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Acute Toxic Effects of levamisole and Ivermectin in Mice

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ABSTRACT

The study's objectives were to investigate the acute toxicity and related biochemical effects of levamisole and ivermectin in mice. The 24 h oral median lethal dose (LD50) of levamisole was determined by the up-and-down method and was 155.5 mg/ kg of body weight. The treated mice showed signs of acute poisoning represented by excessive grooming, lacrimation, piloerection, straub tail, tachycardia, bulged eyes, tremor, convulsion and finally death within 24 h of treatment. The approximate lethal dose (ALD) of levamisole was 368 mg/kg, and the mice showed signs of poisoning similar to the previous signs of poisoning within 24 h of treatment. The 24 h oral LD50 of ivermectin was 115.2 mg/kg and the mice showed acute signs of poisoning, represented by excessive grooming, lacrimation, closed eyelids, piloerection, tachycardia, rapid respiration, depression, flat body appearance, paralysis and finally death within 24 h of treatment, while the approximate lethal dose of ivermectin was 121 mg/kg and also with the presence of severe poisoning signs as mentioned before. Non-lethal toxic doses of levamisole at 100 and 150 mg/kg and ivermectin at 75 and 100 mg/kg led to significant blood biochemical changes after 24 h of treatment, represented by a significant increase in the activity of the enzymes alkaline phosphatase (ALP), lactate dehydrogenase (LDH), glutamate dehydrogenase (GDH), and a significantly increased total bilirubin concentration in the blood plasma of mice. These results proved the presence of acute toxicity and biochemical effects of both anthelmintics levamisole and ivermectin even though they have wide safety margins.

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INTRODUCTION

Anthelmintics are drugs that are used against nematodes, trematodes, cestodes, and any parasitic organisms inside the body by killing them without causing any harm to the host **(Abongwa *et al*., 2017)**. The mechanisms of action of these types of drugs vary depending on the type of drug. Levamisole is a synthetic imidazothiazole derivative widely used to treat worm infestations in both humans and animals due to its immunomodulatory properties **(Campillo *et al*., 2022).**

Levamisole paralyzes worms by selectively activating the acetylcholine receptors of parasites, allowing the entry of Na+ and Ca2+ for excessive contraction of the muscles of the body, thereby causing paralysis due to its affinity for nicotinic receptors **(Romine *et al*., 2014).** Levamisole works to paralyse the parasite's muscles, then the worms are unable to attach to the mucous membranes, and are expelled through the intestine outside the body **(Campillo *et al*., 2022).**

Nicotinic signs of levamisole poisoning are represented by increased defecation and urination, anxiety, hyperesthesia, muscle tremor, and convulsions **(Sharma *et al*., 2020).**Ivermectin is a macrocyclic lactone isolated from the bacterium *Streptomyces Avermitilis* and it is commonly used against parasitic diseases in domestic and wild animals caused by roundworms, nematodes, and arthropods**(Campbell, 2012).** It has also been used against internal and external worms that affect cattle and birds **(Bhardwaj *et al*., 2020; Khalaf, 2022).** This drug can kill roundworms, intestinal worms, and

lungworms but does not affect flatworms or tapeworms **(Pooda *et al*., 2015).**

Ivermectin acts as a GABA agonist that causes paralysis in sensitive arthropods and nematodes to increase the flow of Cl^- through the cell membranes and stimulate the activity of GABA only in the central nervous system, ivermectin does not easily cross the blood-brain barrier of the host **(Gupta *et al*., 2019).** The harmful effects of ivermectin in mammals included abdominal pain, nausea, tachycardia, asthma, edematous swellings, itching, back pain, ocular problems, cardiac dysfunction, and liver disease **(Kamgno *et al*., 2004).**

Levamisole and ivermectin are considered safe drugs to use in general, although some studies have proven the occurrence of toxic effects in the liver and bone marrow and that they may cause teratogenic effects in foetuses **(Van Genderen, 2008)**. Because of the widespread use of these drugs and the development of parasitic drug resistance in various animal species, especially sheep and goats **(Kaplan & Vidyashankar, 2012)**. Due to the wide use of these anthelmintics, some toxic aspects of them have not been studied, and our interest was to study acute toxic effects and related biochemical changes induced by levamisole and ivermectin in mice.

