EGYPTIAN ACADEMIC JOURNAL OF

BIOLOGICAL SCIENCES

TOXICOLOGY & PEST CONTROL

F

ISSN
2090-0791

WWW.EAJBS.EG.NET

Vol. 13 No. 1 (2021)

www.eajbs.eg.net

Citation :*Egypt. Acad. J. Biolog. Sci.* (F.Toxicology &Pest control) *Vol.13(1)pp71-81(2021)*
DOI: 10.21608/EAJBSF.2021.142524

Egypt. Acad. J. Biolog. Sci., 13(1):71- 81(2021)

Egyptian Academic Journal of Biological Sciences
F. Toxicology & Pest Control
ISSN: 2090 - 0791
http://eajbsf.journals.ekb.eg/

Acute Abamectin Exposure Induces Oxidative Stress Responses in Liver of Male Albino Rats

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ARTICLEINFO
Article History
Received: 28/11/2020
Accepted: 29/1/2021

***Keywords*:**
Abamectin, Hepatotoxicity, Oxidative Stress, Oral, Dermal, Rat.

ABSTRACT

Background: Acute oral and dermal toxicity tests are considered as a regulatory assessment in systemic toxicity of agrochemicals. **Aim**: this study achieved to study the effect of single oral and dermal sub-lethal exposure of abamectin on the oxidative stress biomarkers in the liver of male albino rats. **Methods**: forty rats were divided into three groups as control, oral and dermal. The tested dose was ½ of LD_{50} for oral and dermal experiments. **Results:** exposure to abamectin (ABM) at sub-lethal doses oral or dermal is connected with induction of oxidative stress in the liver of male albino rats. Oxidative stress is evidenced by the increase in lipid and protein oxidation (MDA and PC) biomarkers. As well, antioxidant enzymes such as CAT and GST were increased hepatocytes. On the other hand, glutathione and glutathione peroxidase (GPx) and SOD were markedly reduced. Acetylcholinesterase (AChE) activity in hepatocytes was markedly increased in both oral and dermal exposure. **Conclusion:** this study through light on the importance of responsible use of pesticides in reducing the hazard impact of agrochemicals.

INTRODUCTION

Widespread use of pesticides, significant questions about health hazards resulting from farmers' exposure when applying and applying pesticides or working in treated fields and from residues on food and drinking water have been posted for the general public (Soares, and Porto, 2009). These operations have triggered a variety of unintended poisonings, and even the regular use of pesticides can, in the short and long term, pose significant health risks to farmers and degrade the environment. In countries that are emerging, improper application techniques, poorly maintained or entirely inadequate spraying machines, ineffective handling methods, and also the reuse of old pesticide containers for food and water storage, farmers face major exposure hazards (Asogwa, and Dongo, 2009).

Bio-pesticides are developed from naturally occurring substances that control pests by eco-friendly manner derived, living organisms, their products, or by-products (Mazid, *et al.*, 2011; Kumar, 2015).Avermectins (AVMs) are bio-pesticides extracted from fermentation products of the soil microorganism *Streptomyces avermitilis*. Its family members are containing 16 – member macrocyclic lactones with a disaccharide substituent at the carbon-13 position. These compounds are one of the most active insecticides include ivermectin,

