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Protective role of lycopene on blood haematology parameters in liver cirrhosis: Study in rats

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Abstract: The present study was designed to evaluate the effect of lycopene supplementation on blood haematology parameters in thioacetamide induced liver cirrhosis. Experimental period consisted of 12 weeks, divided into two phases. For this purpose 24 male albino wistar rats were randomly distributed into four groups (n=6). Group I served as control or untreated group, Group II received thioacetamide (200mg/kg b.w, i.p, twice a week) for 6 weeks in the first phase and then saline in the second phase (for next six weeks). Group III received thioacetamide (200mg/kg b.w) in the first phase and lycopene (200 mg/kg b.w) in the second phase. Group IV received saline in the first phase and lycopene in the second phase. Biochemical evaluation was carried out by estimation of blood haematology parameters. Six weeks thioacetamide induction resulted in decreased levels of red blood cells, procalcitonin, P-LCR, Platelets, lymphocytes, MCH, MCHC, Hct and MPV whereas significant increased levels of white blood cells, MID, Granulocytes, MCV, RDW% and PDW% were found. Lycopene supplementation restored these altered values in the thioacetamide +lycopene treated group. Thus, confirms the protective effects of lycopene on blood haematology parameters in liver cirrhosis.

Keywords: Blood haematology parameters, lycopene, thioacetamide, liver cirrhosis.

INTRODUCTION

Cirrhosis is described as the histological growth of rebirth nodules bordered by fibrous bands with response to chronic liver injury. The strongly developed stage of the liver fibrosis is actually cirrhosis that occurs with the destruction of the hepatic vasculature. The space of Disse becomes full with scar tissue and endothelial sequences are misplaced in cirrhotic condition (Schaffner & Popper, 1963). Animal models of liver fibrosis and cirrhosis may be developed by a number of toxins and chemical agents. In the liver, these agents induce direct harm to liver cells and generate secondary inflammatory reactions then lead towards the activation of hepatic stellate cells. These agents generally include CCl_4 (Zhang *et al*., 2009), thioacetamide (Karantonis *et al*., 2010), dioxin (Pierre *et al*., 2014), sodium arsenate (Wu *et al*., 2009) and ethanol (Tan *et al*., 2013). Intake of these chemicals for a long period showed an outer appearance of cirrhosis and this appearance characterized due to various macro liver nodules, hepatocarcinoma, cholangiomas and cell adenomas.

TAA was used only to produce cirrhosis and fibrosis (Kornek *et al*., 2006). Previous researches showed the centrilobular necrosis caused by thioacetamide, activated by the flavin-containing monooxygenase systems of sulfene and sulfine metabolism substance and also activated by the cytochrome P450 (CYP450) (Hunter *et al*., 1977; Porter *et al*., 1979). Wang *et al*. (2000b) reported that the bioactivation of thioacetamide was mainly mediated by hepatic CYP2E1.

Lycopene gained more attention for its health-giving properties, acts as potential antioxidant in a number of food sources, exhibits the properties of protection, cell repairing, and protects tissues against the damaging effect of free radicals (Guns *et al*., 2003). Tomatoes havea sufficient quantity of lycopene, serve as scavenging of free radicals and also defend the cell from oxidative stress. Kattab also reported attenuation of hepatotoxicity through lycopene supplementation (Kattab *et al*., 2003).

MATERIALS AND METHODS

Twenty fours male albino wistar rats (200-250grams body weight) were purchased from the animal house of the Aga Khan University Hospital Karachi, Pakistan. Thioacetamide was purchased from Sigma Aldrich and tomatoes for lycopene extraction were bought from the local market.

Study protocol and drug administration schedule

24 Male Albino Wistar rats were randomly distributed into four groups, each of six rats. The duration of study was 12 weeks and divided into two phases. Each group received following treatment:

Group I: The control (remained untreated)
Group II: Thioacetamide-treated
Group III: Thioacetamide + Lycopene treated
Group IV: Lycopene treated

In phase I, group I and group IV remained untreated throughout the experimental phase and were weighed

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every week, group II and group III received thioacetamide (which was dissolved in 0.9% NaCl) intraperitoneally at a dosage of 200mg/kg body weight, twice a week, for 6 weeks. In phase II, group III and group IV received tomato extract after six weeks of phase 1, (daily, orally at a dosage of 200 mg/kg b.w) for 6 weeks and group I and group II received saline during this phase. At the end of the experimental period, rats were decapitated and the whole blood was collected for blood haematology parameters.

Assessment of haematological parameters

Complete blood counts were performed on the samples of whole blood of control and treated animals, using an automated Hematology analyzer-Medonic M32M (Japan). This analyzer consistently differentiates normal Red blood cells (RBCs), white blood cells (WBCs), Hemoglobin (HGB), Mean corpuscular volume (MCV), Platelets (plts) etc from abnormal populations, thereby decreasing the chances of error.