MATERIALS AND METHODS

Ethical approval

The use of experimental animals and the trials were approved according to the ethical code number (UM-VET-2022.041) from the Scientific Council of the Department of Physiology, Biochemistry, and Pharmacology at the College of Veterinary Medicine, University of Mosul, Iraq. The study is part of a master's thesis.

Animals

Forty-one Swiss-derived male and female mice at the age of 2-3 months were used in this study. Their weights ranged between 20 and 38g. We raised mice in the animal house of the College of Veterinary Medicine, University of Mosul, and housed them under standard conditions characterized by 10–12 hours of light and darkness at a temperature of 22 ± 2 ºC. The mice were raised in special plastic cages prepared for this purpose and always provided with water and food, which were provided from local factories in the city of Mosul.

Preparation of drugs

Levamisole HCl (VAPCO, Jordan) doses were dissolved in 10 ml of distilled water for oral administration by gavage. Different doses of levamisole (100 and 150 mg/kg body weight) were given to evaluate the toxic effects of the drug. **Ivermectin (** Pioneer Company, Sulaymaniyah, Iraq) was dissolved in 10 ml of propylene glycol (99%)(Sigma Chemicals, USA) (Trailovic **and Nedeljkovic, 2011)** for oral dosing by a gavage needle. They gave different doses (75 and 100 mg/kg) to evaluate the toxic effects of the drug.

Experimental design

1.The median lethal dose (LD50) of levamisole and ivermectin orally in mice by the up-and-down method (Dixon, 1980)

We conducted many initial experiments on mice to obtain an appropriate dose that was selected for use in subsequent experiments on levamisole and ivermectin.

1.1. LD50 of levamisole

We use five mice (male and female) with body weights of 25–29 g. A dose of 300mg/kg of levamisole was selected as the first dose on the first day to determine the LD50, and then other mice were dosed with different doses of levamisole up and down to reach the LD50. After dosing, we recorded the signs of poisoning that appeared on the mice immediately, then read the result for each mouse individually after 24 h, then calculated the LD50 based on tabular values **(Dixon, 1980)** and using the following equation:

LD50 = xf+kd

xf=the last dose used

K= the tubular value.

d = the amount of increase and decrease in the dose.

1.2. LD50 of ivermectin

We use five mice (male and female) with body weights of 29–38 g. A dose of (100 mg/kg) b.w.t. of ivermectin was selected as the first dose, and the test was conducted as described above.

2. Approximate lethal dose (ALD) of levamisole and ivermectin, orally in mice by the Deichman method (DePass, 1989).

2.1. ALD of levamisole in mice

Four mice (male and female) with body weights of 25–32 g, were orally dosed with levamisole at a starting dose of (108 mg/kg,, and this dose represents approximately 70% of the LD50 of levamisole. The mice were monitored within 2 h for any signs of poisoning. After 24 h, the results were read which represented the survival or death of the mouse, and when the mouse survived, another mouse was dosed with the previous lethal dose multiplied by 1.5, and the same method was followed several times. The ALD of levamisole is the first dose that kills the treated mice **(Hassan and Al-baggou, 2022).**

2.2. ALD of ivermectin in mice

Two mice (male and female) with body weights of 32–35 g, were orally dosed with ivermectin at a starting dose of 81 mg/kg, and this dose represents approximately 70% of the LD50 of ivermectin. Afterward, the test was completed as described above to determine the ALD.

3. Effects of non-lethal toxic doses of levamisole and ivermectin on the Alkaline phosphatase (ALP), Lactate dehydrogenase (LDH), Glutamate dehydrogenase (GDH) enzyme activity, and

Total Bilirubin concentration in mice

Twenty-five (male and female) mice with body weights of 28–36 g were divided into 5 groups (5 mice per group) and then treated as follows:

Group 1: the control group dosed with propylene glycol at 5 ml/kg b.w.t. and distilled water at 5 ml/kg, orally.

