Effect of lycopene supplementation on lipid profile, blood glucose and electrolyte homeostasis in thioacetamide induced liver cirrhosis

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Abstract: Lycopene is a fat-soluble carotenoid pigment that gives tomatoes their red color and capacity for scavenging free radicals. The current study was designed to evaluate the effect of lycopenesupplementation on blood glucose, lipid profile and electrolyte homeostasis in thioacetamide induced liver cirrhosis. Experimental period was consisted of 12 weeks, divided into two phases (each of six weeks). For this purpose 24 male albino wistar rats were randomly distributed into four groups (n=6). Group I served as control, Group II received thioacetamide (200mg/kg b.w, i.p, twice a week) in the first phase and then saline in the second phase. Group III received thioacetamidein the first phase and lycopene in the second phase. Group IV received saline in the first phase and lycopene in the second phase. Thioacetamide toxicity was evidenced by decrease in body weight, plasma glucose and HDL level, plasma and intra-erythrocyte sodium and potassium and increase in liver weight, HDL level, plasma and intra-erythrocyte sodium and potassium and cholesterol, triglyceride, LDL and plasma glucose level. Thus, confirms the protective role of lycopene in thioacetamide induced liver cirrhosis.

Keywords: Thioacetamide, lycopene, lipid profile, blood glucose, electrolytes.

INTRODUCTION

Lycopene is a natural pigment synthesized by plants and microorganisms but not by animals. It is a carotenoid, an acyclic isomer of b-carotene and has no vitamin A activity (Sonia *et al.*, 2021). It is a highly unsaturated, straight chain hydrocarbon containing 11 conjugated and two non-conjugated double bonds. Recent interest in lycopene has focused on its antioxidant properties. However, other mechanisms such as modulation of intercellular gap junction communication, hormonal and immune system and metabolic pathways are also beginning to be investigated (Edward *et al.*, 2022).

As a polyene it undergoes cis-trans isomerization induced by light, thermal energy or chemical reactions. Lycopene from natural plant sources exists predominantly in trans configuration, the most thermodynamically stable form. In human plasma, lycopene is an isomeric mixture containing 50% of the total lycopene as cis isomers. All trans, 5-cis, 9-cis, 13-cis and 15-cis are most commonly identified isomeric forms of lycopene (Jessica et al., 2015). The biological significance of these isomers of lycopene is unclear. Lycopene, ingested in its natural trans form found in tomatoes, is poorly absorbed. Recent studies have shown that heat processing of tomatoes and tomato products induces isomerization of lycopene to the cis form which in turn increases its bioavailability. However, there is some indication that isomerization reactions may be taking place in the body. High concentration of cis isomers were also observed in human

serum and prostate tissue, suggesting that tissue isomerases might be involved in *in vivo* isomerization of lycopene from all trans to cis form (Masaki *et al.*, 2019).

It is found in several fruits and vegetables such as watermelon, guava, apricots and papaya, but the major sources of lycopene are tomatoes and tomato products in developed and developing countries in varying different forms (Muhammad et al., 2020). The decrease in chronic diseases like cardiovascular diseases and cancer have been associated with the dietary intake of lycopene. Lycopene is an antioxidant known to provide protection against cellular damage caused by reactive oxygen species (Lenoreand Susan, 2000). It is one of the most potent antioxidants among the dietary carotenoids. It is readily absorbed from different food sources, distributes different tissues and maintains its antioxidant to properties in the body. Although the antioxidant properties of lycopene are thought to be primarily responsible for its beneficial properties, evidences are accumulating to suggest that other mechanisms such as modulation of intercellular gap junction communication, hormonal & immune systems and metabolic pathway may also be involved. It is suggested to have anti-cellproliferative, anticarcinogenic and antiatherogenic activities. Epidemiological and a small number of animal and experimental studies have provided evidence in support for its protective role in heart disease and cancer. Thioacetamide is an organosulfer compound (C₂H₅NS). It can enter in human body through the inhalation and dermal contact. When contact with eye or skin it may cause serious irritation. Repeated or many time exposures

to this chemical may cause liver damage, or hepatotoxicity and the severe condition may cause death of person. It is a popular model toxicant because of its outstanding solubility in the water, a prolonged injury and recovery pattern (up to 120 h) giving significant time to study mechanisms and a broad range of use from a single dose-induced acute liver injury, subchronic exposure leading to liver fibrosis and chronic exposure resulting in liver cancer (Arnon *et al.*, 2005).

