EFFECTS OF THYME EXTRACT ON HEPATOTOXICITY INDUCED BY FENITROTHION IN ADULT MALE MICE: A HISTOLOGICAL, HISTOCHEMICAL AND IMMUNOHISTOCHEMICAL STUDY

EL-NAGGAR, S. M.,¹ SELIM, A. A.² AND EL-MAHALAWAY, A. M.³

¹Department of Basic Sciences, IbnSina National College for Medical Studies –Jeddah 21323, Kingdom of Saudi Arabia. ²Department of Biology, Faculty of Applied Sciences, Umm Al-Qura University, Makkah 24832, Kingdom of Saudi Arabia. ³Departments of Histology and Cell Biology, Benha Faculty of Medicine, Benha University, Benha 13511, Egypt. E. mail: abeerelmahalaway@yahoo.com, Cell: 00966552509725

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Abstract: Fenitrothion (Sumithion) is an organophosphorus pesticide, used worldwide in agricultural practice. It is toxic to animals and humans. Thyme commonly used as food flavor and germ killer. The current work was undertaken with the objective to evaluate the protective effects of Thyme extract on hepatotoxicity induced by fenitrothion (sumithion) in adult male mice. Forty male mice were included in study and divided into 4 groups (each group included 10 mice). Group I: the animals received tape water for 4 weeks. Group II: The animals received daily oral dose of fenitrothion "1/30 LD50 (20 mg/kg body weight) by gastric tube for 4 week. Group III: The animals received daily oral dose of Thyme extract (500mg/kg body weight/day) by gastric tube for 4 weeks and group IV) animals received both fenitrothion and Thyme extract for 4 weeks. Liver specimens were prepared for histological examination (H&E), histochemical examination of glycogen and protein and immunochemical detection of caspase-3. Finally quantitative analysis of DNA fragmentation was done. Microscopically group II showed many histological changes in liver sections in the form of loss of the hepatic architecture and apoptosis of hepatocytes with pre-cancerous changes that was supported by highly expressed caspase-3 reaction in the cytoplasm and nuclei of hepatocytes. Marked decrease PAS positive reaction and protein were detected in most hepatocytes. DNA fragmentation were significantly increased (32%) in comparison with all groups. Group IV showed improvement of histological and histochemical changes in the tissue. Thyme extract possess a hepato-protective against fenitrothion as it had antioxidant, anti-inflammatory and anti-genotoxic activities.

Key words: Fenitrothion, Thyme, Liver toxicity

INTRODUCTION

Liver has a wide range of functions in the body, including metabolism of nutrients, excretion of waste metabolites and detoxification of endogenous and exogenous harmful substances [1]. Hepatic damage is caused by chemicals or infectious agents associated with distortion of metabolic functions that may lead to progressive liver fibrosis and ultimately cirrhosis causing liver failure [2].
causing rapid twitching of voluntary muscles and finally paralysis [4].

Fenitrothion is an insecticide belonging to the organophosphate family. It is now widely used for controlling a wide range of insects, flies, mosquitoes, cockroaches residual contact spray for farms and public health programmers [4]. Exposure to fenitrothion cause serious health hazard both in developing and developed countries. It effects many organs and systems of body such as the liver, kidney, thyroid gland, nervous system, immune system and reproductive system [3].

_Thyme_ is an versatile and evergreen herb with culinary, medicinal and ornamental uses. In ancient Egypt, Thyme is used for embalming and in temples in ancient Greeks. It is also commonly added to bath-water. The Romans used the Thyme for flavoring the cheese and alcoholic beverage [5,6]. Thyme oil is used as a germ-killer in mouthwashes and liniments. It is also applied to the scalp to treat baldness and to the ears to fight bacterial and fungal infections [7]. The leafy parts of Thyme belonging to the Lamiaceae are often added to meat, fish and food and also used as herbal medicinal plants [8]. Thyme also possesses various beneficial effects such as analgesic, antiseptic, carminative, antimicrobial and antioxidative properties, lowering blood pressure and blood cholesterol and used as growth promoters to improve production in poultry [9-13]. Looking into divers properties of this herb the current work was undertaken with the objectives to evaluate the protective effects of Thyme extract on hepatotoxicity induced by fenitrothion in adult male mice.