Group 2: mice orally dosed with levamisole at 100 mg/kg.

Group 3: mice orally dosed with levamisole at 150 mg/kg.

Group 4: mice orally dosed with ivermectin at 75 mg/kg.

Group 5: mice orally dosed with ivermectin at 100 mg/kg.

After treatment, all the mice were monitored for 2 hours, and we recorded all the signs of poisoning that appeared on them. 24 h after treatment, we anaesthetized the mice with ether (Thomas Baker Limited, UK) and collected the blood from the venous plexus of the eye to obtain plasma to measure the activities of ALP and LDH and total bilirubin concentration) with commercial kits from(Biolabo, France, whereas the ELISA technique was used to measure the glutamate dehydrogenase(GDH) activity (Sunlong Biotech Co., Ltd., China).

Statistical Analysis

The parametric data were first subjected to a statistical analysis using the one-way analysis of variance (ANOVA) test, and then they were put through the least significant difference test (LSD) utilizing SPSS software version 20, with a significant difference level of ($P \leq 0.05$).

RESULTS

1.1. Oral LD50 of levamisole

LD50 of levamisole in mice was (155.5 mg/kg) .Signs of poisoning are represented as excessive grooming, lacrimation, piloerection, straub tail, tachycardia, bulged eyes, tremor, convulsion, and finally death in highly toxic doses (Table 1).

Table 1: Oral LD50 of levamisole

LD_{50} of levamisole	155.5 mg/kg orally
Range of doses of levamisole	400-100=300 mg/kg b.wt
The first dose	300 mg/kg b.wt
The last dose	100 mg/kg b.wt
Up and down levamisole dose	100 mg/kg b.wt
No. of mice	(5) oxxxx
Poisoning signs	Excessive grooming, lacrimation, piloerection, straub tail, tachycardia, bulged eyes, tremor, convulsion, death.

X=Death O=Survival

1.2. Oral LD50 of ivermectin.

LD50 of ivermectin in mice was (115.25 mg/kg) after oral dosing. Signs of poisoning are represented by excessive grooming, lacrimation, closed eyes, piloerection, tachycardia, rapid breathing, depression, flat body appearance, paralysis, and finally death in highly toxic doses (Table 2).

Table 2: Oral LD50 of ivermectin

LD_{50} of ivermectin	115.25 mg/kg orally
Range of doses of ivermectin	100-50=50 mg/kg b.wt
The first dose	100 mg/kg b.wt
The last dose	100 mg/kg b.wt
Up and down ivermectin dose	50 mg/kg b.wt
No. of mice	(5) oxxoo
Poisoning signs	Excessive grooming, lacrimation Piloerection, Straub tail, rapid respiration, tachycardia, closed eyes ,paralysis flat body appearance, convulsion, death.

X=Death O=Survival

2.Approximate lethal dose (ALD) of levamisole and ivermectin in mice.

2.1. ALD of levamisole

ALD of levamisole orally was (368 mg/ kg), Signs of poisoning represented excessive grooming, lacrimation, bulged eyes, piloerection, straub tail, tremor, tachycardia, convulsions, death within 24 h of treatment.

2.2. ALD of ivermectin

ALD of ivermectin orally was (121.1 mg/ kg). Signs of poisoning are represented by excessive grooming, lacrimation, closed eyelids, piloerection, tachycardia, rapid respiration, depression, flat body appearance, paralysis, and finally death within 24 h of treatment.

3. Effects of non-lethal toxic doses of levamisole and ivermectin on (ALP, LDH, GDH) activities and total bilirubin concentration in mice

3.1. Effects of levamisole and ivermectin on ALP activity in the blood plasma of mice

The oral administration of levamisole in toxic doses (100 and 150mg/kg), caused a slight increase in the ALP activity (225± 3.94) and (255±5.25) IU/L, respectively, in the blood plasma of mice 24 h after treatment in comparison with the mice of the control group (224±7.18) IU/L.

The oral administration of Ivermectin in toxic doses (75 and 100 mg/kg) led to a significant increase in the ALP activity (259± 5.59) and (281±4.94) IU/L, respectively, 24 h after oral treatment in comparison with the control group (224±7.18) IU/L) (Table 3; Fig. 1).

