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(RESEARCH ARTICLE)



Protective effects of vitamin E and grape seed oil against acute hepatorenal ivermectin toxicity in mice: biochemical and histopathological studies

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Abstract

Ivermectin (IVM), a broad spectrum anthelmintic drug, is considered a safe drug; however, there are few reports about its toxic effects in particularly at accidental overdose exposure. Therefore, the current study was designed to investigate the potential protective roles of vitamin E (Vit E) and grape seed oil (GSO) against the acute hepatorenal toxicity of IVM in mice. Mice were divided into four equal groups. Control vehicle group was administrated corn oil (0.2 ml/animal), IVM group was administrated IVM (6.5 mg/kg b.w.), Vit E+IVM group was administrated Vit E (200 mg/kg b.w.) plus IVM and GSO+IVM group was administrated GSO (0.2 ml/animal) plus IVM. All treatments were orally administrated daily for 3 weeks while IVM is administered as a single oral dose one day before the end of the experiment. The results revealed that IVM induced significant elevation in serum ALT and AST activities; urea and creatinine levels without any significant change in glucose level. No marked histopathological alterations were observed in hepatic tissue with several pathological alterations in the kidneys of IVM- intoxicated mice. However, pretreatment of mice with either Vit E or GSO ameliorated the IVM- induced biochemical and histopathological alterations. In conclusion, Vit E and GSO may provide a similar promising protective value against IVM acute hepatorenal intoxication.

Keywords: Ivermectin; Vitamine E; Grape seed oil; Hepatorenal toxicity; Histopathology

1. Introduction

Pesticides including insecticides, herbicides, fungicides, rodenticides, and others, are being used extensively throughout the world for controlling industrial, agricultural, domestic and public health pests [1]. The indiscriminate use of pesticides causes tremendous environmental pollution and health hazards to target and non-target organisms [2]. Among them, ivermectin is frequently used to control parasitic infestations in many animal species [3].

Ivermectin (IVM) is semisynthetic macrocyclic lactone produced from *Streptomyces avermitilis*. It has antiparasitic effects against gastrointestinal and lung nematodes, arthropods and certain ectoparasites [4]. It is considered the drug of choice for treatment of *Onchocerciasis*, *Ascariasis* and *Enterobiasis* in human [5].

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The antiparasitic action of IVM is referred to its agonist effect on glutamate and gamma-aminobutyric acid (GABA)-gated chloride channels, which cause influx of chloride causing CNS inhibition and paralysis [6]. IVM is metabolized primarily via the oxidative pathway in liver by microsomal cytochrome P450, its metabolites are excreted mainly in feces and to less extent in urine [7, 8].

Ivermectin poisoning causes CNS depression and sometimes coma resulting in death [6]. Beside its neural effects, IVM has toxic effects on liver and kidney at either therapeutic or toxic doses in albino rats [9]. Cumulative evidences have shown that pesticide poisoning disrupts redox homeostasis along with induction of oxidative damage. The disruption of redox homeostasis during IVM poisoning is due to the increased production of reactive oxygen species (ROS) and the reduction in endogenous antioxidant defense system [10, 11].

Vitamin E is a lipid soluble antioxidant naturally presents in all biological systems and protects cell membranes against lipid peroxidation (LPO) which is induced by overproduction of ROS and reactive nitrogen species (RNS). It acts as membrane stabilizer and a chain-breaking antioxidant that prevents propagation of lipid peroxidation reactions in cellular membrane [12, 13]. Therefore, several *in vivo* and *in vitro* studies confirmed the protective effect of Vit E against different pesticides toxic insults [14-17].

Grape (*Vitis vinifera*), one of the most widely consumed fruits, have been of interest worldwide because of the nutritional properties of the natural product (raw and dried fruit) and the pharmaceutical properties of its derivatives, such as peel and seed extracts [18]. Grape seed oil (GSO) is a by-product of wine making process and has gained use as culinary oil because of its high levels of phenolic compounds, fatty acids, vitamins, and phytosterols. GSO has a powerful antiatherosclerotic, anti-inflammatory, antioxidant, antitumor and anti-apoptotic [19, 20] effects.