**MATERIALS AND METHODS**

In this study, 40 male albino mice (6-8 wk old) with an average body weight of 20 ± 3 gram were used. Animals were placed in individual metabolic cages and housed in a constant temperature of 22±2°C, and relative humidity of 60±5%. Mice were housed on a 12-h light: dark and provided with standard basal diet and liberal supply of tap water.

**Used drugs:** Thyme ( _Thymus vulgaris_ L) was purchased from the local market in Cairo. Fenitrothion its trade name Sumithion (Fenitrothion 50% EC) was purchased from Kaffer Elzayat Co. for Insecticide Ind. Kaffer Elzayat, Egypt.

**Preparation of Thyme extract:** The leaves of Thyme were grounded into powder using a grinder. One hundred grams of fine-powder were subjected to extraction with 200 ml boiling distilled water in covered flask until complete exhaustion and left for 30 min. Thereafter, the extract was cooled and filtered using Whatman No.1 filter paper to remove particulate matter. The filtrate was dried using freeze dried system (Dum-Dry Freeze Dryer, Model PAC-TC -V4 , FTS system, Inc., Stone Ridge ,NY,USA). The required doses were taken and reconstituted in 10 ml of distilled water just before oral administration [14].

**Animal groups:**

**Group I (Control group):** The animals received tap water for 4 weeks.

**Group II (Fenitrothion):** The animals were treated with 1/30 LD50 (20 mg/kg body weight ) of fenitrothion daily orally by gastric tube for 4 weeks [15].

**Group III (Thyme group):** The animals were received Thyme extract (500mg/kg body weight/day) daily orally by gastric tube for 4 weeks [14].

**Group IV (Fenitrothion and + Thyme group):** The animals received 1/30 LD50 20 mg/kg body weight of the fenitrothion and Thyme extract (500mg/kg body weight/day) daily orally by gastric tube for 4 weeks.

At the end of the experiment, the mice were killed by cervical decapitation and liver specimens were taken. Paraffin sections were prepared for histological examination (stained with H&E and periodic acid-Schiff) [16,17]. The sections were also stained with mercuric bromophenol blue procedure for histochemical examination of glycogen and general proteins [18].

Some sections were stained by standard avidin–biotin peroxidase method for immunohistochemically detection of caspase-3 expression [19]. Briefly, the sections were deparaffinized, hydrated and then incubated overnight with the mouse monoclonal primary antibody to caspase-3 (Ab-7, Mouse Mab. MS.). Sections were rinsed in phosphate buffered saline and few drops of biotinylatedgoat-anti-mouse polyclonal secondary antibody were applied for 10 minutes. Sections were rinsed then treated with 2
drops of the prepared diaminobenzidine tetra-hydrochloride (DAB) substrate chromogen solution for 15 minutes until the desired brown color was obtained. Sections were counterstained with Mayer’s haematoxylin and mounted with aqueous mounting medium. Control sections were stained after omission of the primary antibody.

**Quantitative analysis of DNA fragmentation:** The method of DNA fragmentation was carried out according to Perandones et al. [20]. The liver specimens of the control and experimental groups were collected immediately after sacrificing the animals. About 0.25g of the liver tissues was mechanically dissociated in 400 μl hypotonic lysis buffer (10mM tris, 1mM EDTA and 0.2% triton X-100, ph 8.0). The cell lysate was centrifuged at 12.000 Xg for 15 min. The supernatant containing small DNA fragments was immediately separated as well as the pellet containing large pieces of DNA, were used for the diphenylamine (DPA) assay. The pellet was resuspended in 400 μl of hypotonic lysis buffer. 400 μl 10% trichloroacetic acid (TCA) was added to both the supernatant and the resuspended pellet and incubated at room temperature for 10 min. The tubes were centrifuged at 2000 rpm for 15 min. at 4°C. After discarding the supernatant, the precipitate was resuspended in 400 μl 5% TCA, incubated at 80°C for 30 min. and then allowed to cool at room temperature. After centrifugation, one volume of the extracted DNA was added to two volumes of colorimetric solution (0.088 M diphenylamine (DPA), 98% V/V glacial acetic acid, 1.5%V/V sulphoric acid and 0.5% V/V 1.6% acetald-ehyde solution). The samples were stored at 4°C for 48h. The colorimetric reaction was quantities spectrophotometrically at 578 nm. The percentage of DNA fragmentation was expressed by following formula:

\[
\text{Fragmented DNA(%) = } \frac{\text{OD(S)}}{\text{OD(S)} + \text{OD(P)}} \times 100
\]

OD(S) = optical density of supernatants
OD(P) = optical density of pellets.