The final damage form of liver injury due to various factors involved, known as cirrhosis. Various researches have reported the intake through diet as a supplementation of medium or long poly unsaturated fatty-acids reduce liver cirrhosis. Therefore, the proposed study was designed to evaluate the effects of lycopene supplementation on lipid profile, blood glucose and electrolyte homeostasis in thioacetamide induced liver cirrhosis.

MATERIALS AND METHODS

Experimental design

Twenty four Albino Wistar rats weighing 200-250gm were purchased from DOW University of Health Sciences, Karachi. Animals were acclimatized to the laboratory conditions before the start of experiment and caged in a quite temperature controlled animal room $(23+4^{\circ}C)$.

The experiments were conducted with ethical guidelines of internationally accepted principles for laboratory use and care in animal research (health research extension act of 1985). The experimental work and biochemical estimations were carried out in animal house and clinical biochemistry and hematology research lab of Biochemistry Department, Federal Urdu University, Karachi (ERC No.2003).

Tomatoes were used as a lycopene source and were purchased from local market of Karachi and identified. Thioacetamide and other chemicals used in this study were purchased from Sigma Aldrich and Merck.

- Group I: Control group and remained untreated
- Group II: Received thioacetamide (at a dose of 200mg/ kg body weight, i.p, twice a week, for 6 weeks).
- Group III: Received thioacetamide (at a dose of 200mg/kg b.w, i.p, twice a week, for 6 weeks) and received tomato juice (orally, daily, at a dose of 200 mg/kg b.w) for next 6 weeks.
- Group IV: Received tomato juice orally (for 6 weeks daily).

In phase I, group I and group IV remained untreated throughout the experimental phase and were weighed every week, group II and group III received thioacetamide, for 6 weeks. In phase II, group III and group IV received tomato extract after six weeks of phase I, for 6 weeks and group I and group II received saline during this phase. After 24 hours of last dose of treated groups, rats were decapitated and the blood was collected from the neck wound in the heparin coated tubes. The collected blood was mixed gently and then transferred to centrifuge at 2000 rpm for 20 minutes. Plasma was separated, collected and stored at -70°C until analysis.

Assessment of plasma glucose and lipid profile

Plasma Glucose and lipid profile were estimated by using commercially available Merck Kits and MicroLab, 300 semi auto biochemistry analyzer.

Estimation of plasma sodium and potassium

Plasma was diluted 1:100 with 0.1N HCl and was used for simultaneous determination of sodium and potassium. The emission intensities of standards and samples were recorded against the respective blank solutions. The emission intensities of sodium and potassium were recorded at 589 and 768nm respectively on flame photometer, PFP7 (Jenway, UK).

Erythrocyte membrane preparation

The packed red cells extracted by centrifugation at 4°C, 450g for 15 minutes were resuspended and diluted in 25 volumes of 0.011 mol/L Tris-HCl buffer at p H 7.4. The hemolyzed cells were then centrifuged for 30 min at 12,000 rpm at 4°C and the membrane pellet was resuspended in 30 ml of 0.01l mol/L Tris-HCl buffer. This centrifugation step was repeated three times. The final concentration of the membrane suspension was \sim 4mg protein/ml of Tris buffer. The membrane suspension was stored at -70°C until the assay was performed.

Estimation of intraerythrocyte sodium and potassium

Heparinized blood was centrifuged and plasma was separated. Buffy coat was aspirated and discarded. Erythrocytes were washed three times at room temperature by suspension in the magnesium chloride solution (112mmol/L), centrifugation at 450g at 4°C for 5 minutes and aspiration of the supernatant as described earlier (Fortes and Starkey, 1977). Final supernatant was retained for the estimation of intraerythrocyte sodium and potassium concentration. Neither electrolyte was detectable in the final wash. Washed erythrocytes were then used for the estimation of intraerythrocytes sodium and potassium.

STATISTICAL ANALYSIS

Results are presented as mean \pm standard deviation (S.D). Significant differences among control, TAA-treated, TAA+lycopene treated and lycopene treated rats, values evaluated by one way ANOVA using SPSS (Version 22). Statistical probability of *P<0.05 were considered to be significant.

RESULTS

Effect of thioacetamide and lycopene administration on body weight of treated groups compared with normal control

Significant decrease in the body weight was observed in TAA treated Group $(170.7\pm11, P<0.05)$ as compared to control whereas increase in body weight was observed in TAA + lycopene treated group as compared to TAA treated group $(182.2\pm3.4, P<0.05)$. Increase in the body weight was observed in lycopene treated group $(201.3\pm3.9, P<0.05)$ as compared to control group (table 1).