abamectin, emamectin, eprinomectin, and doramectin. The commercial product of abamectin (ABM) is a mixture of approximately 80% of avermectin B1a and ≤ 20 % avermectin B1b (Fig. 1). It is a potent anti-parasitic agent with a wide range of activities to eliminate gastrointestinal nematodes, lung worms and nasal bots in human and many animal species (agricultural and domestic animals). In addition, it is developed to control ants and cockroaches in commercial baits (Campbell, 1990; Geary, 2005). Abamectin has also, been extensively used as insecticide, acaricide, and nematicide to control pests in a wide variety of agricultural products such as fruits, vegetables and ornamental crops (Campbell, 2012). The mechanism of action of abamectin is interaction with the gamma-aminobutyric acid (GABA) system and Cl channels responsible for regulating the neural basal tone in the brain and nerve cells of the central nervous system, (Turner, and Schaeffer, 2018;Subbanna, *et. al.,* 2020). It blocks electrical activity in nerve and muscle preparations. The mass of the medium is interrupted by electrical activity in neuromuscular preparations by increasing the membrane conductance to ions of chloride (McCavera, *et al.,* 2007; Kolar *et al.* 2008; Subbanna, *et al.,* 2020). Abamectin exposure induced multi-organ damages, such as kidney, liver, stomach, nervous system, and testes (Hsu *et al.* 2001; Khaldoun-Oularbi *et al*., 2013 & 2017). In addition oxidative, immunological damage, cytotoxicity and genotoxicity occurred mammals, birds and fish (Zhu *et al.,* 2013; Huang *et al.,* 2019; Srivastava, *et al.,* 2020).

The harmfulness of pesticides may vary based on either the type of contact, (i.e. dermal, oral, or respiratory), by dose (concentration) and basic periods despite the poisonous nature of the chemical (Meenakshi *et al.,* 2012). Dermal exposure is one of the most common and effective routes through which pesticide applicators are exposed to pesticides (Anderson and Meade, 2014). Dermal absorption can occur when blending, packing, disposing of, and/or washing pesticides due to a splash, spill, or spray drift (Salvatore *et al.,* 2008). When workers handle (e.g., mix) concentrated pesticides, the chance of skin absorption increases (e.g., one containing a high percentage of active ingredients (Dennis *et al.,* 2010). The key unintended oral exposure to pesticides is the transition of pesticides from the main marked package to an unidentifiable bottle or food container (Gilden *et al.,* 2010) and careless handling of pesticides without hand washing (USEPA, 2007).

The liver is a central organ in the human body that plays an essential role in the metabolism and detoxification of xenobiotics also the biosynthesis of energetic macromolecules for different essential functions (Djordjevic *et al.,* 2011). Hepatotoxicity is therefore an important endpoint in the evaluation of the effect of particular xenobiotics (Mossa *et al.,* 2012). The highest levels of ABM were detected in the liver and fat, owing to its lipophilic nature, (Gonzalez, *et al.,* 2009, Batiha, *et al.,* 2020). Therefore, the liver can be used as an index for the toxicity of abamectin in vertebrate animals (Anderson, and Borlak, 2007).

Advanced studies observe that insecticide toxicity may be related to the enhancement production of ROS (Bosse, *et al.,* 2011; Campos, *et al.,* 2016). Also, the production of ROS has been proposed as a mechanism through which foreign biomechanics and pathologies can produce oxidative stress and cause damage to various tissues (Clark, *et al.,* 1995; Zama, *et al.,* 2007).

So, the objective aim of this study is the collection of data between occupational exposure to sub-lethal doses of bio-pesticides (abamectin) through dermal or oral exposure single exposure and the oxidative stress biomarkers in hepatic tissues of male albino rats during acute toxicity period.

MATERIALS AND METHODS

Insecticide:

The commercial formulation of abamectin (Vertemic ® 1.8 % EC) (Fig.1) was supplied by Central Agricultural of Pesticides Laboratory (CAPL), Agricultural Research Centre (ARC), Dokki, Giza, Egypt.

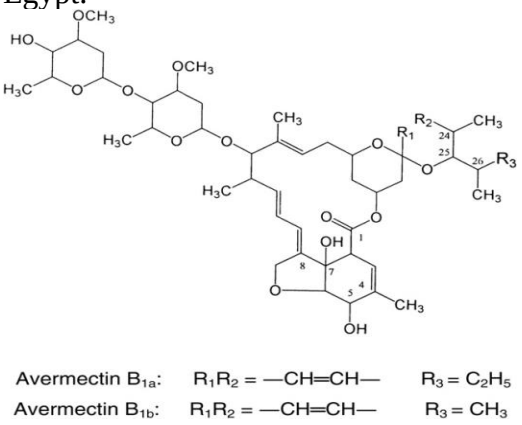

Fig. 1. Chemical structures of abamectin components avermectin B1a and B1b

Preparation of Tested Animals:

