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Effect of sub-acute exposure to abamectin (insecticide) on liver rats (*Rattus norvegicus*)

Effet de la toxicité subaiguë de l'abamectine (insecticide) sur le foie des rats (Rattus norvegicus)

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Abstract – Objective: Extensive use of pesticides has harmful effects; they can damage human health as well as the environment. Abamectin (ABM) has been widely employed and is one of the most commonly used pesticides in Algeria. **Methods:** To evaluate the toxic effects of ABM, twenty-eight male and female rats (*Rattus norvegicus*) were randomly assigned to four groups. Groups 1 and 3 were the male and female control groups, respectively, which received distilled water. The experimental male and female groups, 2 and 4, received 2.13 mg/animal/day of abamectin, administered orally over 28 days. The animals were maintained in the same conditions without treatment for 14 days after this period. Plasma samples at 14, 28 and 42 days were used to determine biochemical parameters and avermectin B1a residues in rat plasma. Quantities of B1a in the liver were evaluated at the end of the experiment (day 42). In this study a UHPLC–MS/MS method was used to determine B1a residues in the plasma and liver. **Results:** Abamectin caused an increase ($p < 0.05$) in the glucose count and levels of ASAT, ALAT and γ-Gt in male and female rats at 14, 28 and 42 days. All experimental animals showed the time-dependent presence of B1a residues in the plasma samples at 14 and 28 days but, after 42 days, there were no residues in the plasma of ABM-treated rats. B1a residues in the liver were detected in male and female experimental rats at the end of the experiment. Abamectin caused histopathological damage of the liver tissues in the form of dilated veins, leucocyte infiltration and degenerative hepatocytes. **Conclusion:** Our results show that ABM perturbs liver function in the rat.

Key words: Abamectin, rat, liver, histology, biochemical parameters, UHPLC MS/MS

Résumé – Objectif : L'utilisation intensive de pesticides a des effets néfastes sur la santé humaine et l'environnement. L'abamectine (ABM) a été largement utilisé partout dans le monde et est l'un des insecticides les plus utilisés en Algérie. **Méthodes :** Afin d'évaluer les effets toxiques de l'ABM sur la fonction hépatique, vingt-huit rats mâles et femelles « *Rattus norvegicus* » ont été répartis au hasard en quatre groupes. Deux groupes témoins mâle et femelle recevaient de l'eau distillée (1 mL/rat/jour). Deux groupes traités mâle et femelle recevaient 2,13 mg/animal/jour d'abamectine, administré par voie orale pendant 28 jours. Les animaux ont été maintenus dans les mêmes conditions, sans traitement pendant 14 jours après cette période. Les échantillons de plasma aux 14^{e}, 28^{e} et 42^{e} jours ont été utilisés pour déterminer les paramètres biochimiques et les résidus de l'abamectine B1a. Les quantités de B1a dans le foie ont été évaluées à la fin de l'expérience (J42). Dans cette étude, une méthode UHPLC-MS/MS a été utilisée pour déterminer les résidus de l'abamectine dans le plasma et le foie. **Résultats :** L'abamectine a provoqué une augmentation ($p < 0,05$) de la glycémie et des enzymes ASAT, ALAT et γ-GT chez les rats mâles et femelles. Les résidus de l'abamectine ont été détectés dans le plasma de tous les rats traités à J14 et J28 en fonction du temps alors qu'à la fin de l'expérimentation une absence totale de B1a a été constatée. Dans le foie, à J42, B1a a été détecté à différentes concentrations chez les rats traités (mâles : 83 ng/g et femelles : 362 ng/g). Les résultats histopathologiques montrent que l'abamectine a provoqué des changements dans l'histologie

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du foie, à savoir : une dilatation des veines, une infiltration des leucocytes et une dégénérescence des hépatocytes.
Conclusion : Nos résultats montrent que l'ABM perturbe la fonction hépatique chez le rat.

Mots clés : Abamectine, rat, foie, histologie, paramètres biochimiques, UHPLC MS/MS

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1 Introduction

Pesticides are estimated to be responsible for approximately 4% of all deaths from accidental poisoning, mainly in the developing world [1]. The use of substances toxic to man and to a variety of forms of life has become an overall health problem.

The macrocyclic lactons (MLs) include two chemical families: avermectins (abamectin, ivermectin, doramectin, eprinomectin and selamectin) and milbemycins (nemadectin, moxidectin, d-milbemycin, etc.) [2].