The blood was drained from the tail vein using capillary tubes into Eppendorf tubes containing heparin (20 ml, 200 IU/ml). The plasma was separated by centrifugation and used for analysis of alanine amino transferase (ALT), aspartate amino transferase (AST)[23], alkaline phosphatase (ALP)[24], total proteins [25] and Bilirubin [26].

**GROUPS:**

**Group I:** (Control group) showed hepatocytes radiated from the central vein separated by blood sinusoids. Blood sinusoids were lined by endothelial and kupffer cells. The hepatocytes appeared polyhedral with granular acidophilic cytoplasm and large, central, rounded nuclei. The nuclei of hepatocytes were vesicular with prominent nucleoli. Some hepatocytes were binucleated (Fig. 1).

**Group II** (Fenitrothion group): Liver sections showed an obvious histological changes as distortion in the hepatic architecture and some apoptotic hepatocytes were shrunken with deeply stained nuclei. While others showed dissolution of their nuclei (karyolysis) (Fig. 2). Pleomorphic hepatocytes with different size and shape with deeply acidophilic cytoplasm and large hyperchromtic nuclei (precancerous change) were seen. Concretion of inspissated bile were seen in between hepatocytes (Fig. 3).

**Group III** (Thyme group): No histological changes were observed as compared to control group.
Table 1: Total hepatic DNA fragmentation in different experimental groups. a* (group II compared with group I) (P< 0.01), b (p<0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>DNA Fragmentation (%) mean±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>11±1.4b</td>
</tr>
<tr>
<td>Group II</td>
<td>32±2.7a*</td>
</tr>
<tr>
<td>Group III</td>
<td>12±1.5b</td>
</tr>
<tr>
<td>Group IV</td>
<td>17±1.9b</td>
</tr>
</tbody>
</table>

Table 2: Showing the mean area % of caspase-3 expression and ± SD in different experimental groups. SD = standard deviation. Group II compared with group I (P< 0.05)* Group IV compared with group II ( P< 0.05)

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean area %</th>
<th>±SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>0%</td>
<td>0</td>
</tr>
<tr>
<td>Group II</td>
<td>20.81%</td>
<td>1.0755</td>
</tr>
<tr>
<td>Group III</td>
<td>0%</td>
<td>0.6243</td>
</tr>
</tbody>
</table>

Table 3: Showing changes in the malondialdehyde and reduced glutathione in different experimental groups. SD = standard deviation, Group II compared with group I (P< 0.05)* Group IV compared with group II( P< 0.05)*

<table>
<thead>
<tr>
<th>Group</th>
<th>MDA (nmol/g tissue)</th>
<th>GSH (μg/g tissue)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>27.6±3.02</td>
<td>1.30±0.17</td>
</tr>
<tr>
<td>Group II</td>
<td>97.64±3.82</td>
<td>0.80±0.09</td>
</tr>
<tr>
<td>Group III</td>
<td>28.45±2.28</td>
<td>1.43±0.25</td>
</tr>
<tr>
<td>Group IV</td>
<td>45.34±1.0755</td>
<td>1.57±0.15</td>
</tr>
</tbody>
</table>

Table 4: Showing changes in liver function tests in different experimental groups. SD = standard deviation, Group II compared with group I (P< 0.05)* Group IV compared with group II( P< 0.05)*

<table>
<thead>
<tr>
<th>Group</th>
<th>Serum ALT(U/L)</th>
<th>Serum AST(U/L)</th>
<th>Serum ALP(U/L)</th>
<th>Total Bili (mg/dl)</th>
<th>Total protein (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group I</td>
<td>25.06±0.36</td>
<td>60.50±4.37</td>
<td>103.76±5.28</td>
<td>0.63±0.03</td>
<td>8.52±0.85</td>
</tr>
<tr>
<td>Group II</td>
<td>74.40±0.82</td>
<td>110.20±4.49</td>
<td>154.25±5.15</td>
<td>3.45±0.30</td>
<td>4.55±0.15</td>
</tr>
<tr>
<td>Group III</td>
<td>28.40±0.48</td>
<td>62.10±3.25</td>
<td>109.93±4.78</td>
<td>0.66±0.04</td>
<td>5.92±0.22</td>
</tr>
<tr>
<td>Group IV</td>
<td>41.45±0.29</td>
<td>87.57±4.52</td>
<td>125.12±6.34</td>
<td>0.95±0.04</td>
<td>6.82±0.61</td>
</tr>
</tbody>
</table>