Mature male albino Wistar rats (*Rattus norvegicus*) were used to evaluate the acute hepatotoxicity of abamectin by oral and dermal intubation. Forty rats aged 3 – 4 months and weighing 160 - 180 g were purchased from the breeding unit of the Mammalian and Aquatic Toxicology Department, CAPL, ARC, Dokki, Giza, Egypt. The animals were divided into three groups, randomly. The first group (ten rats) was kept as a control without any treatment. The 2nd group (15 rats) was used to per-oral intubation (P. O.) and the 3rd group (15 rats) was used to per-cutaneously exposure (P. C). The animals were housed in plastic cages, with five rats per cage, and allowed to acclimatize under standard conditions at an ambient temperature of 25 ± 2°C with 55 – 64% relative humidity and 12/12 h photoperiod (light/dark cycles) for 1 week. The rats were allowed free access to a standard pellet diet and water *ad libitum.*

Before 24 hours of the dermal application (P. C.) of insecticide, the trunk of the test animals are clipped free of hair with electric clippers (Oster Corp., Model A2, Milwaukee, WI, USA) using a size 40 blade without disturbing the derma to prevent bleeding of the skin. The clipped area (10% of the skin surface) moistened and washed with sterile distilled water to remove extraneous matter. The trunk of the animal treated with abamectin is wrapped with gauze and rubber damming. The gauze is removed twenty-four hours after application of insecticide, and the treated sites are washed with sterile distilled water.

Application Design:

The acute oral and dermal LD_{50} values of abamectin (Vertemic® 1.8% EC) were determined according to the method of Weil (1952). The animals were given 1/2 LD_{50} of abamectin (mg/kg bw) as a single dose. All animals were treated according to the guidelines of acute oral toxicity (OCED, 2008, No. 425) and acute dermal toxicity (OCED, 2017, No. 402) in rodents. Observation is done daily for 14 days and responses are recorded. The rats (treated and untreated) are sacrificed and necropsy after 14 days.

Tissue Preparation:

After 1, 7, 14 days of the experiment, the liver was removed from rats under anesthesia and washed with cold saline buffer. Washed tissues were immediately stored at – 80 ºC. For determination enzymatic activities, tissues were homogenized in ice-cold 50mM sodium

phosphate buffer (pH: 7) containing 0.1 mM ethylendiaminetetraacetic acid (EDTA) yielding 10% (W/V) homogenate. The homogenates were centrifuged at 12.000 g for 30 min at 4 ºC. The supernatant was used for the investigation of enzyme activities washed with cold saline buffer.

Biochemical Assay:

Acetylcholinesterase (AChE) activity was assayed in liver tissues by the method of Ellman, *et al.,* (1961). Total protein (TP) level was quantified by the procedure of Pradford (1976). Lipid peroxidation was estimated as the concentration of thiobarbituric acid reactive products (malondialdehyde, MDA) (Ohkawa, *et al.,* 1979). Protein carbonyl (PC) content was assayed using the mentioned method Yan *et al.,* (1995). Superoxide dismutase (SOD), catalase (CAT) and glutathione - s - transferees (GST) activity was measured by the methods of Marklund and Marklund, (1994); Aebi, *et al.,* (1984) and Habig, *et al.,* (1973) respectively. Total reduced glutathione (GSH) content and glutathione peroxidase activity were measured by Beutler, *et al.,* (1963)method.

Ethical Statement:

This study was conducted in accordance with ethical procedures and policies approved by the Institutional Animal Care and Use Committee of Zagazig University (No. ZU-IACUC/2/F/38/2019).

Statistical Analysis:

The data obtained from the biochemical analysis of various groups are represented as mean ± standard error (M ± SE) in tables. The significance of the difference between the groups was calculated by one-way analysis of variance (ANOVA) followed by Duncan's test at $P \leq 0.05$ (*) 0.01 (**), and 0.001 (***) using the SPSS - PC computer software package version 25.