Table 3: Effects of levamisole and ivermectin on the ALP, LDH, and GDH activities in the blood plasma of mice 5mice/group.

Treatment group	Enzyme activity (ALP) IU/L	Enzyme activity (LDH) IU/L	Enzyme activity (GDH) pg/ml
Control (D.wt+propylene glycol)	224± 7.18	84.6± 4.91	277.3± 6.47
Levamisole 100mg/kg	225± 3.94 bcd	128.8± 2.92*bd	287.7± 7.55bcd
Levamisole 150mg/kg	255± 5.25*ad	160.2± 5.03*ac	323.8± 13.19*ad
Ivermectin 75 mg/kg	259± 5.59*ab	122.6± 3.07*bd	340.6± 19.61*ab
Ivermectin 100 mg/kg	281± 4.94*abc	153± 2.50*ac	370.1± 10.26*ab

* The value is significantly different compared with the control group at (P≤0.05).

A,b,c: The different letters in the same column are siginificant at (P≤0.05).

3.2. Effects of levamisole and ivermectin on LDH activity in the blood plasma of mice

The oral administration of levamisole in toxic doses (100 and 150 mg/kg) caused significant increases in the activity of LDH in the blood plasma (128.8± 2.92) and (160.2±5.03) IU/L, respectively 24 h after oral treatment of mice, in comparison with the control group (84.6± 4.91) IU/L.

The oral administration of ivermectin in toxic doses (75 and 100 mg/kg) caused a significant increase in the activity of LDH (122.6± 3.07) and (153±2.50) IU/L, respectively, 24 h after the treatment compared with the control group (84.6± 4.91) IU/L (Table 3; Fig.1).

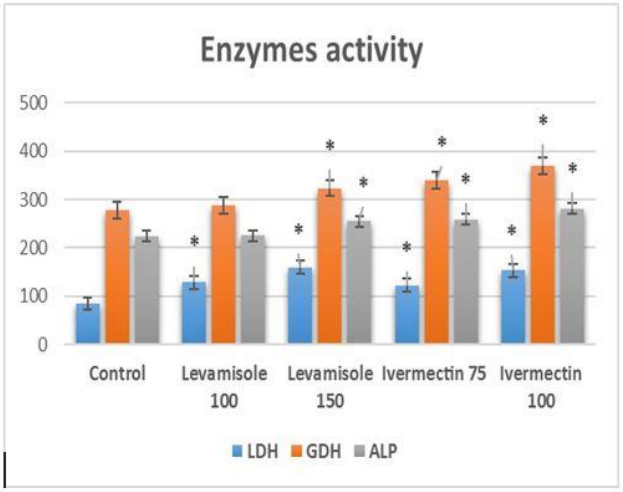

Fig.1: Effects of Levamisole and ivermectin on ALP, LDH, and GDH activity in the blood plasma of mice after 24 h.

3.4. Effects of levamisole and ivermectin on GDH activity in the blood plasma of mice

The oral administration of levamisole at a dose of (100 mg/kg) caused a slight increase in the activity of GDH (287.7± 7.55) pg /ml in the blood plasma of mice 24 h after oral treatment in comparison with the control group (277.3± 6.47) pg /ml, while the oral administration of levamisole at a dose of (150 mg/kg) caused a significant increase in the activity of GDH 24 h after oral treatment (323.8±13.19) pg /ml in comparison with the control group (277.3± 6.47), While, oral administration of ivermectin in toxic doses (75 and 100 mg/kg) causes a significant increase in the activity of GDH (340.6± 19.61) and (370.1± 10.26) pg/ml, respectively, 24 h after oral dosing in comparison with the control group (277.3± 6.47) pg/ml (Table 3; Fig. 1).

3.5. Effects of levamisole and ivermectin on total bilirubin concentration in the blood plasma of mice

The oral administration of levamisole in toxic doses (100 and 150 mg/kg) b.w.t. resulted in a significant increase (1.02± 0.005) and (1.22±0.03) mg/ dl, respectively, in the concentration of total bilirubin in the blood plasma of mice 24 h after oral treatment compared with the control group (0.8± 0.035 mg/dl).