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Fig. 1: A photomicrograph of a liver section from group I showing cords of hepatocytes (H) radiating from central vein(V). Hepatocytes have vesicular nuclei and granular acidophilic cytoplasm. Several sinusoids (S) lined by endothelial cells & Kupffer cells separate the cords of hepatocytes (H&E X 400).

Fig. 2: A photomicrograph of a liver section from group II showing disorganized hepatic architecture. Hepatocytes of some area show karyolysis of their nuclei, but hepatocytes of other areas are shrunken with deeply acidophilic cytoplasm and deeply stained nuclei (arrow). Wide sinusoids are present between (S). (H&E X 400).

Fig. 3: A photomicrograph of a liver section from group II showing loss of hepatic architecture. There is a variation in shape and size of hepatocytes, some cells have large hyperchromatic nuclei and acidophilic cytoplasm (arrow). Concretions of inspissated bile can be seen between the hepatocytes (arrow). (H&E X 400).

Fig. 4: A photomicrograph of a liver section from group IV showing nearly normal hepatic architecture but central vein is dilated (V). Notice presence of some hepatocytes in prophase (1) and prominent endothelial (1) and Kupffer cells (1) (H&E X 400).

Fig. 5: A photomicrograph of a liver section from group I showing intense PAS positive reaction in the cytoplasm of central hepatocytes (around central vein) (Fig. 5).

Fig. 6: A photomicrograph of a liver section from group II showing apparent focal decrease PAS positive reaction of hepatocytes and absence of PAS reactions in some hepatocytes (PAS X 400).

Fig. 7: A photomicrograph of a liver section from group II showing apparent focal decrease PAS positive reaction in some hepatocytes (PAS X 400).

Fig. 8: A photomicrograph of a liver section from group IV showing apparent decrease PAS positive reaction in some hepatocytes with moderate reactions in other hepatocytes and around central vein. (PAS X 400).

Fig. 9: A photomicrograph of a liver section from group I showing dark blue protein granules in the cytoplasm of hepatocytes (Mercuric bromophenol blue X400).

Group IV (Fenitrothion and Thyme group): This group showed nearly normal hepatic architecture but some central veins were dilated.

Some hepatocytes were seen in prophase and hepatic sinusoid lined by prominent endothelial and Kupffer cells (Fig. 4).

Histochemical examination: 1-PAS reaction:

Group I (Control group): Liver sections showed an intense PAS positive reaction in the cytoplasm of peripheral hepatocytes and moderate reaction in the cytoplasm of central hepatocytes (around central vein) (Fig. 5).

Group II (Fenitrothion group): Liver sections showed apparent focal decrease of PAS positive reaction of hepatocytes (Fig. 6) and absence of PAS positive reactions of hepatocytes (Fig. 7).

Group III (Thyme group): No change were observed in the intensity of the PAS reaction as compared to control group.

Group IV (Fenitrothion and Thyme group): Liver sections showed a decrease of PAS positive reaction in some hepatocytes with moderate reactions in other hepatocytes and around the central vein (Fig. 8).

2. Mercuric bromophenol blue:

Group I (Control group): Liver sections showed high concentration of total protein (bluish granules) in the cytoplasm of hepatocytes (Fig. 9).
Group II (Fenitrothion group): Liver sections showed apparent decreased protein bluish granules in the cytoplasm of hepatocytes (Fig. 10). Protein clumps (clumps of bluish granules) especially in blood sinusoids were present (Fig. 11).

Group III (Thyme group): No histochemical changes were observed for protein bluish granules in the cytoplasm of hepatocytes as compared to control group.

Group IV (Fenitrothion and Thyme group): Liver sections showed many protein bluish granules in the cytoplasm of hepatocytes (Fig. 12).