Ethical approval

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 haematology research lab of biochemistry department, Federal Urdu University, Karachi (Certificate reference number, 2003).

STATISTICAL ANALYSIS

Results are presented as mean± standard deviation (S.D). Significant differences among control, TAA-treated, TAA-treated + lycopene treated and lycopene treated rats, values evaluated by one way ANOVA using SPSS (Version 22). Statistical probability of **P<0.01, *P<0.05 were considered to be significant.

RESULTS

Effect of thioacetamide and lycopene treatment on body weight in treated groups

A significant reduction in body weights were found in thioacetamide (TAA) treated group (170.7±11, p<0.05) as compare to control (191.1±13, p<0.05), whereas increased body weights were found in thioacetamide + lycopene treated group (182.2±3.4, p<0.05) and alone lycopene treated group (201.3±3.9, p<0.05) as compare to TAA treated group (170.7±11, p<0.05) and control group (191.1±13, p<0.05) respectively (table 1, fig. 1).

Effect of thioacetamide and lycopene treatment on liver weights in treated groups

Twelve weeks induction of thioacetamide was resulted in increased liver weights in TAA treated group (6.8±0.4*) as compare to control group (6.5±0.7*) whereas supplementation of lycopene in second phase resulted in a significant reduction in liver weights in TAA+lycopene treated group (6.7±1.0*) as compared to the TAA treated group. Lycopene treated group also showed increased liver weights (6.6±0.7*) as compared to the control group (table 1, fig. 2).

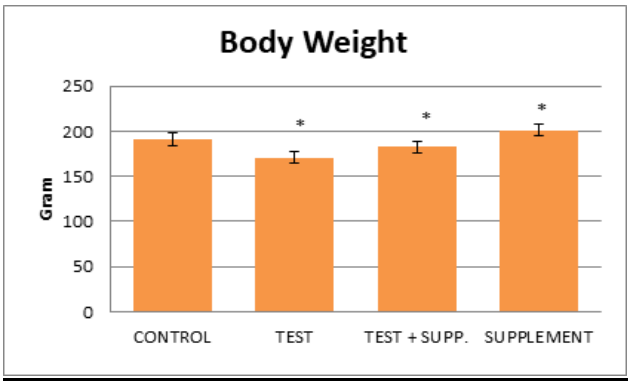

Fig. 1: Effect of thioacetamide and lycopene treatment on body weight in treated groups.

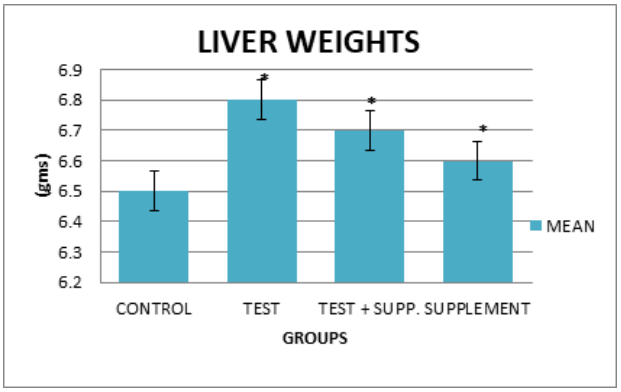

Fig. 2: Effect of thioacetamide and lycopene treatment on liver weights in treated groups.

Effect of thioacetamide and lycopene treatment on white blood cells in treated groups

The concentration of white blood cells was significantly increased in thioacetamide (TAA) treated group (12.0±4.2, p<0.01) as compare to control group (7.3±1.8, p<0.01) whereas the lycopene supplementation in second phase resulted in decreased white blood cells concentration in thioacetamide + lycopene treated group (10.9±2.4, p<0.01) as compare to TAA treated group. Concentration of white blood cells was also found decreased in the lycopene treated group (8.1±2.1, p<0.01) as compared to the control group (table 2, fig. 3).

Effect of thioacetamide and lycopene treatment on haemoglobin in treated groups

Table 2 fig. 4 showed the decreased concentration of haemoglobin in thioacetamide (TAA) treated group

(10.1±1.6, p<0.01) as compare to control group (12.7±1.2, p<0.01) whereas after lycopene supplementation, the concentration of haemoglobin is increased in thioacetamide + lycopene treated group (11.6±1.8, p<0.01) as compare to TAA treated group (10.1±1.6, p<0.01). Concentration of haemoglobin is increased in the lycopene treated group (13.7±3.0, p<0.01) as compared to control group (12.7±1.2, p<0.01).