The oral administration of ivermectin in two doses (75 and 100 mg/kg) b.w.t. also led to a significant increase in the concentration of total bilirubin (1.1± 0.023) and (1.29±0.022) mg/dl, respectively, 24 h after oral treatment compared with the control group (0.8± 0.035 mg/dl) (Table 4; Fig. 2).

Table 4: Effects of levamisole and ivermectin on total bilirubin concentration in blood plasma in mice.

Treatment	Total Bilirubin mg/dl
Control (D.wt + propylene glycol)	0.80±0.035
Levamisole 100mg/kg	1.02±0.005*bcd
Levamisole 150mg/kg	1.22±0.03*ac
Ivermectin 75 mg/kg	1.10±0.023 *abd
Ivermectin 100 mg/kg	1.29±0.022*ac

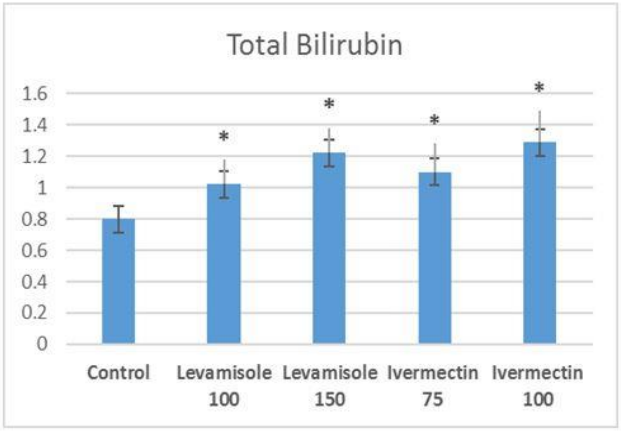

Fig. 2: Effects of Levamisole and ivermectin on the total bilirubin concentration in blood plasma in mice.

DISCUSSION

Levamisole and ivermectin are commonly used against parasitic diseases in humans and animals **(Zoghroban *et al.*, 2023).** The widespread and indiscriminate use of these drugs outside the use controls has contributed to the widespread development of drug resistance, especially in sheep and goat parasites, as well as in pigs, horses, and cattle parasites **(Shoop and Soll, 2002; Charlier *et al.*, 2023)**. We were interested in studying the acute toxic effects of levamisole and ivermectin at the level of acute toxicity and biochemical changes in mice. Although it is difficult to extrapolate laboratory animal studies to humans or even other animal species, the interpretation of the present results should be dealt with cautiously and should be taken as a guide at present for any future studies involving humans and animals. In light of the present toxicity results, we recommend further long-term, preferably mechanistic, studies to follow.

Levamisole paralyses the muscles of the parasite by selectively activating Ach receptors, so the worms are unable to attach to the mucous membranes, then expelled through the intestine outside the body **(Campillo *et al.*, 2022).** Ivermectin does not easily cross the blood-brain barrier of the host, it acts as a GABA agonist that causes paralysis in nematodes to increase the flow of Cl^- through the cell membranes and stimulate GABA only in the CNS **(Gupta *et al.*, 2019)**.

The current study showed that the median lethal dose of levamisole in mice by oral dosing and calculated by the up-and-down method **(Dixon,1980)** was 155.5 mg/kg. The reported signs of toxicity resulting from levamisole poisoning in mice included excessive grooming, lacrimation, piloerection, straub tail, bulged eyes, tremor, tachycardia, convulsions, and death **(Rehni and Singh, 2010)**, while the LD50 in mice was 210 mg/kg, in rats 480 mg/kg **(Lynn, 2008), and in chicks** 1474 mg/kg **(Mansoor, 2004).** LD50 of ivermectin in mice was 115.25 mg/kg, with signs of severe intoxication represented by excessive grooming, lacrimation, closed eyelids, piloerection, tachycardia, rapid respiration, depression, flat body appearance, paralysis, and death **(Swor *et al.*, 2009)**, whereas in previous studies in mice, rats, and dogs, LD50 values were (20.9, 51.5, and 80 mg/kg, respectively), while the LD50 was high in chicks, 525.5 mg /kg **(Al-Najmawi and Al-Zubaidy, 2022)**. The existence of variations in the lethal dose between these animals may be due to the different types and compositions of these drugs as well as the difference in solvents and compounds added to them **(El-Saber Batiha *et al.*, 2020)** and the type of animal may have a role in the different absorption of these drugs and their toxic effects in the animal's body **(Tawfeek *et al.*, 2021).**