These chemical classes are naturally occurring products. Avermectin is produced by the soil actinomycete bacterium *"Streptomyces avermitilis"* [3]. Avermectin derivatives are among the most common active compounds applied as veterinary drugs for food-producing animals, especially in aquaculture, and as plant protection agents in the agricultural sector, to control insects and mites on a wide range of agricultural products such as fruit, vegetable and ornamental crops [3–5].

Ivermectin (IVM) and abamectin (ABM) were the first macrocyclic lactones developed in the early 1980s. Other compounds have been marketed recently, such as moxidectin, doramectin, eprinomectin and emamectin benzoate [6]. ABM is known to be more toxic and moxidectin (MOX) less toxic when compared with IVM [7].

Abamectin (ABM) is a mixture of avermectin B1a (>90%) and avermectin B1b (<10%) [8, 9]. These two components, B1a and B1b, have very similar biological and toxicological properties [10]. Abamectin has been used extensively all over the world and is still one of the most commonly used pesticides in Algeria. It affects inhibitory synapses via a mode of action involving glutamate-sensitive chloride channels [8, 11]. ABM poisoning can impair the function of hepatocytes. Castanha Zanoli *et al.* have shown that ABM perturbs the mitochondrial bioenergetics [7].

A number of reports have been published on High-Performance Liquid Chromatography (HPLC) analysis of avermectins [6, 12, 13] and abamectin [14–18] in environmental, food, milk and other matrices using different extraction and detection methods. Recently, a liquid chromatography-tandem mass spectrometry and fluorescence detection method was used to determine avermectin and milbemycin residues in bovine muscle [19]. Liver tissues are regarded as the matrix of choice for the determination of residues but are particularly difficult to work with, due to the complex matrix interference that may be present [20]. Histological changes provide a rapid means for detecting the effects of pesticides in various animal tissues and organs.

This study therefore aims to evaluate the marker avermectin B1a residue in the plasma and liver, to provide the first detailed description of pathology in the liver during subacute ABM exposure, and to further investigate the effect of abamectin on some biochemical parameters in rats.

2 Materials and methods

2.1 Chemicals

A commercial formulation of abamectin (Avermectin B1, MK-936), named "Vertimec® 1.8 EC" (Syngenta Agrochemicals, Greensboro, USA) was used in the experiments. All biochemical reagents used were obtained from commercial sources (BIOLABO S.A., France).

A pure reference standard of abamectin (>98.7%, purity, Syngenta Agrochemicals, Greensboro, USA) was purchased from the Ministry of Agriculture and Rural Development (Direction de la Protection des Végétaux et des Contrôles Techniques DPVCT, Algeria). Acetonitrile and formic acid (HPLC grade) were purchased from Biosolve Chimie (Valkenswaard, the Netherlands). All other reagents were of analytical grade.

2.2 Animals and abamectin exposure protocol

Twenty-eight male and female albino rats (*Rattus norvegicus*) were obtained from the Centre de recherché et du development [CRD-SAIDAL El Harrach, Algérie] and kept under conditions of a constant 12-h light/dark cycle and controlled temperature (25 ± 2 °C). They were accustomed to laboratory conditions for 8 days. All animals had free access to a commercial standard pellet diet (ONAB: Office National des Aliments de Bétail, Algiers) and water *ad libitum*.

At the start of the study, the male rats were approximately 9 weeks old (weight 160−180 g) and the female rats were about 3 months old (weight 250−280 g). The study was performed according to OECD test guideline 407 with some deviations [21]. The number of animals in each dose group was increased from 5 to 7 male and female rats per group. The tested concentration was chosen based on preliminary experiments, using this experimental model. Only one high dose was given (2.13 mg/animal/day), which was the highest dose chosen in the study of Elbetieha and Daas [22].

The rats were randomly assigned to 4 groups of 7 animals each and were treated as follows.

Group 1: Control male rats.
Group 2: Abamectin-treated male rats.
Group 3: Control female rats.
Group 4: Abamectin-treated female rats.

Each rat received a single daily gavage dose of distilled water (controls) or abamectin at a dose of 2.13 mg/animal/day (abamectin-treated groups) for 28 consecutive days.

The animals were weighed every day. The body weight was determined throughout the acclimation, experimental and post-experimental periods. At the end of the experiments, the rats were euthanized by cervical decapitation under light diethyl ether anesthesia and the liver was isolated and weighed.