Immunohistochemical result:

Group I (Control group): The liver of the control rat showed negative immune reaction to caspase - 3 { no brownish staining in the cytoplasm and nuclei of hepatocytes (no apoptosis)} (Fig. 13).

Group II (Fenitrothion group): This group showed highly expressed caspase-3 reaction in the cytoplasm of hepatocytes. Positive immunohistochemical staining of caspase-3 demonstrated brown cytoplasmic and nuclear staining (index for the degree of nuclear apoptosis) (Fig. 14).

Group III (Thyme group): No detectable changes were observed to caspase-3 reaction in this group compared to that of the control group.

Group IV (Fenitrothion and Thyme group): This group showed less expressed caspase-3 reaction in the cytoplasm of hepatocytes (weak brownish staining in the cytoplasm and nuclei) (Fig. 15).

DNA Fragmentation: DNA fragmentation in mice liver analyzed by diphenylamine reaction procedure (table 1 and histogram 1). The results revealed that, the treatment with fenitrothion (group II) produced a highly statistical significant DNA fragmentations (32%)(p<0.01) in comparison to control group I (11%). However, the Thyme extract (group III) produced no statistical significant change of DNA fragmentation (12%) (p>0.05) in comparison to control group. The Thyme extract produced significantly decrease in the DNA fragmentation, induced by the fenitrothion from 32% to 17% in fenitrothion and thyme group (group IV).

Morphometric result: The mean area % of caspase-3 expression for all groups was represented in table 2 and histogram 2. Caspase-3 expression were incre-ased in group II compared with group I (P < 0.05). Caspase-3 expression were decreased

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Fig. 10: A photomicrograph of a liver section from group II showing apparent decreased protein bluish granules in cytoplasm of hepatocytes (Mercuric bromophenol blue X 400). Fig. 11: A photomicrograph of a liver section from group II showing protein clumps especially in blood sinusoids (arrow) (Mercuric bromophenol blue X 400). Fig. 12: A photomicrograph of a liver section from group IV showing many protein bluish granules in cytoplasm of hepatocytes. (Mercuric bromophenol blue X 400). Fig. 13: A photomicrograph of a section in the liver from control group showing negative caspase-3 immunostaining in cytoplasm and nuclei of hepatocytes(Caspase-3 immunostaining, X 400). Fig. 14: A photomicrograph of a section in the liver from group II showing highly expressed caspase-3 reaction in the cytoplasm and nuclei of hepatocytes (C) (Caspase-3 immunostaining, X 400). Fig. 15: A photomicrograph of a section in the liver from group IV showing minimally expressed caspase-3 reaction in the cytoplasm and nuclei of hepatocytes (C) (Caspase-3 immunostaining, X 400).
in group IV as compared to group II (P < 0.05). All changes were significant.

**Biochemical results:** As shown in table 3, the MDA was significantly increased in group II compared to control group I. However study shows significantly decreased MDA in group IV as compared to group II. Likewise, reduced GSH was significantly decreased in group II as compared to control group I, but recovered in group IV as compared to group II.

Table 4 represents the liver injury marker of ALT, AST, ALP, total Bilirubin were significantly increased in group II compared to control group I, but were significantly decreased in group IV compared to group II. Total protein was significantly decreased in group II compared to control group I, but was significantly increased in group IV compared to group II.

**DISCUSSION**

The liver is the primary organ involved in xenobiotic metabolism and thus could be injured by many chemicals and drugs [27]. Fenitrothion (Sumithion) was a widely used organophosphorus insecticide for controlling a wide range of pests. It could produce toxic and adverse effects on liver, kidney, thyroid gland and other biological systems [4]. A large Number of medicinal plants and their purified constituents (such as Thyme extract and its constituents) had been shown a beneficial therapeutic potential for curing a variety of illnesses [28].

The histological and histochemical examination of the liver sections from group II showed distortion in the hepatic architecture. Some hepatocytes showed an apoptotic changes, while the other hepatocytes showed karyolysis of their nuclei. This was supported by the presence of highly expressed caspase-3 reaction and the increased DNA fragmentation in the present study. Our results were in agreement with the previous studies stated that, the exposure to organophosphorus pesticides led to severe hepatocellular degeneration and necrosis [29-34]. Caspase-3 is a key factor in the apoptotic pathway, and caspase-3 expression is positively correlated with apoptosis [35].

