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RESEARCH ARTICLE

A STUDY OF SOME BIOCHEMICAL AND HISTOPATHOLOGICAL CHANGES IN MALE LABORATORY RATS TREATED BY PESTICIDE ABAMECTIN

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ABSTRACT

Abamectin is widely used as an insecticide, acaricide, and anthelmintic. The present study assessed the effects of repeated administration of Abamectin (Vapcomic- 1.8% EC) injection formulation on albino male rats the various biochemical parameters and histopathological changes were noted. Two groups each of five of albino male rats were utilized in the current investigation. Abamectin was administered interaperitoneal which treated with (0.1 mg\kg, 0.6 mg\kg) body weight daily for 15 days. At the end of the study period blood samples were collected from all the groups to measure plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST activities, and the levels of total protein and cholesterol level changes in biochemical parameters were more intense in male rats from group T2 than those reported in group T1. The levels of ALT AST were significantly elevated in rats from group T2 when compared to the control group. In group T1 and T2 showed a significant decrease in the levels of total protein and cholesterol.

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INTRODUCTION

Pesticides are the chemical formulation increasingly used in agriculture, animal husbandry and public health operation to kill the insects, weeds and fungus and to get rid of insect transmitted diseases. The frequent and continuous use of pesticide has resulted in their widespread distribution in the environment. These pesticides are toxic not only to insects and pests but also at different levels to animals and human beings (Mondal *et al*, 2012). Pesticides are estimated to be responsible for approximately 4% of all deaths from accidental poisoning, mainly in the developing world (Colosio and Moretto, 2008).

In 2009, Thailand imported abamectin to eliminate several kinds of insects such as cotton Leafhopper (Seeduangkaew *et al*., 2015). Abamectin (ABA) belongs to the family of avermectins, which are the macrocyclic lactones produced by a soil bacterium (actinomycete), *Streptomyces avemitilis*, obtained through naturally occurring fermentation (Fisher and Mrozik, 1989). It is used to control motile stages of mites and some other insects on fruits and vegetables and has limited plant systemic activity. The biochemical composition or their alterations are influenced from their environmental stress and being reported by (Al-Kahtani, 2011). Abamectin has been used extensively all over the world and is still one of the most commonly used pesticides in Yemen. It affects inhibitory synapses via a mode of action involving glutamate-sensitive chloride channels (Campbell *et al*., 1983; Yoon *et al*., 2004). Abamectin is highly toxic to insects and may behighly toxic to mammals (Lankas and Gordon, 1989). So the detoxification of abamectin may affect the function of hepatocytes although permanent liver damage is not usually revealed immediately (Hsu *et al*, 2001). After getting in the insect body, abamectin has the effect on the nervous system including neuron and muscle and especially the synapse in the brain resulting in blocking blood flow and eventually causing death (Al-kahtani, 2011). Abamectin revealed significant increases in the liver function parameters (i.e. ALT, AST activities acid phosphatase activity, serum albumin, glucose and total protein levels). Also, kidney function parameters (uric acid and creatinine concentration were severely affected (Eissa and Zidan, 2010). There are problems associated with chemical insecticides, such as health hazards (Abd-Elhady, 2012). In toxicity studies, a variety of biochemical parameters are measured to evaluate a broad range of physiological and metabolic functions affecting target organ identification and

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tissue injury assessment (Akhtar *et al*., 2012). Combinations of some common biochemical parameters provide better information from pattern recognition, e.g. enzymes like ALT and AST for hepatotoxicity, and urea and creatinine for glomerular function. (Evans, 1996)

ABA poisoning can impair the function of hepatocytes. Research conducted by Hsu *et al*. (2001) showed elevated levels of the enzyme aspartate aminotransferase (AST) in the blood serum of rats after exposure to ABA by gavage at doses between 1 and 20mg/kg body weight. The maximum activity was obtained with a dose of 20mg/kg of body weight 1h after ingestion Therefore; the main target of the present study is to investigate their side effects on some biochemical parameters and histopathological changes in liver of mal albino rats.

MATERIALS AND METHODS

Pesticides Used

Abamectin (1.8% E.C; 100 mL): a mixture containing a minimum of 80% avermectin B1a (5-O-demethylavermectin) and a maximum of 20% avermectin B1b (5-O-demethyl-25-de-(1-methylpropyl)-25-(1-methylethyl), was supplied by VAPCO Manufacturing CO. Ltd.