In view of the clinical importance of IVM in animals and humans and the dearth of literature on the host toxicity, the current study was designed to investigate the potential protective roles of vitamin E and grape seed oil against the acute hepatorenal toxicity of IVM in mice.

2. Material and methods

2.1. Experimental animals

Forty mature healthy female mice (30-35 g) were donated from Department of Husbandry and Animal Wealth Development, Faculty of Veterinary Medicine, University of Sadat City, Egypt. Mice were housed in polypropylene cages with mesh wire tops and kept in a natural ventilated room (23 ± 3 °C, 45-60% RH, 12 h light/ 12 h dark cycle), provided with standard commercial diet and clean tap water *ad libitum*. Mice were acclimatized to the laboratory environmental conditions for 2 weeks prior to the start of experiment. The study was ethically approved by the International Animal Care and Use Committee IACUC, Faculty of Veterinary Medicine, University of Sadat City.

2.2. Chemicals

Ivermectin (Avimec, Arab Veterinary Industrial Company) was purchased from local Veterinary Pharmacy. Vitamin E (400 mg oily capsules, Pharco Pharmaceutical Company) was purchased from local pharmacy. Grape seeds oil (*Vitis vinifera* seed oil) was purchased from Harraz Group for Medicinal Plants, Cairo, Egypt.

Diagnostic kits for assaying serum glucose level, ALT and AST activities were purchased from Spinreact Company, Spinreact Ctra. Sta. Coloma, Girona, Spain. Diagnostic kits for assaying serum urea and creatinine levels were purchased from Biodiagnostics Company, Cairo, Egypt. Other utilized chemicals were of analytical grade and commercially available.

2.3. Experimental design and animal grouping

Mice were weighed, randomly allocated into four equal groups. Control vehicle group (corn oil) was orally administered corn oil (0.2 ml/animal) daily for 3 weeks. IVM group was administered IVM as a single oral dose, 6.5 mg/kg b.w., 1/5 oral LD50 on the last day of the experiment. Vit E+IVM group was orally administered Vit E, 200 mg/kg b.w. [21] plus IVM administration. GSO+IVM group was orally administered GSO, 0.2 ml/animal [22] plus IVM administration. The dose of IVM was selected according to oral LD50 in mice, 33 mg/kg b.w. [23]. All treatments were orally administered daily for 3 weeks while IVM is administered as a single oral dose one day before the end of the experiment.

2.4. Samples collection

At the end of the experiment and after 24 hours of IVM administration, mice were fasted overnight, anaesthetized using diethyl ether and sacrificed for samples collection. Blood samples were collected in clean and dry glass centrifuge tubes for serum collection and then stored at -20°C for further serum biochemical analysis. Liver and kidney of each mice were collected and fixed in 10% neutral buffered formalin solution for the histopathological investigation.

2.5. Serum biochemical analysis

Serum ALT and AST activities [24, 25]; glucose [26], urea [27] and creatinine [28] levels were estimated using commercial kits following the manufacturer's instructions.

2.6. Histopathological examination

Following necropsy, tissue specimens from liver and kidneys were collected and rapidly fixed in 10% neutral buffered formalin solution. The fixed specimens were trimmed, washed, dehydrated in ascending grades of ethyl alcohol, cleared in methyl benzoate and processed through the conventional paraffin embedding technique. 3-5 µm sections were obtained from paraffin blocks using microtome (LEICA RM 2135) then routinely stained by hematoxylin and eosin (H & E) stain according to Bancroft et al., [29]. Stained slides were microscopically analyzed using light microscopy. Histopathological Photos were photographed using a digital Leica photomicroscope (LEICA DMLB Germany).

2.7. Statistical analysis

Values are presented as mean ± standard error (SE). Statistical significance of data was determined by one-way ANOVA (Analysis of Variance) followed by Duncan's Multiple range test for post hoc analysis. All statistical analyses were performed using SPSS (Statistical Package for Social Sciences) Version 16 released on 2007.

3. Results

3.1. Effects on animals' general health conditions

No mortalities were recorded along the period of the experiment. Mice of corn oil group did not exhibit any clinical manifestations. However, after a single oral dose administration of IVM (6.5 mg/kg b.w.) alone or after Vit E or GSO treatment, mice showed short time of excitatory symptoms accompanied by abdominal respiration followed by depressive stage. These signs were more predominant in IVM- intoxicated mice and relieved after short period of insecticide administration.