Some studies reported that, organophosphorous insecticides induces apoptosis [4,36]. Several studies revealed a reduction of DNA fragmentation under the effect of different insecticides as a result of inhibition DNA synthesis or severe DNA damage [12,37-39]. Some scientists [40] found that the DNA fragmentation in kidney homogenates were markedly increased to 4.8 fold after cisplatin administration. Our studied group II revealed a marked variations in size and shape of hepatocytes with loss of normal hepatic architecture. Some cells revealed a large hyperchromatic nuclei with acidophilic cytoplasm. Globules of inspissated bile were seen inbetween abnormal hepatocytes. According to Rubin and Strayer [41] marked variations in the size and shape of hepatocytes might be a pre-cancerous condition. Moreover, the accumulation of bile globules in between the abnormal hepatocytes of group II was a result of hepatocellular damage and damage of canalicular membrane [41]. Fenitrothion insecticides had the ability to inhibit the cytochrome P450 (CYP) enzymes which responsible for xenobiotics detoxification and thus enhanced the liver damaging effects [4].

Mossa et al. [33] stated that the mechanism of action of organophosphorus pesticide on the cell was mediated through the increased production of free radicals and the oxidized products of oxidative stress such as reactive oxygen species, causing damage to the various membrane components of the cell, leakage of cytoplasmic enzymes and might enhanced the apoptotic process.

The histochemical examination of the liver sections from group II showed apparent focal decrease of PAS positive reaction in most hepatocytes and some hepatocytes were devoid of glycogen granules. Most of the hepatocytes also showed decrease in protein bluish granules in their cytoplasm. Protein clumps especially in blood sinusoids were also seen. Several studied reported a significant reduction of tissue glycogen in liver, kidney, heart and skeletal muscles of variety of animals under the effect of different insecticides resulted from inhibition of biosynthetic enzymes and stimulation of glycogenolysis enzymes as phosphorylase which accelerated the glycogen breakdown [42-47].

The decreased protein could be attributed to the disruption of lysosomal membranes under the effect of various toxicants and organophosphorus
insecticide leading to the liberation of their hydrolytic enzymes in the cytoplasm resulting in marked lysis and dissolution of the target material [47]. Rubin and Strayer [41] declared that the changes in gene expression and protein production were seen in cases of persistent stress and cell injury and increased degradation of protein by proteosomes and protein laden in Kupffer cells represented adaptation to stress. Our studied group II revealed a significant increase of total bilirubin and a significant decrease of total protein as compared to control groups. Some authors [48]) explained the reduction of total protein could be due to the changes in the metabolism and the synthesis of the proteins and free amino acid in liver. Serum bilirubin was considered as an index for the assessment of hepatic function and any abnormal increase indicates hepatobiliary disease and severe disturbance of hepatocellular architecture [49].

Our studied group II revealed a significant increase of MDA and a significant decrease of GSH as compared to control group. These results were in agreement with the previous studies [33,34,48]. Our studied group II revealed a significant increase of AST, ALT and ALP as compared to control group. AST, ALT and ALP are cytosolic marker enzymes reflecting hepatocellular damage and necrosis as they release from the cytoplasm into blood circulation [34].

In present study group IV show recoveries of biochemical parameters, histological and histochemical properties of liver. Moreover, there were signs of mitotic activity of some hepatocytes and minimally expressed caspase-3 reaction in the cytoplasm and nuclei of hepatocytes. Endothelial and Kupffer cells were activated and released certain cytokines that played a role in remodeling of tissue architecture and recovery of the original structure of liver cell plates [41]. These results are in agreement with findings of some investigators who reported the protective effect of Thyme against hepatotoxicity [8,50].

Thyme extract act as free radical scavenger [50,51], antioxidant, antiapoptotic, antigenotoxic [52] and hepatoprotective. It causes significant improvements in histological architecture and biochemical parameters of liver as evident in present study and also demonstrated by earlier workers.

CONCLUSION

Fenitrothion causes many histological, histochemical and immunological changes in liver of mice as it induces the production of reactive oxygen species causing damage to membranes and organelles. Thyme extract possess hepatoprotective effects against fenitrothion as it has antioxidant, anti-inflammatory and antigenotoxic in nature. Hence, eating Thyme along with healthy diets together with decrease of pesticides concentration in agriculture should be considered.

REFERENCES