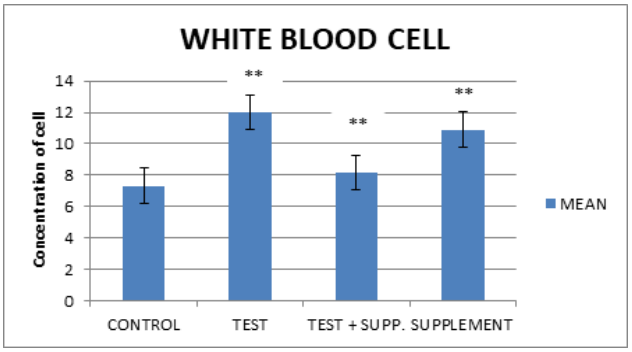

Fig. 3: Effect of Thioacetamide and lycopene treatment on White Blood Cell in treated groups.

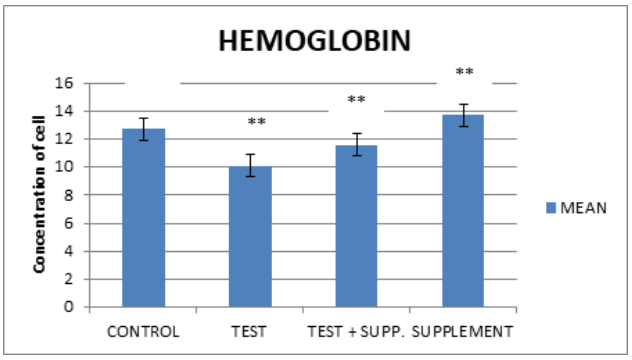

Fig. 4: Effect of thioacetamide and lycopene treatment on haemoglobin level in treated groups.

Effect of thioacetamide and lycopene treatment on Red Blood Cells in treated groups

The concentration of red blood cells (RBCs) was markedly decreased in thioacetamide (TAA) treated group (5.0±0.8, p<0.01) as compare to control group (6.3±0.1, p<0.01) whereas the concentration of red blood cells was increased in thioacetamide + lycopene treated group (5.9±0.9, p<0.01) as compare to TAA treated group (5.0±0.8, p<0.01). Concentration of red blood cells was increased in lycopene treated groups (6.8±0.09, p<0.01) as compared to control (6.3±0.1, p<0.01) (fig. 5).

Effect of thioacetamide and lycopene treatment on Procalcitonin in treated groups

The concentration of Procalcitoninwas slightly decreased in thioacetamide (TAA) treated group (0.37±0.03, p<0.01) as compare to control (0.38±0.07, p<0.01) whereas the concentration of procalcitonin was markedly reduced after supplementation of lycopene in thioacetamide + lycopene treated group (0.35±0.08, p<0.01) as compare to TAA treated group (0.37±0.03, p<0.01). Concentration of Procalcitoninwas also found low in lycopene treated groups (0.33±0.07, p<0.01) as compared to control (0.38±0.07, p<0.01) (fig. 6).

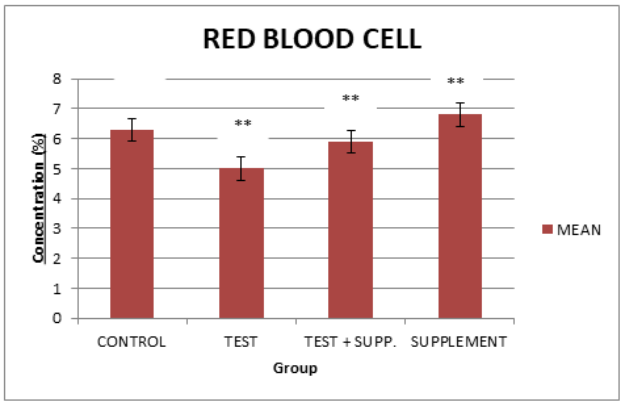

Fig. 5: Effect of thioacetamide and lycopene treatment on Red Blood Cell in treated groups.

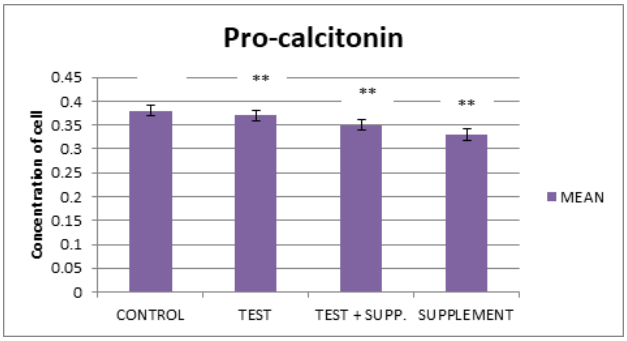

Fig. 6: Effect of thioacetamide and lycopene treatment on procalcitonin in treated group

Effect of thioacetamide and lycopene treatment on Platelets Large Cell Ratio (PLCR) in treated groups

PLCR was significantly reduced in thioacetamide (TAA) treated group (4.64±0.7, p<0.01) as compare to control group (5.36±2.3, p<0.01) whereas six weeks supplementation with lycopene resulted in increased PLCRin thioacetamide + lycopene treated group (5.35±0.5, P<0.01) as compare to TAA treated group (4.64±0.7, p<0.01). PLCR was found similar in lycopene treated groups (5.36±1.2) and in control groups (5.36±2.3) (fig. 7).