Effect of thioacetamide and lycopene administration on liver weights of treated groups compared with normal control

Thioacetamide treatment significantly Increased the liver weights of TAA treated rats (6.8 ± 0.4 , P<0.05) as compared to control, TAA + lycopene treated rats showed the increase in liver weights (6.9 ± 1.0 , P<0.05) as compared to TAA treated group whereas increased in the liver weights were observed in lycopene treated rats (6.6 ± 0.7 , P<0.05) as compared to control (table 1).

Effect of thioacetamide and lycopene administration on blood glucose level of treated groups compared with normal control

Decreased level of plasma glucose was shown by TAA treated rats (78 \pm 21.70, P<0.05) as compared to control. Lycopene administration resulted in increased level of plasma glucose in TAA + lycopene treated group (88 \pm 21.70) as compared to TAA treated group as well as in lycopene treated group (118.8 \pm 27, P<0.05) too as compared to control group (table 2).

Effect of thioacetamide and lycopene administration on total cholesterol of treated groups compared with normal control

Increased level of total cholesterol was shown by TAA treated group (95.4 \pm 16.73, P<0.05) as compared to control group. Marked reduction in total cholesterol was found in TAA + lycopene treated group (71.6 \pm 8.54) as compared to TAA group. Alone lycopene administration resulted in increased level of total cholesterol (58.4 \pm 28.03) as compared to control group (table 2).

Effect of thioacetamide and lycopene administration on triglyceride level of treated groups compared with normal control

Increased level of triglyceride was shown by TAA treated group (78.2 \pm 25.44, P<0.05) as compared to control. The TAA + lycopene administration showed significant decrease in triglyceride concentration (71.6 \pm 8.54) as compared to TAA treated group, whereas lycopene supplementation showed decreased in triglyceride concentration in lycopene treated group (38.8 \pm 14.42, P<0.05) as compared to control (table 2).

Effect of thioacetamide and lycopene administration on LDL level of treated groups compared with normal control

Increased level of LDL was shown by TAA treated group $(66.78\pm10.40, P<0.05)$ as compared to control. The TAA + lycopene administration showed decrease in LDL concentration (50.12±6.68) as compared to TAA group, whereas lycopene supplementation showed decreased in LDL concentration in lycopene treated group (37.66±13.10, P<0.05) as compared to control (table 2).

Effect of thioacetamide and lycopene administration on HDL level of treated groups compared with normal control

Decreased level of HDL was shown by TAA treated group $(16.14\pm5.61, P<0.05)$ as compared to control group. Significant increased HDL level was found in TAA + lycopene treated group $(21.48\pm2.68, P<0.05)$ as compared to TAA treated group and in lycopene treated group $(24.52\pm12.79, P<0.05)$ as compared to control group(table 2).

Effect of thioactamide and lycopene administration on plasma electrolyte concentration of treated groups compared with normal control

The concentration of plasma Na⁺ was found decreased in TAA treated group (103 ± 8.5 , P<0.05) as compared to control group whereas it was increased in TAA + lycopene treated group (110 ± 18.0 , P<0.05) as compared to TAA treated group. Concentration of plasma Na⁺was found decreased in lycopene treated group (116 ± 34.0 , P<0.05) as compared to control group (table 3).

Effect of thioactamide and lycopene administration on plasma potassium concentration of treated groups compared with normal control

The concentration of plasma K⁺ was found decreased in TAA treated group $(3.9\pm1.0, P<0.05)$ as compared to control group whereas a marked increase was found in plasma K⁺ concentration in TAA + lycopene treated group $(4.6\pm2.4, P<0.05)$ as compared to TAA treated group. Lycopene treated group showed reduced plasma potassium concentration $(4.8\pm2.3, P<0.05)$ as compared to control $(6.6\pm0.7, P<0.05)$ group (table 3).

Effect of thioacetamide and lycopene administration on intracellular sodium in treated groups compared with normal control

Table 3 shows that the concentration of intracellular Na⁺ is decreased in thioacetamide (TAA) treated group ($3.15\pm0.4 \text{ p}<0.05$) as compared to control whereas the concentration of intracellular Na⁺ is increased in thioacetamide + lycopene treated group ($3.8\pm0.8 \text{ p}<0.05$) as compared to TAA treated group. Concentration of intracellular Na⁺ is decreased in lycopene treated group ($3.5\pm0.4 \text{ p}<0.05$) as compared to control ($4.6\pm0.5 \text{ p}<0.05$).