RESULTS

The oxidative stress (OS) has been measured using different markers, both bio-molecules oxidized (lipids, proteins, and DNA) and antioxidants (enzymes and non-enzymatic antioxidants), besides oxidants (reactive oxygen species), everything in biological samples (Sánchez-Rodríguez and Mendoza-Núñez, 2019).

The determined abamectin (Vertemic® 1.8% EC) oral and dermal LD_{50} was 20 and 500 mg/kg bw for male rats respectively. The result analyses of the non-enzymatic oxidative stress biomarker are presented in Table (1). A significant risein liver MDA levels was noticed in all groups ($p \leq 0.001$) except, a significantly decreased after 1 and 14 days from treated with a single dose by dermal and oral respectively, was observed. In addition, there was a significant increase in liver PC levels of groups that were treated with a sub-lethal dose of abamectin (ABM) by gavage and topical after 1 and 7 days of exposure compared to theuntreated group ($p \leq 0.001$). Moreover, a significant decrease in liver glutathione (GSH) content was seen in groups after 7 days with each treatment compared to the control group while a significant increase was observed after 1 day of the oral treatment.

We showed also an increase significantly in liver AChE activity in groups treated with abamectin by oral and dermal compared to the untreated group (Table, 2). Also, we determined the enzymatic oxidative stress aspects and tabulated them in table (2). The Liver CAT specific activities showed a significant increase in groups treated by oral and dermal after 1 and 7 days of treatment with the single-dose meanwhile, the reduction after 14 days by dermal exposure was recorded compared to the control group ($p \leq 0.001$). A significant decrease in the specific activities of liver GPx was observed among the groups expect, in a group treated orally after 14 days was increased ($p \leq 0.001$) compared to the control group. Also, the liver SOD activities were inhibited at groups 7 and 14 days after treated per-oral,

while the significant increase ($p \leq 0.01$) with the single dose of abamectin per-courteously after 1 and 14 days of the treatment and there were no significant differences in liver SOD activities after 1 day and 7 days of groups treated by orally and dermal respectively. The specific activity of glutathione-s-transferase (GST) was depressed ($p \leq 0.001$) after 1 day of treatment with the sub-lethal dose of ABM with both two routes of exposure (R. E.), then this effect returned to the normal range after 7 days. DA levels among the groups.

Table 1: Influence of acute exposure on non-enzymatic oxidative stress (MDA, PC, GSH) in the liver of abamectin – treated male rats.

Biomarkers	E. R.	Cont.	Days after exposure			Gen. Cor.
			1	7	14	
MDA (nM/ml)	P. C.	13.705 ± 0.4562	11.026 ± 0.3732*	18.654 ± 0.6946***	24.273 ± 1.013***	- 0.722
	P. O.		17.966 ± 0.3128***	17.427 ± 0.3183***	6.117 ± 0.1556***	
PC (nM/ml)	P. C.	52.314 ± 0.9532	83.626 ± 2.686***	107.502 ± 1.779***	55.639 ± 1.397	0.720
	P. O.		94.792 ± 4.141***	78.159 ± 3.435***	49.85 ± 1.768	
GSH (nM/ml)	P. C.	508.8 ± 8.482	533.00 ± 19.849	457.00 ± 16.248*	531.6 ± 12.644	0.714
	P. O.		631.00 ± 19.065***	434.00 ± 22.045**	478.0 ± 6.819	

E. R. = Exposure Route, P. C. = Per-cutaneously, P. O. = Per-oral, and Gen. Cor. = General Correlations.

Table 2: Influence of acute exposure on a specific activity (/mg protein) of AChE, and enzymatic oxidative stress (CAT, GPX, SOD, and GST) in the liver of abamectin – treated male rats.