Experimental Design

The present experiment was carried out on 15 mature male albino rats (156-203g) obtained from the animal house, Faculty of Sciences, Sana'a University, was used for the study. Rats were kept at a constant environmental condition throughout the period of the experiment; water and food were supplied ad libitum.

Experimental animals were randomly distributed into three groups, of five animals each: Group (1) the rats in this group were daily interaperitoneal injection of dropped water (0.1mg/kg) for a period of 15days, without any ingredient of Abamectin. Group (2) these animals were daily interaperitoneal injection with Abamectin as Low dose at a level of 0.1mg/kg body weight for a period of 15days. Group (3) animals in this group were daily interaperitoneal introduced of Abamectin as High dose at a level of 0.6mg/kg body weight for a period of 15days. At the end of 15days, blood samples were individually collected from each rat immediately after slaughtering in dry clean centrifuge tubes. Plasma was separated after centrifugation (3000 rpm for 15min) plasma samples were used to estimate the activities of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (Reitman and Frankel, 1957), total protein (Domas, 1975) and cholesterol (Schettler *et al*., 1975).

Histological studies

Suitable pieces of liver were removed and fixed for histopathological investigation. All the liver samples from each of the experimental groups 1, 2, and 3 were kept in 10% buffered formalin. The organs were dehydrated in ethanol (70 to 100%), and then the samples cleared in xylene and embedded in paraffin. Tissue sections were examined under a light microscope after staining with haematoxylin and eosin (H and E) (Culling, 1963; Lillie, 1965).

Statistical analysis

Data were statically evaluated by using one way ANOVA. Wherever the ANOVA values were found to be significant, Duncan's new multiple range test (DMRT) was applied (SPSS computer software). The values were considered significant when $p < 0.05$.

RESULTS

The obtained results clearly showed the effect of abamectin on ALT and AST activities, during the duration of 15 days (experimental duration) with using two different ways of concentration of abamectin (0.1 and 0.6mg/kg), the results demonstrated that there was a significant increase in ALT and AST activities, at $P \leq 0.05$. Whereas, treated-group1 (T1) showed a lightly increase of 27.32 ± 0.20 U/l of ALT and 27.06 ± 0.11 U/l of AST while in treated-group 2 (T2), there was a significant increase of 30.06 ± 0.09 U/l of ALT and 38.36 ± 0.39 U/l of AST, as compared to the values obtained in the control group, that were 24.62 ± 0.18 U/l & 21.62 ± 0.25 U/l ALT and AST respectively Table 1.

Table 1. Effects of abamectin on ALT and AST activities in the liver of albino male rats

Treatment / Parameter	Abamectin treatment for 15 days	
	ALT(S-GPT)* (U/l)	AST(S-GOT)** (U/l)
Control	24.62 ± 0.18	21.62 ± 0.25
T.1(0.1 mg/kg/bw)	27.32 ± 0.20	27.06 ± 0.11
T. 2 (0.6 mg/kg/bw)	30.06 ± 0.09	38.36 ± 0.39

The mean difference was significant at the $P < 0.05$ level;
* **ALT** = Serum Alanine transferase; **S-GPT** = (Serum Glutamic-Pyruvic Transaminase - ALT)
** **AST** = Aspartate Amino transferase; **S-GOT** = (Serum Glutamic-Oxalocetic Transaminase - AST).

Table 2. Effect of abamectin on total protein and cholesterol levels of experimental groups

Treatment / Parameter	Abamectin treatment for 15 days	
	Total protein (mg/100mL)	Mean of Cholesterol Con. (mg/100mL)
Control	5.01 ± 0.03	35.02 ± 0.31
T. 1(0.1 mg/kg/bw)	4.09 ± 0.11	32.50 ± 0.64
T. 2 (0.6 mg/kg/bw)	3.05 ± 0.05	32.18 ± 0.49

The mean differences were significant at the $P < 0.05$ level in comparison with control group.