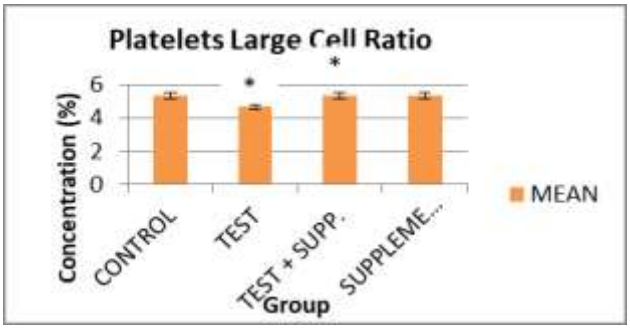

Fig. 7: Effects of thioacetamide and lycopene treatment on Platelets large cell ratio in treated groups.

Effect of thioacetamide and lycopene treatment on platelets in treated groups

The twelve weeks thioacetamide induction resulted in decreased Platelets (PLT) concentration in thioacetamide (TAA) treated group (533±77, p<0.05) as compared to control (632±73, p<0.05) whereas lycopene supplementation increased PLT concentration in thioacetamide + lycopene treated group (577±68, p<0.05) as compared to TAA treated group (533±77, p<0.05). Alone lycopene treated group (627±61, p<0.05) also showed increased PLT concentration as compared to TAA treated group (533±77, p<0.05) but decreased as compare to control group (632±73, p<0.05) (fig. 8).

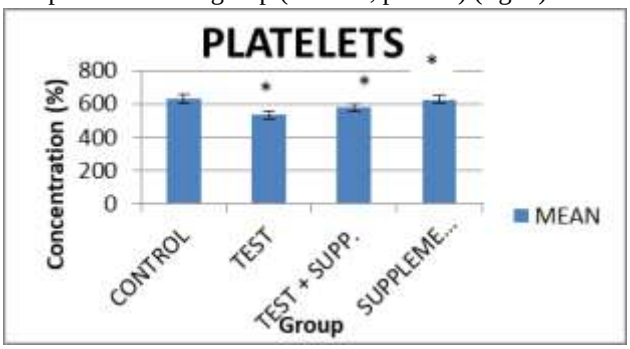

Fig. 8: Effect of thioacetamide and lycopene treatment on platelets in treated groups

Effect of thioacetamide and lycopene treatment on Lymphocyte in treated groups

Thioacetamide induction resulted in decreased lymphocyte count in thioacetamide (TAA) treated group (4.8±1.2, p<0.01) as compare to control group (5.2±1.3, p<0.01) whereas the lycopene supplementation resulted in increased lymphocyte count in thioacetamide + lycopene treated group (6.6±2.4, p<0.01) as compare to TAA treated gup. Alone lycopene treatment showed increasedlymphocyte count in the lycopene treated group (7.5±2.2, p<0.01) as compared to control group (5.2±1.3, p<0.01) (fig. 9).

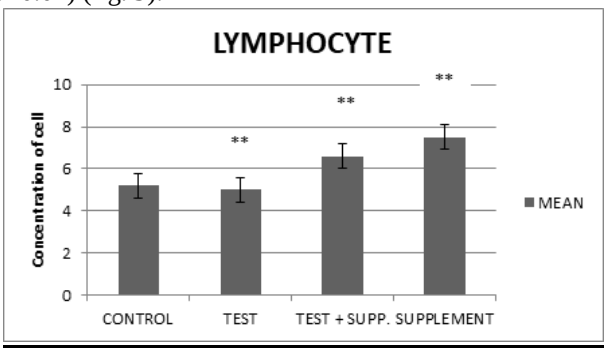

Fig. 9: Effects of Thioacetamide and lycopene treatment on Lymphocytes in treated groups.

Effects of thioacetamide and lycopene treatment on Monocyte (MID) in treated groups

Twelve weeks thioacetamide induction resulted in increased monocytes concentration in thioacetamide (TAA) treated group (2.5±1.4, p<0.01) as compare to control (1.3±0.3, p<0.01) whereas the concentration of monocytes is decreased in after lycopene supplementation in thioacetamide + lycopene treated group (2.0±0.6, p<0.01) as compare to TAA treated group. Concentration of monocytes increased in lycopene treated groups (1.9±0.7, p<0.01) as compared to control (1.3±0.3, p<0.01) (fig. 10).