3.2. Serum biochemical findings

3.2.1. Serum ALT and AST activities

Oral administration of a single oral dose of IVM (6.5 mg/kg b.w.) induced significant elevations in serum ALT and AST activities ($P<0.05$) compared to corn oil treated group. However, pretreatment with either Vit E (200 mg/kg b.w.) or GSO (0.2 g/mice) daily for three weeks before IVM intoxication significantly reduced serum ALT and AST activities to be within normal corn oil values (Fig. 1).

3.2.2. Serum glucose level

Serum glucose level showed insignificant changes between all treated groups at $P<0.05$ (Fig. 1).

3.2.3. Serum urea and creatinine levels

Regarding to corn oil group, IVM- intoxicated group showed significant increase ($P<0.05$) of serum urea and creatinine levels. Pretreatment with either Vit E or GSO three weeks before IVM- administration significantly reduced the elevated urea and creatinine levels and restored all the values to the normal limits (Fig. 1).

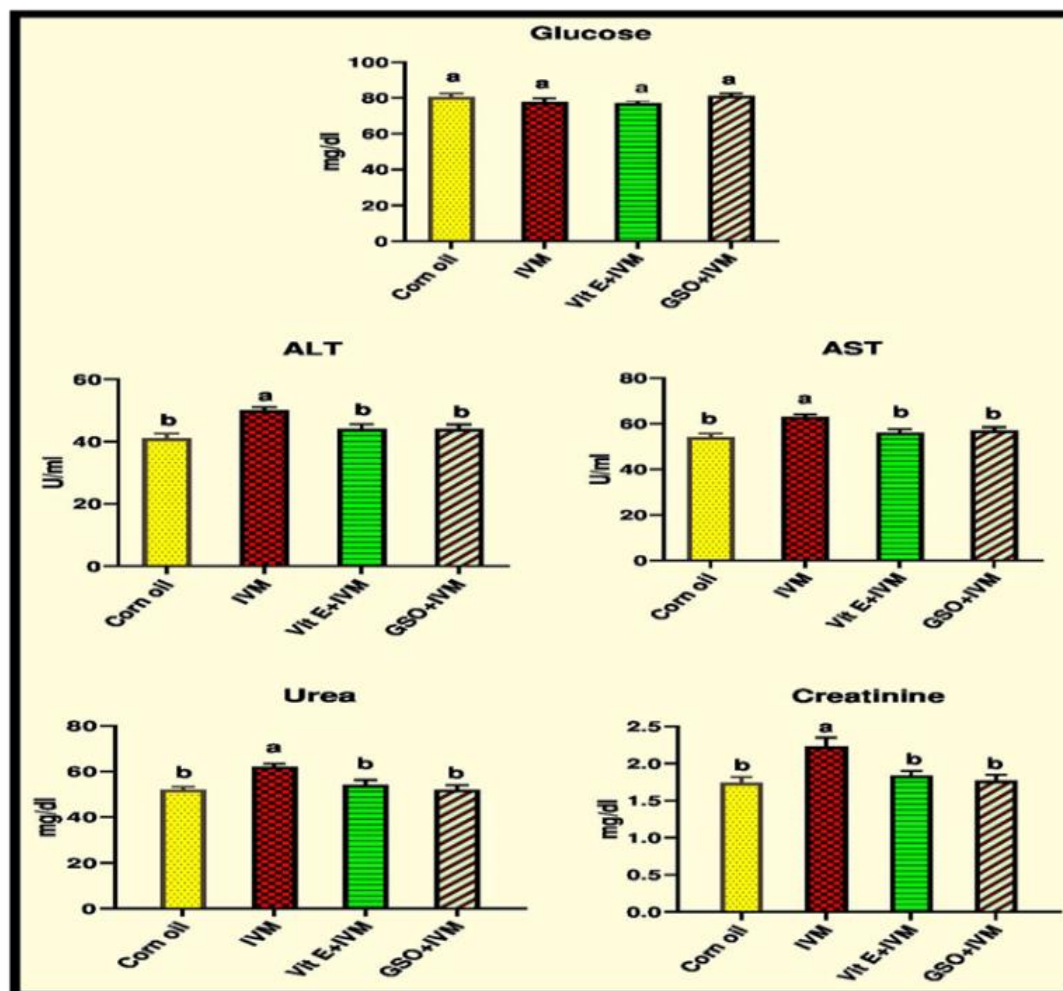


Figure 1 Serum biochemical parameters of the different treated groups. Different letters means significant differences at ($P < 0.05$). IVM: ivermectin; Vit E: vitamin E; GSO: grape seed oil

3.3. Histopathological findings

Histopathological examination revealed no marked pathological changes in the liver of all treated groups.