Table 1: Effect of thioacetamide and lycopene administration on body weight and liver weight of treated groups compared with normal control

Parameters	Control	Thioacetamide treated	Thioacetamide + Lycopene treated	Lycopene treated
Body Weight	191.1 ± 13	$170.7 \pm 11*$	$182.2 \pm .3.4*$	$201.3 \pm 3.9*$
Liver Weight	6.5 ± 0.7	$6.8 \pm 0.4*$	$6.9 \pm 1.0*$	$6.6 \pm 0.78*$

Table 2: Effect of thioacetamide and lycopene administration on plasma glucose and lipid profile of treated groupscompared with normal control.

Parametersmg/dL	Control	Thioacetamide treated	Thioacetamide + Lycopene	Lycopene treated
Plasma Glucose	93.2±25.49	78±21.70*	88±21.70*	118.8±27.86*
Total cholesterol	53.8±12.44	95.4±16.73*	71.6±8.54*	58.4±28.03*
Triglyceride	45.4±13.33	78.2±25.44*	53±18.81*	38.8±14.42*
LDL	40.88±21.88	66.78±10.40*	50.12±6.68*	37.66±13.10*
HDL	17.52 ± 9.40	16.14±5.61*	21.48±2.68*	24.52±12.79*

Values are mean \pm standard deviation. Significant difference among control, TAA treated, TAA + lycopene and lycopene treated group by one-way ANOVA *P<0.05.

Table 3: Effect of thioacetamide and lycopene administration on plasma electrolyte homeostasis in treated groups compared with normal control

Parameters(mmol/L)	Control	TAA treated	TAA + Lycopenetreated	Lycopene treated
Plasma Sodium	125 ± 9.8	$103 \pm 8.5*$	$110 \pm 18*$	$116 \pm 34^*$
Plasma Potassium	6.6 ± 0.7	$3.9 \pm 1.0*$	$4.6 \pm 2.4*$	$4.8 \pm 2.3*$
Intracellular sodium	4.6 ± 0.5	$3.15 \pm 0.4*$	$3.8 \pm 0.8*$	$3.5 \pm 0.4*$
Intracellular Potassium	109 ± 20.3	$74 \pm 22.1*$	$82 \pm 32.4*$	$94 \pm 18.1*$

Values are mean \pm S.D. significant difference among control, TAA-treated, TAA-lycopene and lycopene treated group by one-way ANOVA *P<0.05.

Effect of thioacetamide and lycopene administration on intracellular potassium in treated groups compared with normal control

Table 3 shows that the concentration of Intracellular K⁺ is decreased in thioacetamide (TAA) treated group (74±22.1 p<0.05) as compared to control whereas the concentration of Intracellular K⁺ is also decreased in thioacetamide + lycopene treated group (82±32.4 p<0.05). Concentration of Intracellular K⁺ is decreased in lycopene treated group (94±18.1 p<0.05) as compared to control (109±20.3 p<0.05) but increased as compared to TAA treated group.

DISCUSSION

Liver functions as an endogenous metabolism center for nutrients, such as carbohydrates, proteins and lipids and also participates in disposal of waste metabolites. The organ also handles the metabolization or excretion of exogenous drugs and other xenobiotics. In this regard, liver plays a major role in protecting and detoxifying the body from foreign substances (Svetlana *et al.*, 2023). Thioacetamide was selected for experiment because it causes liver Cirrhosis that histologically similar to human liver cirrhosis (Li *et al*, 2002). In addition, thioacetamide administration either orally, intraperitoneally or both are organized methods in the development of fibrosis and cirrhosis pattern in rats (Zhen *et al*, 2020). Following results may be assigned to the effects of thioacetamide which can cause hepatocyte damage and renal damage through biotransformation of the thioacetamide to thioacetamide sulfone and sulphene via cytochrome P-450 (Okuyama *et al.*, 2003).