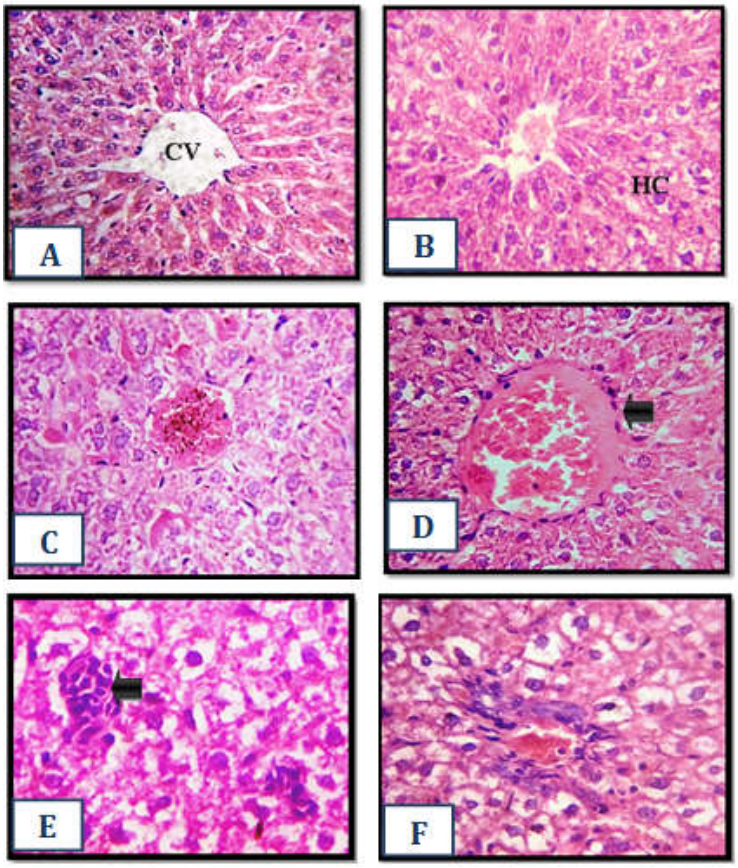

Figure 1. Photomicrograph of the rat liver sections (with 0.1 mg/kg/bw), A) Normal hepatocytes architecture with normal central vein (CV). B) Mild hydropic changes (HC). C) Mild congested central vein. D) Mild liver amyloid. E) Mild inflammatory region. F) Mild infiltration of mononuclear cells and hydropic changes. 40 X all sections

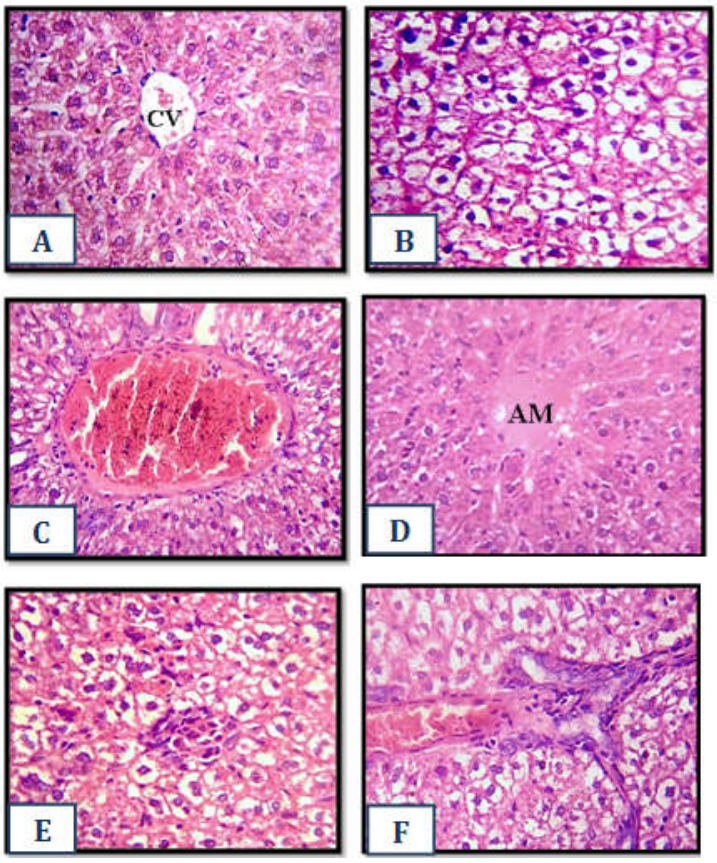

Figure 2. Photomicrograph of the rat liver sections (with 0.6 mg/kg/bw), A) Normal hepatocytes architecture with normal central vein (CV). B) Hydropic changes. C) Congested central vein. D) Liver amyloid (AM). E) Inflammatory region and hydropic changes. F) Infiltration of mononuclear cells and hydropic changes. 40 X all sections

Results obtained in Table 2 showed the effects of abamectin on total protein contents and cholesterol concentration in serum of treated male rats with abamectin and control groups. The results showed that the total protein in serum was significantly reduced in the treated rats after 15 days of exposure to the insecticides in comparison to control animals. On the other hand, serum cholesterol value was significantly decreased in comparison to control groups, at $P \leq 0.05$.