The kidneys of corn oil- administrated mice showed no pathological changes (Fig. 2a). However, IVM- intoxicated mice showed various pathological changes in the kidneys, including intertubular edema and hemorrhage, edema in the interstitial tissue and around glomeruli, vacuolation of glomerular tuft, narrowing of Bowman's space, coagulative necrosis and karyorrhexis in the lining epithelium of renal tubules (Fig. 2b). Pretreatment with Vit E improved the renal picture as presented by minimal edema and slight cloudy swelling in the epithelium lining of some renal tubules (Fig. 2c). Similarly, GSO administration enhanced the renal architecture with only mild hydropic degeneration in lining epithelia of some renal tubules (Fig. 2d).

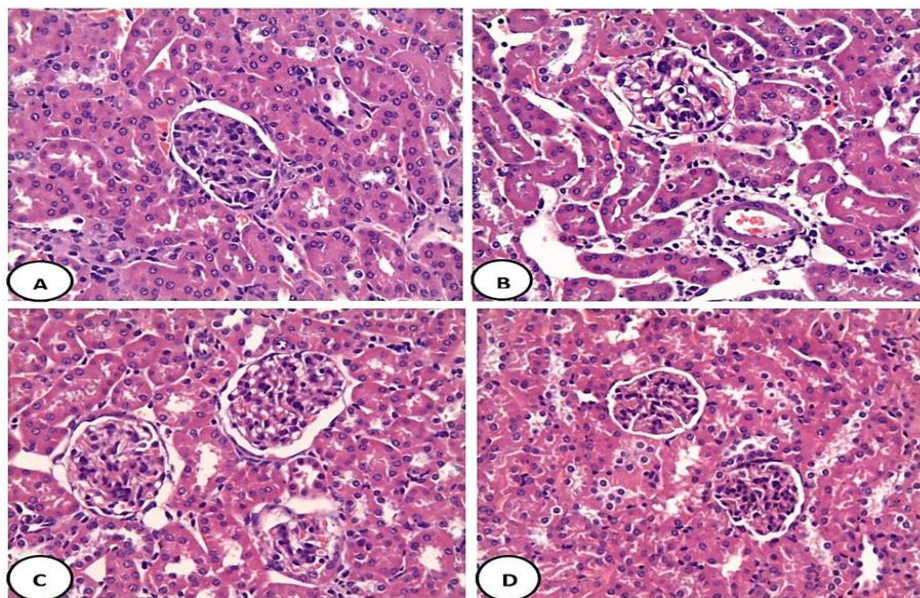


Figure 2 Representative photomicrographs of kidney of mice in different groups (H&E, X20).

A: Corn oil group: showing no pathological changes. B: IVM group: showing intertubular edema and hemorrhage, edema in the interstitial tissue and around glomeruli, vacuolation of glomerular tuft, narrowing of Bowman's space, coagulative necrosis and karyorrhexis in the lining epithelium of renal tubules. C: Vit E+IVM group: showing minimal edema and slight cloudy swelling in the lining epithelium of some renal tubule. D: GSO+IVE group: showing mild hydropic degeneration in the lining epithelia of some renal tubules.