In the present study, the prolonged administration of TAA to the rats caused visual and quantifiable responses, which were recognizable by the alterations in the body and liver weights and levels of serum molecular markers. All these indications were of cirrhosis and supported the past reports that TAA contributes to the development of cirrhosis through multiple mechanisms of action, like the oxidation of its metabolic products, oxidative stress and decreased antioxidant defenses and lipid peroxidation. According to the results (table 1), the resultant body weight of intoxicated rats with thioacetamide was consequently reduced than that of the healthy normal rats. These results majorly showed that thioacetamide causes consequent decrease in the gain of body weight. During the six-week-long study, the hepatotoxic rats lacked in gaining body weight as compared with the controls. Using the same experimental model of cirrhosis, the previous studies reported the same and attributed this outcome to the lower levels of nutrient absorption, energy utilization and metabolic efficiency as the major factors affecting the inability of the rats to gain weight after being exposed to

TAA (Alshawsh, 2011). Factoring the reduced body weight into the calculation yielded significantly high ratios of liver weight. Table 2 revealed the effects of thioacetamide on liver weight that resulted in increase in the liver weight of thioacetamide treated rats due to the development of liver cirrhosis. These findings are in agreement with other reports (Suzan and Abdou, 2015). The hepatocyte proliferation is a critical determinant for the survival of liver from an injury. Based on this, the up regulation of the hepatocyte activity in response to the exposure to TAA toxicity is likely to be the cause of the recorded increase in the liver weight.

The other results showed the significant increase in cholesterol, triglycerides and LDL while decrease in HDL and glucose level in thioacetamide treated rats as compared to control (table 2). The glucose concentration in blood is dependent on the potentiality of the liver to absorb or produce glucose, the liver performs this function due to its ability to form glycogen (Sameh *et al.*, 2014). According to Kruszynska, in severe liver failure blood glucose level decrease in cirrhotic patients (Tsung *et al.*, 2021). The mechanism by which lycopene administration has this partial preventive effect is unknown. Increased free radical levels impair insulin action and glucose disposal in the peripheral tissues (Ceriello and Motz, 2004).

The treatment of rats with toxic thioacetamide causes the increase in plasma lipid contents. Following result is in accordance with that of (Marwan et al., 2022). Cellular biomolecules like lipids are denatured by the highly reactive metabolites of thioacetamide which results in increased concentration of thiobarbituric acid reactive substances (TBARS) that indicates lipid peroxidation (Wang et al., 2004). The results obtained from present study (table 2) also showed, the administration of lycopene causes the decrease in plasma lipid content i.e. total cholesterol, triglycerides and LDL but increase HDL when compared with thioacetamide treated rats, the decrease in plasma lipid content may be because of the inhibition of enzyme that plays key role in cholesterol synthesis known as 3-hydroxy-3-methyl glutaryl co enzyme A (HMG-CoA) reductase and also by the increased degradation of LDL (Sesso and Gaziame, 2003).

Table 3 showed the decrease in plasma and intracellular sodium and potassium of treated groups as compared to control. The mechanism that involved in lipid peroxidation not only generates oxygen free radicals or reactive oxygen species (ROS) but it also involves in the decrease of intracellular free radicals scavengers by the alteration of antioxidant defense system (Abul and Dashti, 2002). The chronic exposure to Thioacetamide also decreased the plasma sodium and potassium concentration. According to (Mates *et al.*, 1999), DNA can be damaged by lipid peroxidation products which results in the inhibition of protein synthesis as well as inhibition of Na^+/K^+ ATPase. The study is related to decrease in Na^+ and K^+ concentration in plasma (table 3). The changes in Na^+ and K^+ with damage to cell membrane causes the problem in Na^+/K^+ ATPase pump and cell membrane disorder. The results of lycopene treated rats showed improve plasma Na^+ and K^+ contents as the lycopene provides the stability to cell mechanism. The chemical structure of lycopene consisting of polyene chain that contain 11 conjugated double bonds. The polyene chain of lycopene has an important radical scavenging properties (Sirag, 2007).

Rao and Agarwal observed that, dietary supplementation of lycopene from traditional tomato products increased lycopene concentration in plasma and reduced oxidative damage to lipids and proteins. The importance of lycopene may be mainly attributed to its effective antioxidant capability against hydroxyl radical. He concluded that, lycopene is effective in scavenging reactive oxygen species (ROS) as superoxide anion, hydroxyl radical, singlet oxygen and lipid free radicals (Ruth and George *et al.*, 2021).

CONCLUSION

In conclusion, the present data indicated that, thioacetamide-induced hepatotoxicity might be related to oxidative damage. Tomato juice has been proven effective in counter activity and ameliorating some of the biomarkers indicative of toxicity. Further studies could be carried out to study the mechanism through which lycopene attenuates thioacetamide induced toxicity.

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