2.2.1 Sample preparation

An ultra-performance liquid chromatography tandem mass spectrometry (UPLC–MS/MS) method employing electrospray ionization (ESI) was developed for the determination of avermectin B1a in the plasma and liver of rats using methyl clonazepam as the internal standard (EI).

The standard calibration curve samples of ABM at concentrations of 0, 1, 5, 10, 25, 50, 100, 250, 500 and 1 000 ng/mL were prepared by serial dilutions with plasma from stock solution of 20 μg/mL.

2.2.2 Plasma and liver sample extractions

For the standard and plasma sample analyses, 100 μL EI (methyl clonazepam + hydroxyethyl theophiline) and 500 μL of ACN were sequentially added into a 100-μ L plasma sample then vortexed briefly. After centrifugation at 10800 rpm for 8 min, the supernatant was evaporated.

The rat liver samples were cut into small pieces and placed in a glass tube; 1 000 μL of ACN were sequentially added to 2.5 g of liver sample, then vortexed. The mixing and extraction steps were performed using a vortex for 2 min and ultrasonication for 15 min. Then, after centrifugation at 10 800 rpm for 8 min, the clear liquid phase was collected and was evaporated.

The plasma and liver residues were reconstituted in 100 μL of the mobile phase [(A): (87%) ammonium formate solution and (B): (13%) acetonitrile (ACN) and formic acid]. After centrifugation at 4 000 rpm for 10 min, 15 μL of the supernatant was then injected.

2.2.3 UPLC-MS/MS conditions

The chromatographic separation was performed on an Acquity UPLC (Waters Corporation, MA, USA). Analytes were separated using an Acquity UPLC HSS C18, 2.1 × 150 mm, 1.8-μm column (Waters Corporation, MA, USA) maintained at 50 °C.

The mobile phase was a binary mixture of formate buffer 5 mM pH 3.0 (A) and acetonitrile containing 0.1% formic acid (B) at a flow rate of 400 μL/min (0 min = 50% A; 1–3.25 min = 5% A; 4–5 min = 87% A). An injection volume of 15 μL was used.

Detection was performed using a Waters TQ Detector tandem quadrupole mass spectrometer (Waters Corporation, MA, USA) equipped with a Z-Spray^{TM} source and ES probe. The instrument was controlled using Waters MassLynx^{TM}v4.1. Ionization was performed in ES+. Source conditions were as follows: source temperature was maintained at 100 °C; capillary voltage: 3 kV; extractor cone: 3V; cone gas flow rate: 0 L/h; desolvation gas flow rate and temperature: 200 L/h and 250 °C, respectively.

All data were processed using the QuanLynx application manager (Waters Corporation, MA, USA).

In order to establish appropriate multiple reaction monitoring (MRM) conditions, the cone voltage was adjusted to maximize the intensity of the protonated molecular ion and collision-induced dissociation (CID) of both species was performed. Molecular ions (*m/z* 890.6 and 330.1 for abamectin and the IS, respectively), were selected in Ql and the corresponding daughter ions (*m/z* 567.1 and 305.2 for abamectin and *m/z* 284.0 and 255.1 for the IS) were detected in Q3 after collision with argon, used as the collision-activated dissociation gas.

2.3 Biochemical levels

Blood samples (~3 mL) were collected into EDTA tubes via the supra-orbital sinus on days 14, 28 and 42. Plasma samples were obtained after centrifugation at 4 000 revolutions per minute for 15 min, and stored at –20 °C until analysis. The following clinical chemistry parameters of plasma were measured using a Hitachi 912 Clinical Chemistry Analyzer: aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transpeptidase (γ-Gt) enzyme activities, and concentrations of glucose (GLUC).

A commercial kit (BIOLABO S.A., France) was used according to the manufacturer's instructions in these analyses.

2.4 Histopathogical analysis

The liver was excised from all rats and fixed in 10% neutral formalin buffer. Tissue sections (5-μm thick) were cut and stained with hematoxylin and eosin for histopathological studies.

2.5 Statistical analysis

Statistical analysis was performed using Statistica version 10.0 (StatSoft Inc., Tulsa, USA). Data were calculated using one-way analysis of variance (ANOVA) followed by the Newman-Keuls and Duncan's post-hoc tests. Data were expressed as the mean ±SE. $P < 0.05$ was considered as the level of significance.

3 Results

The present study investigated the effect of repeat doses of 2.13 mg/animal/day of abamectin on biochemical parameters, residues of B1a in the plasma and liver, and the histopathology of the liver on male and female rats.