4. Discussion

Ivermectin is one of the most frequently used drugs in pharmacotherapy of parasitic diseases in domestic and wild animals. It is widely recommended for field applications due to easy route of administration and potent larvicidal activity [30]. However, ivermectin and other avermectins very often produce side-effects in hosts. Cumulative evidences have confirmed the implication of oxidative stress in IVM-induced toxicity [10, 31]. Therefore, considerable attention has been gained toward using of natural antioxidants to overwhelm the oxidative damages of pesticides. In the light of this, the current study aimed to evaluate the potential protective roles of vitamin E and grape seed oil against the hepatorenal toxicity of IVM in mice.

The liver and kidneys have vital role in the metabolism and excretion of xenobiotics, consequently leading to toxic cellular damages [32]. In the current study, estimation of liver and kidney biomarkers with histopathological examination has curial value for assessment of the hepatorenal toxicity of IVM in mice and help in evaluation of the potential ameliorative role of the Vit E and GSO.

Ivermectin caused significant elevations in serum ALT and AST activities in mice, this result is in agreement with Qureshi [10], who recorded increase in serum ALT and AST activities after IVE single IP injection (10 and 15 mg/kg b.w.) in rats. The increase in hepatic function enzyme activities is considered to be indicators for cytotoxicity and disruption of cellular membrane integrities leading to leakage of these enzymes and their release into blood [33]. Also, the biotransformation of IVE to more electrophilic and oxidative metabolites induces oxidant/antioxidant disturbance leading to several biochemical and histopathological changes [10, 34].

Unexpectedly, there were no marked histopathological changes in hepatic tissues in all treated groups. Chiu and Lu [35] demonstrated that a single oral dose of IVE results in peak plasma levels at 4 to 8 hrs post oral administration, with a half-life of 24 hrs. This means that oral single dose of IVE rapidly absorbed and eliminated. This may illustrate the recorded renal pathological changes without marked hepatic changes that probably occurred later in time.

Regarding to serum renal biomarkers, significant increase in serum urea and creatinine levels were recorded in IVM-intoxicated mice. The serum biochemical changes were correlated with histopathological alteration in kidney tissue. In consistent with our finding, Arise and Malomo [36] recorded significant urea and creatinine levels in rats orally administered a human therapeutic dose of IVM; daily for 15 days. Similarly, rats subcutaneously injected either therapeutic or double therapeutic doses of IVM, once weekly for eight weeks increased serum urea, creatinine and uric acid levels in association with changes in renal histologic structure [37].

Serum urea and creatinine are renal biomarkers used to evaluate kidney functions [38] and hence, elevation of their levels in IVM- intoxicated rats reflects its nephrotoxic effects which may be attributed to the reduction of glomerular filtration rate and the dysfunction of the kidney tubules [39]. Also, IVM is known to cause inhibition of renal excretion of substances that are substrates of *p*-glycoprotein [40] and induction of oxidative renal damage [11] leading to retention on urea and creatinine in blood.

In this study Vit E ameliorated serum biochemical and histopathological changes induced by IVM as indicated by significant reduction in serum ALT, AST activities and urea, creatinine levels associated with improvement of renal histologic structure. Similarly, previous studies proved the hepatorenal protective effect of Vit E against abamectin [15] and fipronil [17] toxicities. Vitamin E is well known to be potent natural antioxidant; it has important functional properties in membranes lipoprotein, it exerted an efficient antioxidant role by neutralization of ROS and up-regulation of antioxidant enzymes and reduction in lipid peroxidation [41, 42].

Pretreatment of mice with GSO three weeks before IVE intoxication returned serum liver and kidney biochemical changes to be within normal levels with improvement of renal histological pictures. The same findings were recorded either after grape seed oil and extract administrations against hepatorenal toxicity of diazinone [22], cisplatin [43] and fumonisin B1 [44]. The protective effects of GSO are referred to its polyphenolic contents that have free radicals scavenging properties [43, 44].

5. Conclusion

In the light of the above findings, we can conclude that administration of IVM as a single oral dose induced changes in serum liver and kidney biomarkers accompanied by histopathological alterations in the kidney of mice. Pretreatment of mice either with Vit E or GSO three weeks before IVM intoxication markedly and equally reversed these alterations referring to their antioxidant defensive mechanisms.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there are no conflicts of interest.

Statement of ethical approval

This study was ethically approved by the International Animal Care and Use Committee IACUC, Faculty of Veterinary Medicine, University of Sadat City.

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