Biomarkers	E.R.	Cont.	Days after exposure			Gen. Cor.
			1	7	14	
AChE (µM/min)	P. C.	249.86 ± 11.59	292.70 ± 13.07*	291.07 ± 5.66*	299.49 ± 9.9**	0.709
	P. O.		289.78 ± 13.63*	279.64 ± 7.25	341.04 ± 15.16***	
CAT (U)	P. C.	5.387 ± 0.1657	2.021 ± 0.295	6.39 ± 0.21**	3.57 ± 0.18***	-
	P. O.		7.115 ± 0.2715***	6.816 ± 0.3404**	5.761 ± 0.3015	
GP_x (nM/min)	P. C.	66.866 ± 1.311	40.373 ± 0.6324***	41.257 ± 0.9491***	45.237 ± 0.6345***	-
	P. O.		53.902 ± 1.834***	57.197 ± 1.462***	79.602 ± 1.667***	
SOD (U)	P. C.	4.578 ± 0.0788	5.021 ± 0.1167**	4.622 ± 0.0673	4.951 ± 0.0423**	-
	P. O.		4.456 ± 0.1189	4.028 ± 0.083***	3.568 ± 0.0247***	
GST (µM/min)	P. C.	25.31 ± 0.9134	15.377 ± 0.5686***	60.1 ± 2.218***	22.356 ± 0.7507	0.677
	P. O.		10.042 ± 0.2375***	28.181 ± 1.177*	24.018 ± 0.9807	

E. R.= Exposure Route, P. C.= Per-cutaneously, P. O.= Per-oral, and Gen. Cor. = General Correlations.

The results of correlation analysis, as shown in Tables (1 & 2), revealed a strong and significant positive correlation between each route of exposure (P. O. and P. C.) in liver PC, GSH, AChE, and GST. On the other hand, negative correlations were observed between P. O. and P. C. in liver MDA.

DISCUSSION

Environmental pollutants stimulate a variety of mechanisms of toxicity on a molecular level and oxidative stress seems to be the common denominator leading to the damage to cellular membrane lipids, DNA, and proteins, as well as modulation of antioxidant enzymes. RS are, due to their high reactivity (e.g., hydroxyl radical formation), prone to caused damage to any type of molecule within the cell, for example, polyunsaturated fatty acids, glutathione, certain amino acids, and so forth (Poljšak and Fink (2014). Human exposure to pesticides can occur through different routes, including occupations dealing with production, transport, delivery and application of pesticides, residing in the places high in pesticide residue, and circulation and accumulation of pesticides in the food chain (Mostafalou and Abdollahi 2017).

Oxidative stress (OS) is the imbalance between oxidant and antioxidant molecules, in favor of oxidants, that cause aging and disease. Many studies have been published that demonstrate the relationship between OS and human health and disease (Sánchez-Rodríguez and Víctor, 2019). The skin is known to contain many of the xenobiotic-metabolizing enzymes found in the liver, and some of these have been shown to be inducible, primarily by polycyclic hydrocarbons (Hodgson, 2011; Baron *et al.*, 2008).

Acetylcholinesterase (AChE) is a key enzyme in the nervous system. It terminates nerve impulses by catalyzing the hydrolysis of neurotransmitter acetylcholine as a specific molecular target of organophosphate and carbamate pesticides, acetylcholinesterase activity and its inhibition has been early recognized to be a human biological marker of pesticide poisoning. ABM in our experiment may have affected both the cholinergic and GABA-ergic interneurons. It is possible that ABM increases the release of ACh via affecting sodium channels of cholinergic nerves. The increase in AChE activity may be involved in mediating acute toxic effects of ABM in rats (Vučević *et al.*, 2009).