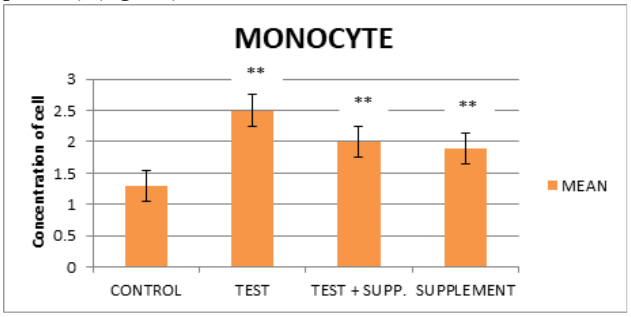

Fig. 10: Effects of thioacetamide and lycopene treatment on Monocyte (MID) in treated groups.

Effect of thioacetamide and lycopene treatment on Mean Corpuscular Hemoglobin (MCH) in treated groups

Mean corpuscular haemoglobin was decreased in thioacetamide (TAA) treated group (19.7±0.3, p<0.01) as compare to control group (20.1±0.6, p<0.01) whereas lycopene supplementation increased mean corpuscular haemoglobin in thioacetamide + lycopene treated group (20.0±0.2, p<0.01) as compare to TAA treated group. MCHwas slightly increased in the lycopene treated group (20.3±0.9, p<0.01) as compared to control group (20.1±0.6, p<0.01) (fig. 11).

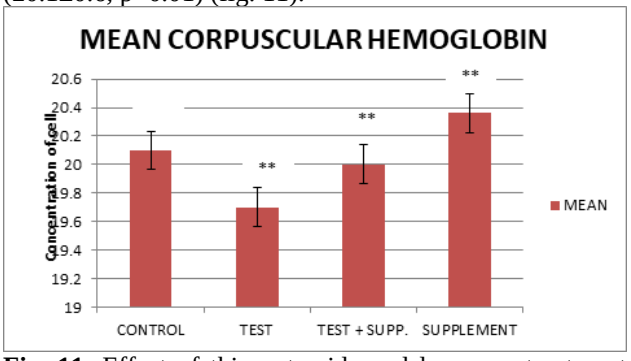

Fig. 11: Effect of thioacetamide and lycopene treatment on Mean Corpuscular Hemoglobin (MCH) in treated groups.

Effect of thioacetamide and lycopene treatment on Mean Corpuscular Hemoglobin Concentration (MCHC) in treated groups

Mean corpuscular haemoglobin concentration was significantly reduced in thioacetamide (TAA) treated group (36.9±0.9, p<0.01) as compare to control group (38.2±0.5, p<0.01) whereas the lycopene supplementation resulted in increased MCHC in thioacetamide + lycopene treated group (37.6±1.4, p<0.01) as compare to TAA

treated group (36.9±0.9, p<0.01). Mean corpuscular haemoglobin concentration was found almost similar in the lycopene treated group (38.3±0.2, p<0.01) and in the control group (38.2±0.5, p<0.01) (fig. 12).

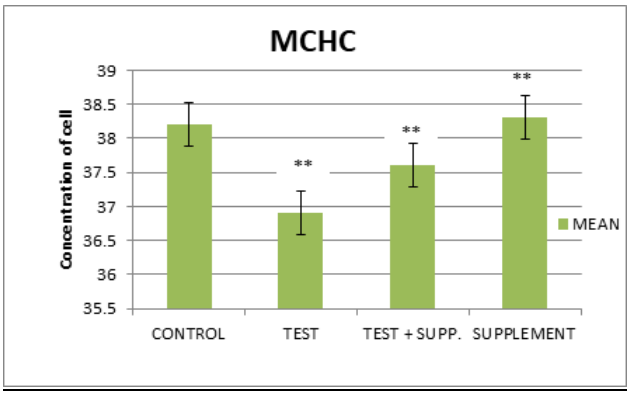

Fig. 12: Effect of thioacetamide and lycopene treatment on Mean Corpuscular Hemoglobin Concentration (MCHC) in treated groups.

Effect of thioacetamide and lycopene treatment on granulocyte in treated groups

Granulocyte concentration was increased in thioacetamide (TAA) treated group (2.8±2.6, p<0.01) as compare to control group (1.0±0.6, p<0.01) whereas lycopene supplementation significantly reduced it in thioacetamide + lycopene treated group (1.5±0.3, p<0.01) as compare to TAA treated group. Granulocyte concentration was slightly increased in the lycopene treated group (1.2±0.5, p<0.01) as compared to control (1.0±0.6, p<0.01) but decreased as compared to the TAA treated group (fig. 13).

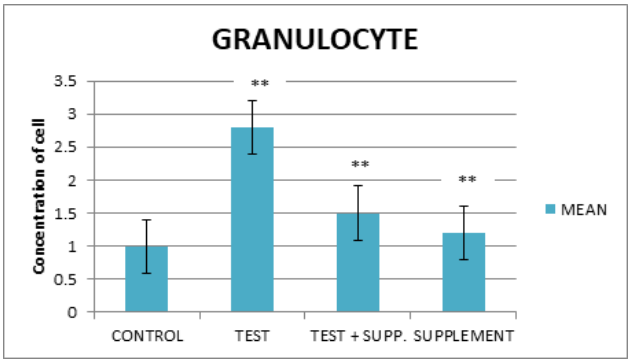

Fig. 13: Effect of thioacetamide and lycopene treatment on granulocyte in treated groups.