Histopatholoigcal study of liver

The transverse section of liver in untreated control group showed usual structures of hepatocytes with normal control vein (Plate 1. A), whereas at lower dose of abamectin pesticide (0.1 mg/kg bw) treated for 15 days, as changes presented by (Figure: 1). These changes include the presence of mild hydropic changes (1. B), mild congested control vein (1. C), mild liver amyloid (1. D), mild inflammatory region (1. E). and mild infiltration of mononuclear cells and hydropic changes (1. F). The higher dose of abamectin pesticide (0.6mg/kg bw) treated for 15 days, as presented by Figures: 2. These changes include the hydropic changes (2. B), congested control vein (2. C), liver amyloid (2. D), inflammatory region and hydropic changes (2. E). and infiltration of mononuclear cells and hydropic changes (2. F).

DISCUSSION

Liver is often the primary target for the toxic effects of xenobiotic. It is known that the detoxification of the toxic materials entered to the body mainly occurs in the liver (Balistreri and Shaw, 1987). The current results showed that the treatment with Abamectin caused a significant increase in the plasma activities of AST, ALT in treated male, compared to the control group, the increased levels of AST and ALT could be due to hepatotoxicity causing permeability alterations and leakage of lysosomal enzymes enhancing the release of enzymes (Choudhary *et al*. 2003; Shrivastava *et al*., 1989).
It is considered that abamectin may have a harmful effect on the hepatic cells (Emam and AbdAlla, 2000). Others found that liver contained high residues of abamectin (Roudaut, 1998), the effect of abamectin on liver function was monitored by a significant increase in the activities of the transaminase enzymes (ALT and AST), ALP and GGT after 21 and 57 days of treatment. These results were consistent with the results reported by (Ali *et al*., 1988; Ghoneim *et al*., 1992 and Soliman *et al*., (2009). The elevation in the liver enzyme activities may be due to liver dysfunction with a consequent reduction in enzyme biosynthesis and altered membrane permeability permitting enzyme leakages into the blood (Mansour and Mossa, 2010). El-Shenawy, (2010) reported that the toxic action in vitro of some insecticides, including abamectin on isolated rat, hepatocytes showed a signi cant increases in ALT and AST activity when hepatocytes were incubated for 30 min with either concentration of ABA. This activity persisted after 120min, the longest time for which data were collected. In addition, the increases of plasma AST and ALT activities may be referred to diffusion of these enzymes from the intracellular sites due to the damage caused by the pesticides on the sub cellular level (Amer *et al.,* 1994). Elevation in the activities of serum ALT and AST treated with ivermactin may have been due to leakage from the organs into extracellular fluids due to change in endothelial permeability (Arise and Malomo, 2009). Regarding the affect of abamectin on total protein, researchers in current study have found that levels of total protein were affected with abamectin in both treated-groups of rats with different concentration. The results demonstrate that the total protein levels were a significantly decreased at level of ($p \leq 0.05$) in serum of both Abamectin-treated groups (T.G.1 and T.G.2), compared to the control group.

The study exhibited that abamectin administration caused a significant reduction in the total protein levels of rat's serum, in agreement with other studies conducted by (Abd-Elhady and Abou-Elghar, 2013 and Ambali, *et al*., 2011). They reported that the treated rats with abamectin, showed a significant reduction ($p \leq 0.05$) in hepatic protein levels, compared to those obtained from the control group. In the present study, the reason for decreased levels of the total protein in the liver of treated rats with abamectin, might be either due to inhibitory action of pesticides on protein synthesis or the increase in the activity of proteases associated with the decrease of soluble and total protein (Abd-Elhady and Abou-Elghar, 2013). The changes in the levels of protein suggest either an increased catabolism of the biomolecules to meet the enhanced energy required for animals under stress or their reduced synthesis due to impaired tissue function (Ivanova-Chemishanska, 1982; Abd-Elhady and Abou-Elghar, 2013). Hamed and Abdel-Razik, (2015), reported that abamectin administration caused no clear interaction on total protein levels, which were oscillating and did not revealed significant changes. Total protein is in accordance with the previously recorded findings of Al-Robai *et al*. (1993). The rate of protein synthesis and/or catabolism in the muscles altering the activities of transaminases and the enzymes concerned with gluconeogenesis. Since liver is a major organ of protein synthesis, any diseases in liver can cause a damage of hepatocytes with alteration of its production capacity, or in case of kidney damage and increased loss of protein or muscle wasting via catabolism (Wallace, 2007). In addition**,** the administrated pesticides containing compounds could cause bloat, thereby reducing appetite in animals (Trease and Evans, 1989).