3.1 Evaluation of body weight and liver weight

During the study period, there were no clinical signs of toxicity in any treatment group. There were no differences between females (control and ABM – female) and males (control and ABM – male), while body weight was significantly lower

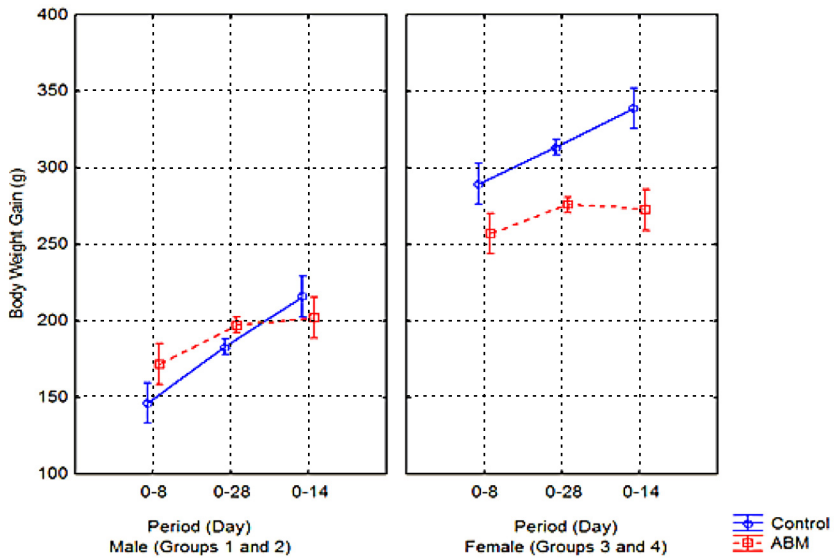

Fig. 1. Effect of abamectin (2.13 mg/animal/day) on the body weight of male (M) and female (F) rats throughout the acclimation (0–8 days), experimental (0–28 days) and post-treatment periods (0–14 days).

Table I. Body weight, and absolute and relative liver weight (liver absolute weight/body weight at the end of the experiment ×100) ($g \pm$ SE) for male (M) and female (F) rats in control and ABM-exposed (2.13 mg/animal/day) groups. [In the acclimation (1 week), experimental (28 days) and post-treatment periods (14 days)].

Groups	Body weight				Liver weight	
	Acclimation	Experimentation	Post-treatment	At the end of experiment	Absolute	Relative
1: Control M	153.66 ± 4.91	183.49 ± 12.78	215.77 ± 6.62	221 ± 1.32	9.26 ± 0.65	4.19 ± 0.20
2: ABM M	165.10 ± 5.20	197.50 ± 11.54	202.11 ± 5.38*	199 ± 2.18*	9.70 ± 0.92*	4.87 ± 0.32*
3: Control F	283.55 ± 5.27	313.18 ± 11.49	276.41 ± 12.24*	342 ± 3.22	14.27 ± 1.87	4.17 ± 0.38
4: ABM F	262.99 ± 4.53	338.88 ± 3.89	272.55 ± 2.69*	271 ± 1.34*	11.71 ± 1.37*	4.32 ± 0.61*

* Statically significantly different ($p < 0.05$) from the control male and female groups ($n = 7$).

in the male than in the female groups during the acclimatization period. During the experimental period, the body weight of the animals in the ABM-female group (group 4) increased significantly ($p < 0.05$) compared with the control group 3. At the end of the experimental study and after a post-treatment period there was a significant decrease in body weight in male and female ABM-treated groups. The relative organ weight of the liver in ABM-treated groups 2 (male) and 4 (female) showed a statistically significant increase ($p < 0.05$). The results of the effects of 2.13 mg/animal/day of ABM on body and liver weight are summarized in figure 1 and table I.

However, body weight gain was significantly lower in ABM-treated groups 2 and 4 than in the control groups (1 and 3) during the post-treatment period; lower mean food consumption was also noted in these groups.

The results showed that treatment with abamectin caused an increase in the liver weight (1.77% in male and 7.51% in female ABM-treated rats compared with the controls).

3.2 Biochemical results

The effects of ABM on biochemical parameters in the rats are given in Table II. ABM exposure caused a significant ($p < 0.05$) increase in glucose count levels in ABM-treated rats but, after 14 days of non-treatment, there were no significant differences between control and ABM-treated groups.