Effect of thioacetamide and lycopene treatment on Mean Corpuscular Volume (MCV) in Treated groups

Mean corpuscular volume was found increased in thioacetamide (TAA) treated group (54.2±3.8, p<0.01) as compare to control (52.7±2.2, p<0.01) whereas the lycopene supplementation resulted in decreased MCV in thioacetamide + lycopene treated group (53.3±0.5, p<0.01) as compare to TAA treated group (54.2±3.8, p<0.01). MCVwas slightly reduced in lycopene treated group (52.2±0.8, p<0.01) as compare to control group (52.7±2.2, p<0.01) but markedly decreased as compare to TAA treated group (54.2±3.8, p<0.01) (fig. 14).

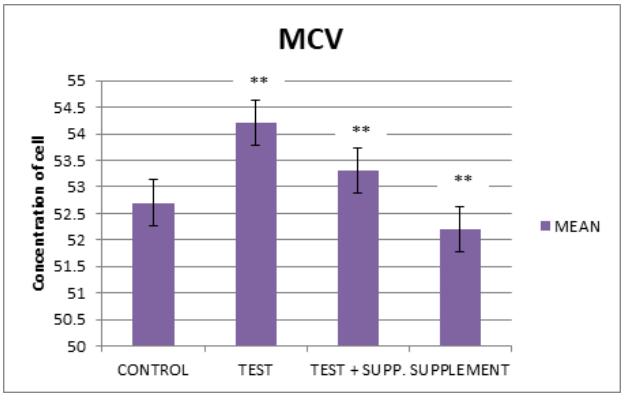

Fig. 14: Effect of thioacetamide and lycopene treatment on Mean Corpuscular Volume (MCV) in Treated groups.

Effect of thioacetamide and lycopene treatment on Hematocrit (Hct) in treated groups

Hematocrit value was significantly decreased in thioacetamide (TAA) treated group (27±4.5, p<0.01) as compared to control group. Whereas the concentration of Hct is increased in thioacetamide + lycopene treated group (31.6±5.0, p<0.01) as compared to TAA treated group. Concentration of Hct is increased in lycopene treated groups (35.9±0.09, p<0.01) as compared to control (33.4±3.4, p<0.01) and TAA treated group (fig. 15).

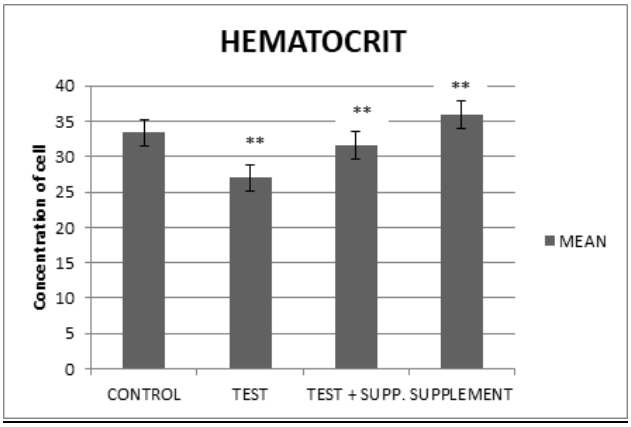

Fig. 15: Effect of thioacetamide and lycopene treatment on Hematocrit (Hct) in treated groups.

Effect of thioacetamide and lycopene treatment on Red blood cell Distribution Width (RDW%) in treated groups

RDWwas significantly increased in thioacetamide (TAA) treated group (17.5±2.8, p<0.01) as compare to control (13.9±1.0, p<0.01) whereas lycopene supplementation resulted in reduced RDWin thioacetamide + lycopene treated group (16.4±1.1, p<0.01) as compare to TAA treated group but was increased as compared to control. RDWwas increased in the lycopene treated group (14.3±0.5, p<0.01) as compared to control (13.9±1.0, p<0.01) but decreased as compared to the TAA treated group (17.5±2.8, p<0.01) (fig. 16).

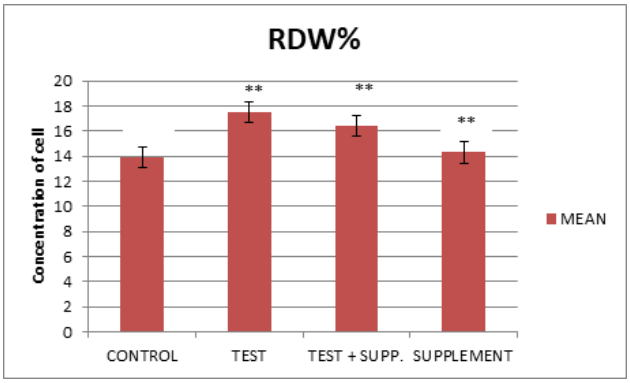

Fig. 16: Effect of thioacetamide and lycopene treatment on Red blood cell Distribution Width (RDW%) in treated groups.

