant enzyme activities, Malondialdehyde levels (MDA), and liver marker enzymes.

Conclusions

From our previous data we conclude that: Induced oxidative damage to liver by adenine lead to disorder in liver function test (ALT and AST) and cause harmful defect in liver. Tomato powder caused enhancement in antioxidant enzymes, liver function test and histological section of liver. The tomato powder contributed the improvement of these parameters especially in dose 20%.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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