Table II also shows some biochemical variables that indicate liver injury in rats. Exposure of male and female rats to ABM produced a significant ($p < 0.05$) increase in plasma ALAT, ASAT and γ-GT activities compared with those of the control groups.

3.3 Plasma and liver abamectin concentrations

Abamectin was found in all plasma samples of male and female ABM-treated rats in a time-dependent manner at 14 and at 28 days of treatment. However, at 42 days there were no residues in the plasma of ABM-treated rats (figure 3).

In male ABM-treated rats, the drug plasma concentration was 148 ng/mL at day 14 and 225 ng/mL at 28 days. However, in female ABM-treated rats, the drug plasma concentration was 193 ng/mL at day 14 and 279 ng/mL at day 28 (figure 2A).

In the liver, abamectin concentrations at the end of the experiment (day 42) were between 362 ng/g (female) and 83 ng/g (male). ABM concentrations were significantly lower in male compared with female rats at 14 days post-treatment (figure 2B).

The results showed that higher avermectin B1a concentrations were recovered in the liver of female ABM-treated rats at 42 days than those measured in male rats. Mean ABM concentrations in the plasma and liver contents in male and female

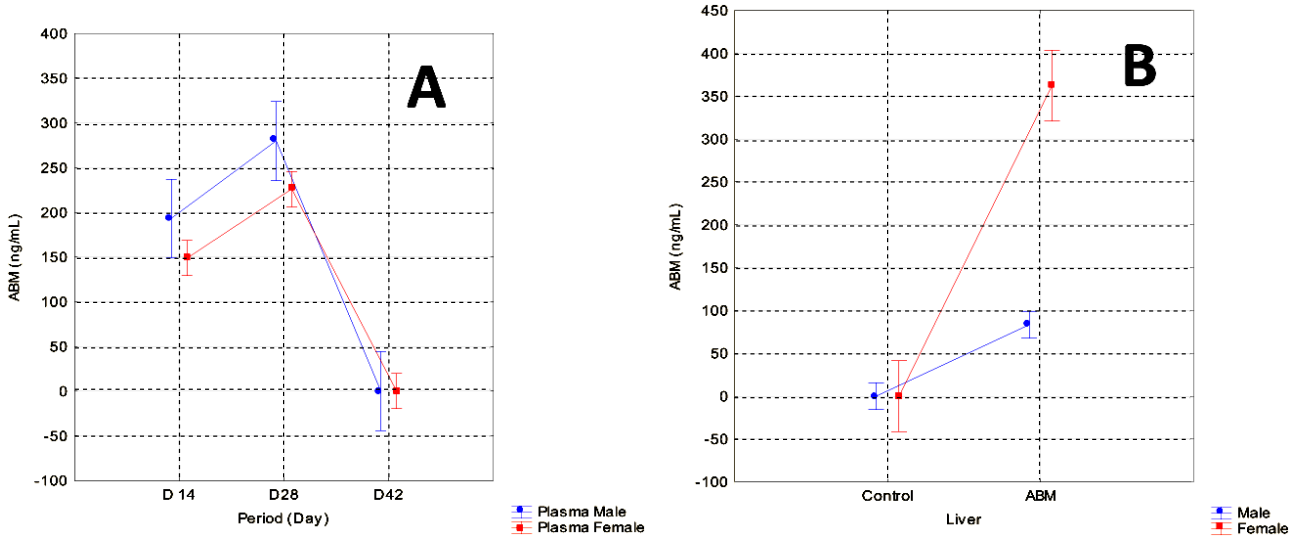

Fig. 2. (A) Plasma ABM [B1a (ng/mL)] concentrations at 14, 28 and 42 days obtained after administration of 2.13 mg/animal/day (daily for 28 days) to male and female rats. (B) Liver ABM [B1a (ng/mg)] concentrations at 42 days (post-treatment period) from male and female ABM-treated rats. Mean (±SE) (n = 3) plasma abamectin (ABM) and mean (±SE) (n = 7) liver abamectin (ABM).

Table II. The overall means (± SE) (n = 7) of plasma glucose, alanine transaminase (ALT), aspartase aminotransferase (AST) and γ glutamyl transpeptidase (γ-Gt); during the treatment (14 and 28 days) and post-treatment periods (42 days) of male (M) and female (F) rats with 2.13 mg/animal/day abamectin.