Effect of thioacetamide and lycopene treatment on Mean Platelets Volume (MPV) in treated groups

MPV was slightly decreased in thioacetamide (TAA) treated group (5.9±0.1, p<0.01) as compare to control (6.2±0.4, p<0.01) whereas the lycopene supplementation was resulted in increased MPV in thioacetamide + lycopene treated group (6.1±0.3, p<0.01) as compare to TAA treated group while MPV was increased in lycopene treated groups (6.3±0.2, p<0.01) as compare to control (6.2±0.4, p<0.01) (fig. 17).

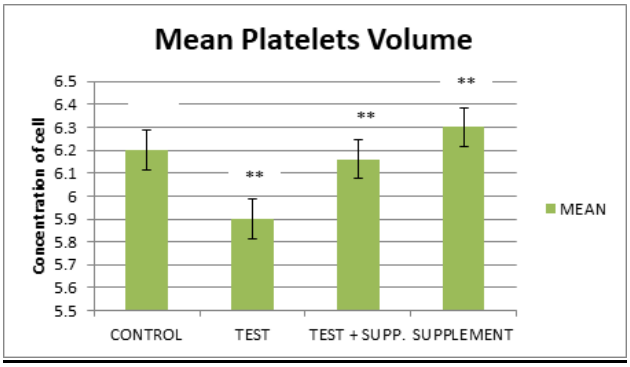

Fig. 17: Effect of Thioacetamide and lycopene treatment on MPV in treated groups.

Effect of thioacetamide and lycopene treatment on Platelets Distribution Width (PDW%) in treated groups

PDW% was found almost similar in thioacetamide (TAA) treated group (38.6±0.8, p<0.01), control group (38.5±0.9, p<0.01), thioacetamide + lycopene treated group (38.5±0.4, p<0.0) and in lycopene treated group (38.05±0.4, p<0.01) (fig. 18).

DISCUSSION

Thioacetamide (TAA) injected into experimental rats resulted in induction of liver cirrhosis which appeared in the form of hematological and biochemical changes in the experimental rats, all of the findings were kind of similar to those of humans cirrhosis and were reported and studied in scientific ways (Caballero *et al*., 2001; Rondo *et al*., 2011; Huet *et al*., 2008; Matsuhashi *et al*., 2005; Gupta and Dixit, 2009).

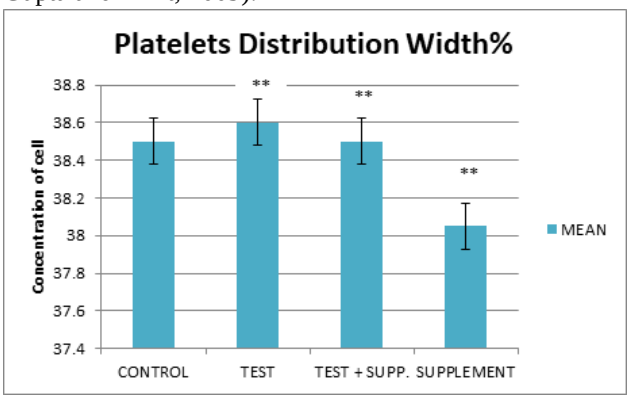

Fig. 18: Effect of thioacetamide and lycopene treatment on PDW in treated groups.

The present study confirms the role of thioacetamide (TAA) in induction of oxidative stress during development of liver cirrhosis and antioxidant property of lycopene in reducing this stress (Akbay *et al*., 1999; Abul *et al*., 2002). However, the cellular molecules are denatured due to the extremely reactive metabolites of TAA (Cheng-Haung *et al*., 2004). The loss of body weight (table 1) was due to inability to absorb nutrients during cirrhotic conditions and the gain of liver weight (table 1) was because of fat accumulation and nodule formation after thioacetamide induction in TAA treated group (Goldberg *et al*., 2018).

In this study, the hematological changes in blood components (table 2) in the experimental rats were analyzed properly for their diagnostic importance. TAA was injected (200 mg/kg b.wt.) for 6 weeks and it showed chemical dependent changes in treated groups. The level of inflammation in blood component was high especially in WBCs (table 2), monocytes (table 2), granulocytes & MCV (table 2), RDW% (table 2) and PDW% (table 2) and was low in Hb (table 4), RBCs (table 2), platelet levels (table 2), mean platelets volume (table 2), lymphocytes (table 2), MCH & MCHC (table 2) and hematocrit (table 2). When the experimental rats were suffering from some kind of conditions (cancer, hemorrhage, viral microbial infections and drug reactions), which may produce leukocytosis. An increased white blood cell (table 2) was due to an increased concentration of leukocytes (granulocyte & monocyte enhancement due to response in disease shows in table 2) in the bone marrow, or release of them from bone marrow can also cause leukocytosis in experimental rats (Olipitz *et al*., 2004). Neutrophils or granulocytes and their derived cytokines play a potential role in the production and appearance of inflammation. The cytotoxic oxygen metabolites and free radicals formed are responsible for any kind of tissue degeneration (Shapiro *et al*., 2006; Hussain and Harris, 2007; Reznick, 2006). In table 2, the significant increase in the level of granulocyte or