The approximate lethal dose of both levamisole and ivermectin in mice by oral administration was also 368 and 120 mg/kg,, respectively. Where we found that the dose of levamisole was rather high compared to the dose of ivermectin due to its wide degree of safety and low toxic effects **(Midthun *et al.*, 2021).** The results of our study of some biochemical parameters in the blood plasma of mice showed the effect of both levamisole and ivermectin at non-lethal toxic doses on (ALP, LDH, and GDH) activities 24 h after oral administration, which was represented by a significant increase in the enzyme's activity after treated mice with different doses of levamisole and ivermectin compared to the control group. The ALP enzyme is a sensitive biomarker of hepatotoxicity in

animals (Qian ***et al.*, 2015)**. The activity of this enzyme increases in the blood when liver cells are damaged and die (apoptosis), and this is important in diagnosing the efficiency of liver function **(Arise and Malomo, 2009; Osama *et al.*, 2015)**. The high doses of levamisole also cause an increase in ALP, and LDH activity in the plasma of carp fish **(Sadati *et al.*, 2021).** A significant increase in the activity of ALP in animals exposed to ivermectin poisoning may be attributed to increased gluconeogenesis, which is an indicator of ivermectin toxicity to the liver **(Odo *et al.*, 2020)**. The activity of the ALP enzyme increases in the blood when the cell is damaged and dies, and this suggests a possible damage to the tissues of the cell membrane leading to leakage of membrane components into the extracellular fluid **(Arise and Malomo, 2009)**.

Ivermectin increases LDH activity in goats and causes necrosis in multiple areas of the liver due to the accumulation of its residues in the liver **(Abdou and Sharkawy, 2004)**. This enzyme is found in various tissues, and we observe its increase in the case of liver diseases due to high doses of ivermectin and levamisole **(Dong *et al.*, 2020).**

Levamisole and ivermectin caused a significant increase in the concentration of total bilirubin in the plasma of mice after 24 h. We recommend additional biochemical measurements to delineate toxic effects and adverse impacts. and these results may indicate the presence of damage to the liver and bile tissues or an increase in the rate of damage in erythrocytes. The reason for the increase in the concentration of total bilirubin may be due to the lack of coenzyme in the breakdown of bilirubin in the body as a result of poisoning with high doses of anthelmintics **(Othman *et al.*, 2022).** It is possible that other factors might be involved in the expression of the toxic effects of these anthelminths; these might include but are not limited to species variation, genetic build-up of the animal, housing conditions, and diet.

CONCLUSION

Levamisole and ivermectin have the potential to cause biochemical changes as toxic effects that were evident in some enzymatic measurements in mice's plasma on the level of ALP, LDH, and GDH activities, and the concentration of total bilirubin when we evaluated the effects of levamisole and ivermectin in mice.

Conflict of interest

The authors declare that no prospective conflicts of interest exist.

REFERENCES

ABDOU, K. A., and SHARKAWY, A. A., 2004. Some toxicological studies on ivermectin in goats. In Proceeding of the 20 Annual meeting of the Egyptian Society of toxicology. Bibliotheca Alexandria, Alexandria University, Alexandria, Egypt, 18-19.

ABONGWA, M., MARTIN, R. J., and ROBERTSON, A. P., 2017. A brief review on the mode of action of antinematodal drugs. Acta veterinaria, 67(2), 137-152.https://doi.org/10.1515/acve-2017-0013.