	Time post-treatment (days)	Group 1 Control M	Group 2 ABM M (2.13 mg/animal/day)	Group 3 Control F	Group 4 ABM F (2.13 mg/animal/day)
Glucose (g/dl)	14	1.04 ± 0.01	1.08 ± 0.04	1.03 ± 0.02	1.03 ± 0.03
	28	1.03 ± 0.00	1.85 ± 0.14*	1.07 ± 0.00	2.47 ± 0.05*
	42	1.04 ± 0.01	1.09 ± 0.09	1.00 ± 0.05	1.02 ± 0.06
AST (IU/L)	14	84.00 ± 7.89	100.80 ± 5.30*	72.69 ± 5.31	105.33 ± 8.04*
	28	75.25 ± 1.75	98.80 ± 6.17*	82.50 ± 6.63	95.66 ± 9.88*
	42	76.40 ± 3.29	73.50 ± 6.06	76.80 ± 3.73	74.33 ± 3.55
ALT (IU/L)	14	30.20 ± 1.65	38.50 ± 4.90*	46.33 ± 0.21	53.60 ± 0.97*
	28	34.60 ± 2.71	43.75 ± 1.25*	44.33 ± 2.92	53.80 ± 0.28*
	42	36.60 ± 3.28	41.50 ± 3.17*	34.33 ± 0.76	55.20 ± 1.10*
γ-Gt (UI/l)	14	7.23 ± 0.35	8.27 ± 0.73*	10.74 ± 0.87	20.00 ± 0.36*
	28	7.34 ± 0.29	8.11 ± 0.68*	10.10 ± 0.20	12.89 ± 0.45*
	42	7.67 ± 0.34	8.99 ± 0.37*	11.12 ± 0.31	13.41 ± 0.95*

* Statistically different from the control group of male and female rats ($P < 0.05$).

rats are compared in figure 2. Also, higher abamectin concentrations than those measured in male rats were recovered in the livers of female ABM-treated rats at 42 days.

3.4 Histological results

The liver of control groups revealed normal hepatocytes arranged in cords which are separated from each other by sinusoids (figure 3A). Kupffer cells are also present along the sinusoidal spaces.

Histological examination of the liver sections (figures 4B–4D) of the ABM-treated groups revealed massive congestion. The main findings were a narrowed appearance of Bowman's space, degeneration of the tubular epithelial lining, a widened lumen, hemorrhage and cellular infiltration. The hepatocytes showed a significant increase in nuclei and cell size, and cell granularity after chronic ABM treatment, thus representing the active metabolizing state of these cells.

4 Discussion

The present study provides additional information on ABM-induced toxicity in the rat, after subacute oral exposure. The oral route seems to be the most relevant in long-term real exposure for the general population, due to residues in food [23] and also in tissues. Abamectin pesticide was chosen in this study because it is used extensively all over the world, including Algeria where the study was performed. Based on the results, the systemic effects of ABM may be described as follows.