Table 1: Effect of thioacetamide and lycopene treatment on Body Weight and liver weight in treated groups

Parameters	Control	TAA-treated	TAA+Lycopene-treated	Lycopene-treated
Body Weights	191.1±13	170.7±11*	182.2±3.4*	201.3±3.9*
Liver Weights	6.5±0.7	6.8±0.4*	6.7±1.0*	6.6±0.7*

Table 2: Effect of Thioacetamide and lycopene treatment on blood hematology parameters in treated groups

Parameters	Control Group	TAA treated Group	TAA+Lycopene treated Group	Lycopene treated Group
White Blood Cell	7.3±1.8	12.0**±4.2	10.9**±2.4	8.1**±2.1
Hemoglobin	12.7±1.2	10.1**±1.6	11.6**±1.8	13.7**±3.0
Red Blood Cell	6.3±0.1	5.0**±0.8	5.9**±0.9	6.8**±0.09
Procalcitonin	0.38±0.07	0.37**±0.03	0.35**±0.08	0.33**±0.07
P-LCR	5.36±2.3	4.64**±0.7	5.35**±0.5	5.36**±1.2
Platelets	632±73	533*±77	577*±68	627*±61
Lymphocyte	5.2±1.3	4.8**±1.2	6.6**±2.4	7.5**±2.2
MID	1.3±0.3	2.5**±1.4	2.0**±0.6	1.9**±0.7
MCH	20.1±0.6	19.7**±0.3	20.0**±0.2	20.3**±0.9
MCHC	38.2±0.5	36.9*0.9	37.6**±1.4	38.3**±0.2
Granulocyte	1.0±0.6	2.8**±2.6	1.5**±0.3	1.2**±0.5
MCV	52.7±2.2	54.2**±3.8	53.3**±0.5	52.2**±0.8
Hct	33.4±3.4	27**±4.5	31.6**±5.0	35.9**±0.09
RDW%	13.9±1.0	17.5**±2.8	16.4**±1.1	14.3**±0.5
MPV	6.2±0.4	5.9**±0.1	6.1**±0.3	6.3**±0.2
PDW%	38.5±0.9	38.6**±0.8	38.5**±0.4	38.05**±0.4

neutrophil (as compared to control) after the i.p. injection of TAA, which may have a response in the result of free radicals resulting from TAA metabolism that cause liver damage and a section of these free radicals released into the blood. So this blood may also disturb the circulating cells and produce a change in their number (Doi *et al*., 1991). In the same way, table 2 shows a decreased level of lymphocytes by TAA metabolism and some previous research also reported about the major neutrophilia and reduced level of circulating lymphocytes by TAA metabolism (Sheikh *et al*., 2006). The complication of liver cirrhosis was the enlargement of spleen in which the number of platelets were decreased and table 2 also shows the decreased amount of platelets. Because the spleen was swelled up by portal hypertension, it causes trapping platelets (Goldberg *et al*., 2018). Table 2 shows decrease in a count of RBCs and Hb contents may cause a decrease in anaemia which was sorted as a macrocytic hypochromic blood image. So, high MCV with a high RDW% occurs in some macrocytic anemia condition (Ballinger, 2007; Jolobe, 2000). The decrease of RBCs level and level of hemoglobin in blood cells indices like MCHC, MCH, noted in this research in table 2, was clearly caused by the megaloblastic image of RBCs and they can disturb hematopoiesis, can destroy erythrocytes and can reduce the production rate of them or their circulation. According to Travlos *et al*. (1996), the cause of liver damage is due to free resulting form of TAA metabolism (Travlos *et al*., 1996). In contrast, intake of the oral tomato juice daily for 6 weeks may have advanced the strength of the cell process, as it includes the lycopene which operates as scavenging of free radicals and also defends the cell from oxidative stress. These findings are also reported by Kattab *et al*., 2003 that the lycopene may clearly decrease hepatotoxicity (Kattab *et al*., 2003). This attained improvement can be the trait of lycopene chemical nature that has a polyene chain which has the essential character of scavenging radical structure (Halliwell & Gutteride, 1999).

CONCLUSION

The current study indicated that thioacetamide-induced hepatotoxicity might be related to oxidative damage. Tomato juice has been proven effective as an antioxidant in counter action of the toxicity produced by TAA.

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