The decrease in total proteins and soluble proteins indicates their metabolic utilization and the increase in the activity of proteases was associated with the decrease of soluble and total protein (Swamy *et al*. 1992). The change in protein content might be due to the imbalance between the rate of protein synthesis and the rate of its degradation in the liver. Similarly, as a result of exposure to different insecticides the protein content in different organs can be affected (El- Bakary, 1993).
The result of the present study showed that abamectin at 0.1 and 0.6mg/kg for a period of 15days significantly increases the levels of total cholesterol in treated male rats, compared to the control group. These results are in a close agreement with that of Eissa and Zidan, (2009) who reported a minor non-significant reduction in cholesterol concentration in albino rats treated with 1/10 the LD50 (18.1/mg/kg) of abamectin for thirty successive days. A significant decrease of cholesterol at level ($p \leq 0.05$) in rats of both 0.1 and 0.6 mg/kg group may be due to hyperthyroidism. Hydroxymethylglutaryl (HMGCoA) reductase is the primary control point for cholesterol synthesis (Sigler *et al*, 1992). Hepatic HMG-CoA reductase is inhibited by phosphorylation of the enzyme. The protein kinase system responsible for the phosphorylation of HMG-CoA reductase is stimulated by intracellular cyclic activated protein kinase (cAMP). Hepatic intracellular cAMP levels are controlled in part by plasma glucagons, which decrease it. Condition that

increases glucagons (e.g. fasting) would decrease cholesterol synthesis (Yang *et al*, 2011).

Results of the present work indicated that abamectin induced histopathological alteration in the liver of male of albino rats. Abamectin caused a marked damage of the liver tissue (at both doses) in the form of hydropic changes, mild congested control vein, mild liver amyloid, mild inflammatory region, mild infiltration of mononuclear cells and hydropic changes. The hepatic function tests (serum ALT and AST activities) corroborated the histopathological lesions in the present study also observed. Many reports had elucidated that hepatocellular damage could be correlated with the disturbed enzymes activities. In this respect, liver tissues which were famous for their rich contents of aminotransferases (AST & ALT) suffer markedly from their loss under many pathological conditions (Rodwell, 1983). The histopathological changes observed in the liver of donkeys were in association with the findings of Abd-Elhady and Abou-Elghar, (2013) in Albino rats. They reported marked degenerative changes of hepato-cytes, congestion, and a marked diffuse necrosis of hepatic tissue was observed in the livers of abamectin treated animals. Such necrobiotic changes were more intense in the livers of the group treated with abamectin for 210 days. Moreover, fibrosis was observed in the portal triads associated with disruption of sinusoids and marked degenerative changes of hepatocytes along with evidence of marked congestion. The portal tract infiltration by lymphocytes and a focus of dysplasia with cytological atypia were observed in Vertimec (Abamectin) treated male rat's liver at both dose levels used (Eissa and Zidan, 2009).

In addition, dilatation and congestion of blood vessels (zigzag arrow), degenerative changes of hepatocytes with granularity in hepatic cells and infiltration with mononuclear cells were demonstrated in the treatment of abamectin. The elevation of ALT and AST levels in this study suggests probable liver tissue damage due to abamectin. This damage may occur in the histopathological lesions in the livers of abamectin- treated rats. The liver is the organ which biotransfors most xenobiotics. Early pathological changes like congestion, haemoharrages, and other necrobiotic changes in the liver are probably associated, due to a decreased free radical (O-2) scavenger formation. Most prominent lesions produced by xenobiotics include vacuolar degeneration, degeneration of hepatic cords and hepatocytes, focal to extensive necrosis, and enlargement and dilation of sinusoids (Yavasoglu *et al*. 2006).
The hepatic function tests (serum AST and ALT activities) corroborated the histopathological lesions observed in the present study. Regarding degeneration and vacuolation of renal or hepatic tissues, the result of current study go paralleled with the results of other investigators (Stebbins *et al*., 2002; Mansour and Mossa, 2005) due to treatment with different pesticides. Also, hepatocellular necrosis and degeneration was recorded in rats treated with dursban and malathion (Mikhail *et al*., 1979; Lox and Davis, 1983).

Conclusion

The results of this study demonstrate that interaperitoneal injection administration of abamectin, at 0.1mg/kg bw and 0.6 mg/kg bw for 15days induces toxic effects on a biochemical function which correlate well with the histopathological changes in the liver although the data on rats cannot be directly applied to human beings, It may be concluded that use of abamectin may cause hazardous effects at various levels to non-target organisms.

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