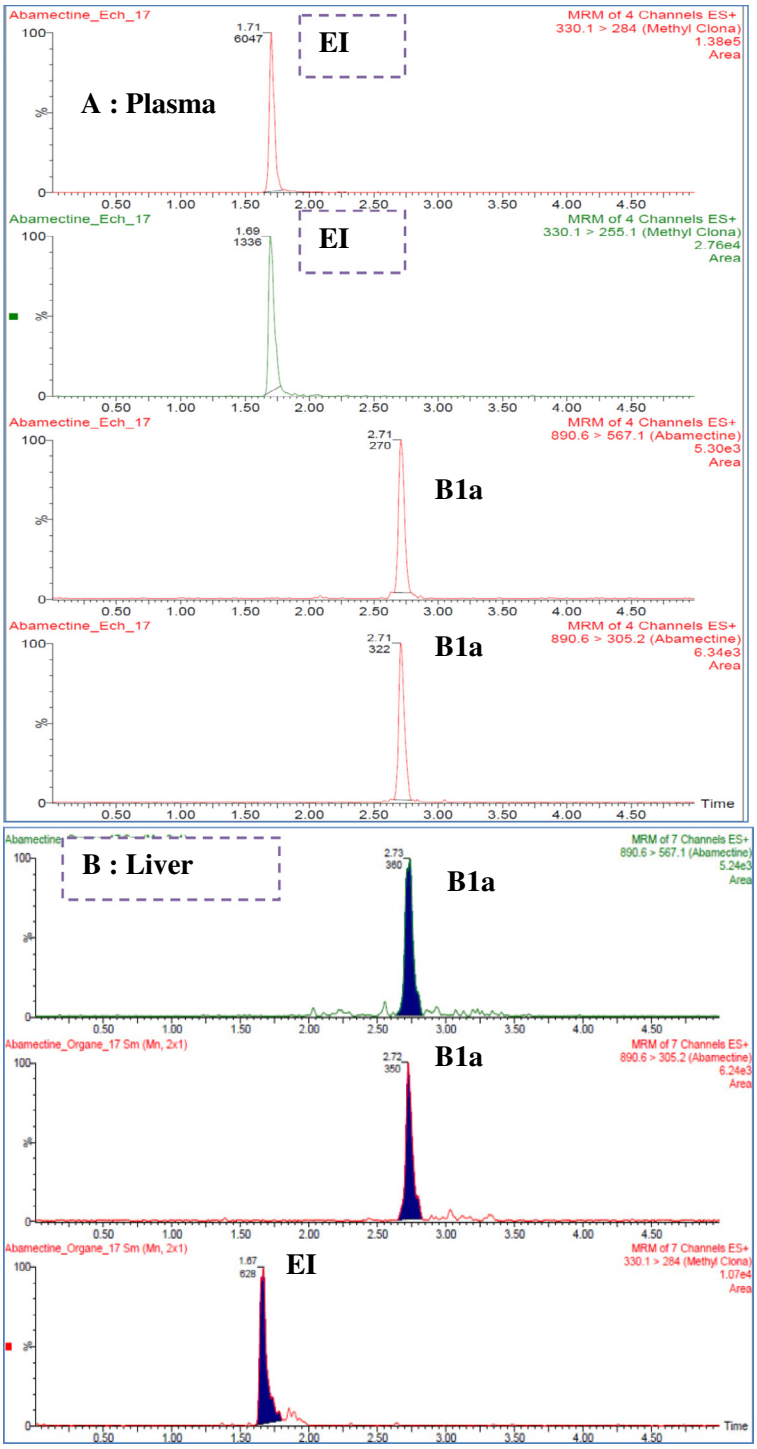

Fig. 3. Chromatograms of the two MRM transitions of ABM B1a in the plasma (A) and liver (B). The mass transitions used are as follows: avermectin B1a: 890.6 > 567.1; 890.6 > 305.2 and EI: 330.1 > 284; 330.1255.1.

In the present study, cellular damage was evaluated by measuring ALT and AST activity. In addition, the antioxidant status of hepatocytes was determined by measuring the level of the GSH-related enzyme, γ-GT. Serum ALT and ALAT aminotransferases are usually employed in assessing the liver function; they are found in the cytoplasm and mitochondria of most cells. ABM poisoning can impair the function of hepatocytes [24]. Our results indicated that the concentration of plasma ASAT, ALAT and γ-GT increased significantly ($p < 0.05$) in male and female rats treated with abamectin, a result in agreement with that of Hsu *et al.*, [24] who showed elevated levels of the cytosolic enzyme of the hepatocytes, aspartate aminotransferase (AST), in the blood serum of rats exposed to 1–20 mg/kg body weight abamectin. However,