ABM markedly increased MDA concentration with acute oral and dermal exposure. As MDA is a product of polyunsaturated fatty acid peroxidation that results through degradation by ROS, this supports the incidence of cell toxic stress. In addition, the elevated concentration of MDA can interact with DNA and proteins causing potentially mutagenic and at herogenic effects (Del Rio *et al.*, 2005). Protein oxidation concludes specific amino acid modification, peptide cleavage and protein cross-linkage. Protein modification affects signal transduction, enzyme activity and proteolysis. Reacting of Lipid peroxidation products with other bio-molecule enhances biochemical lesions. (Akhgari *et al.*, 2003; Kaur and Thakur, 2018). At the molecular level, pesticides can interfere with the redox status and induce membrane lipids peroxidation (Tebourbi *et al.*, 2011).

Catalase is a prominent endogenous antioxidant enzyme. The higher activity of hepatic CAT, noticed in the present study, may have been an adaptive response against H_2O_2 produced by ABM metabolism (Radi *et al.*, 2020). The decrease in liver GSH and GSH-Px after exposure to ABM may lead to excessive free radical generation. These free radicals might be attacking the thiol group of cysteine residues and polyunsaturated fatty acids of biological membranes (Raina *et al.*, 2009).GSH-Px is localized mainly in the cytosol and mitochondria of the liver, so this organ can be accepted as a source of this enzyme. Therefore, decreased GSH-Px activity in the liver might be due to oxidative inactivation of the enzyme protein because of the accumulation of insecticide in the liver (El-Tawil and Abdel, 2001; Giray *et al.*, 2001).

The oxidative stress induced by abamectin intoxication may be related to the ability of ABM to induce mitochondrial dysfunction and disturbance of calcium homeostasis (Maioli *et al.*, 2013). These results are similar to those found by Zhu *et al.* (2013) and Li *et al.*, (2013) whereas, avermectin caused liver damage, inhibition of SOD, and increased MDA levels.

Finley, to achieve the desirable goal of minimum exposure to pesticides, it is essential to shift towards alternative cropping systems that are less dependent on pesticides. This can be realized by focusing more on ecological approaches to crop protection based on available ecological knowledge. The use of advanced ecological knowledge by agronomists is fairly recent.

CONCLUSION

This study was evaluated and trying to understanding the effects of historical exposure to pesticides to increase the abilities of agricultural systems to induce the natural processes of pest regulation and to contribute to the improvement of agricultural production.

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ARABIC SUMMARY

السمية الحادة للأبامكتين المحدثة لإستجابات الإجهاد التأكسدى فى كبد ذكور الفئران الألبينو.

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الخلفية: تعتبر اختبارات السمية الفمية والجلدية الحادة بمثابة تقييم تنظيمي للسمية الجهازية للمواد الكيميائية الزراعية.

الهدف: أجريت هذه الدراسة لدراسة تأثير التعرض لجرعة واحدة تحت مميتة للأبامكتين عن طريق الفم والجلد على المؤشرات الحيوية للإجهاد التأكسدي في كبد ذكور الفئران البيضاء.

الطريقة: تم تقسيم أربعون فأراً إلى ثلاث مجموعات تمثلت فى المجموعة الضابطة والفمية والجلدية. وكانت الجرعة المختبرة 2/1 من LD_{50} للتجارب عن طريق الفم والجلد.

النتائج: إرتبط التعرض للأبامكتين بجرعات تحت مميتة عن طريق الفم أو الجلد بتحفيز الإجهاد التأكسدي في كبد ذكور الفئران البيضاء. إذ إتضح الإجهاد التأكسدي من خلال زيادة المؤشرات الحيوية لأكسدة الدهون والبروتين (MDA) و (PC).بالإضافة إلى أن الإنزيمات المضادة للأكسدة مثلCAT وGST زادت فى خلايا الكبد، بينما انخفض الجلوتاثيون والجلوتاثيون بيروكسيديز بشكل ملحوظ. كما حدثت زيادة فى نشاط إنزيم الأستيل كولين إستريز (AChE) في خلايا الكبد بشكل ملحوظ في كل من التعرض الفمى والجلدى.

الخلاصة: هذه الدراسة تلقى الضوء على أهمية الاستخدام المسؤول والأمثل لمبيدات الآفات في الحد من تأثير مخاطر الكيماويات الزراعية.