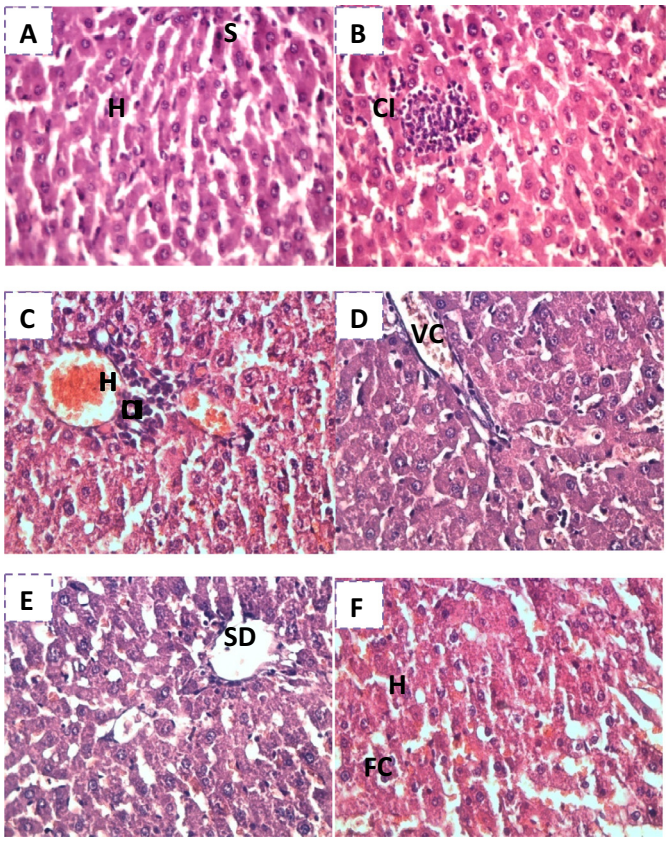

Fig. 4. Photomicrographs of the liver from a control rat (A) showing normal architecture: hepatocytes (H) and sinusoids (S). From male (B, C) and female (D, E, F) treated groups given ABM at the dose of 2.13 mg/animal/day, showing vascular congestion (vc) and hemorrhage (h), cellular infiltration (CI), sinusoidal dilatation (sd) and foamy cytoplasm (FC) . (H&E × 400).

in the present study, after 14 days of non-treatment, no significant changes were observed in ALT activity of ABM-treated rats compared with controls. γ-glutamyl transpeptidase is the sensitive marker enzyme of renal cell injury [25]. El-Shenawy's [26] study of the *in vitro* toxic action of some insecticides, including ABA, on isolated rat hepatocytes showed a significant increase in ALT and AST activity when hepatocytes were incubated for 30 min with either concentration of ABA. This activity persisted after 120 min, the longest time for which data was collected.

These results reflect the increase in plasma membrane permeability resulting from the hepatic damage [27] and observed signs of abamectin liver toxicity, with increased activity of the enzyme AST in rats treated with doses equivalent to 1/10 or 1/100 of the LD50 (18 mg/kg) in the diet of animals over 30 consecutive days.

The biochemical data (table II) showed that the increase in plasma levels of ALAT and γ-glutamyl transpeptidase persisted after 14 days with no further treatment.

The above findings were confirmed by histopathological changes in the liver under the intoxication effect of abamectin. Abamectin caused marked damage of the liver tissues in the form of dilated veins, hemorrhagic spots and degenerative hepatocytes.

ABM exposure caused a significant ($p < 0.05$) increase in glucose count in ABM-treated rats, but after 14 days of non-treatment there were no significant differences between control and ABM-treated groups.

Different MLs have different toxicities in mammals. Enzymes can metabolize MLs but the efflux of parental compounds via active transport has been shown to be the main route of ML elimination [7].

The presence of ATP-binding cassette (ABC) transporters, including P-glycoprotein at the intestinal level, contributes extensively to the elimination of drugs in the feces and provides efficient barriers that protect the organism from the toxicity of most xenobiotics [28].

All avermectins interfered with the transport activity of P-glycoprotein, which acts as a trans-membrane protein, transporting some drugs into and out of cells. Animals showing decreased P-gp activity show greater bioavailability of a drug after oral administration and accumulate greater levels of drugs in their CNS tissue [6].

P-gp is located on the apical surface of the enterocytes and hepatocytes, and thus expels drugs into the intestinal lumen and the bile [29]. Nevertheless, previous studies support the extensive elimination of avermectins (IVM) by the fecal route in rodents [30, 31]. Tests with laboratory animals show that avermectin B1a is not readily absorbed into the bloodstream by mammals; it is rapidly eliminated from the body within 2 days *via* the feces [30].

Accordingly, in the present investigation, the presence of abamectin residues in all plasma samples of ABM-treated rats at 14 and 28 days of treatment and their non-detection at 42 days in the plasma of ABM- treated rats may be due to their elimination by the fecal route.

Pharmacokinetic parameters for IVM are strongly affected by the presence or absence of P-gp [30]. The present data showed that treatment with abamectin induced the accumulation of residues in the liver even after a 14-day period of non-treatment.

Dupuy *et al.* [32] showed an increased accumulation of moxidectin and avermectin in rat hepatocytes after inhibition of P-gp or other ABC transporters. Accordingly, the observed accumulation of residues in the liver suggests a corresponding inhibition of P-gp transporter, which leads to increased concentration of this xenobiotic in the liver. Also, the lipophilic nature of ABM may lead to its accumulation in the liver.

5 Conclusion

In summary, the UPLC MS/MS method was successfully applied to determine avermectin B1a in the plasma and liver after subacute abamectin exposure. Elevation of AST, ALAT and γ-GT activity, histopathological changes and persistence of residues in the liver after 14 days without treatment confirm liver injury in rats after ABM intoxication.

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