AL-NAJMAWI, T. K., and AL-ZUBAIDY, M. H., 2022. Acute toxicity events of ivermectin in chicks' model. Iraqi Journal of Veterinary Sciences, 36(4), 1119-1124. https://doi.org/10.33899/ijvs.2022.133188.2188

ARISE, R. O., and MALOMO, S. O., 2009. Effects of ivermectin and albendazole on some liver and kidney function indices in rats. Afr J Biochem Res, 3(5), 190-197.

BHARDWAJ, K., ABRAHAM, J., and KAUR, S., 2020. Natural product as avermectins and milbemycins for agriculture perspectives. Natural Bioactive Products in Sustainable Agriculture, 259-271. https://doi.org/10.1007/978-981-15-3024-1_12

CAMPBELL, C. W. 2012. History of avermectin and ivermectin, with notes on the history of other macrocyclic lactone antiparasitic agents. Current pharmaceutical biotechnology, 13(6), 853-865. https://doi.org/10.2174/138920112800399095.

CAMPILLO, J. T., EIDEN, C., BOUSSINESQ, M., PION, S. D., FAILLIE, J. L., and CHESNAIS, C. B., 2022. Adverse reactions with levamisole vary according to its indications and misuse: A systematic pharmacovigilance study. British Journal of Clinical Pharmacology, 88(3), 1094-1106. https://doi.org/10.1111/bcp.15037.

CHARLIER, J., HOSTE, H., and SOTIRAKI, S., 2023. COMBAR–Combatting anthelmintic resistance in ruminants. Parasite, 30. https://doi.org/10.1051%2Fparasite%2F2023006

DEPASS, L. R. 1989. Alternative approaches in median lethality (LD50) and acute toxicity testing. Toxicology letters, 49(2-3), 159-170. https://doi.org/10.1016/0378-4274(89)90030-1

DIXON, W. J. 1980. Efficient analysis of experimental observations. Annual review of pharmacology and toxicology, 20(1), 441-462. https://doi.org/10.1146/annurev.pa.20.040180.002301

DONG, Z., XING, S. Y., ZHANG, J. Y., and ZHOU, X. Z., 2020. 14-Day repeated intraperitoneal toxicity test of ivermectin microemulsion injection in wistar rats. Frontiers in Veterinary Science, 7, 1091. https://doi.org/10.3389/fvets.2020.598313.

EL-SABER BATIHA, G., ALQAHTANI, A., ILESANMI, O. B., SAATI, A. A., EL-MLEEH, A., HETTA, H. F., and MAGDY BESHBISHY, A., 2020. Avermectin derivatives, pharmacokinetics, therapeutic and toxic dosages, mechanism of action, and their biological effects. Pharmaceuticals, 13(8), 196. https://doi.org/10.3390/ph13080196.

GUPTA, R. C., MUKHERJEE, I. R. M., MALIK, J. K., DOSS, R. B., DETTBARN, W. D., and MILATOVIC, D., 2019. Insecticides. In Biomarkers in toxicology, 455-475. Academic Press. https://doi.org/10.1016/B978-0-12-814655-2.00026-8

HASSAN, F. S., and Al-BAGGOU, B. K., 2022. Some Biochemical changes induced by Toxic Effects of

Sulfur in Mice. Journal of Applied Veterinary Sciences 7(4), 97–103. https://dx.doi.org/10.21608/javs2022.155557.1173.

KAMGNO, J., GARDON, J., GARDON-WENDEL, N., DUKE, B. O., and BOUSSINESQ, M., 2004. Adverse systemic reactions to treatment of onchocerciasis with ivermectin at normal and high doses given annually or three-monthly. Transactions of the Royal Society of Tropical Medicine and Hygiene, 98(8), 496-504. https://doi.org/10.1016/j.trstmh.2003.10.018.

KAPLAN, R. M., and VIDYASHANKAR, A. N., 2012. An inconvenient truth: global worming and anthelmintic resistance. Veterinary parasitology, 186(1-2). 70-78. https://doi.org/10.1016/j.vetpar.2011.11.048.

KHALAF, W. K. 2022. Detection of Internal Parasites in Turkeys in Erbil city. Journal of Applied Veterinary Sciences, 7(4), 1-5. https://dx.doi.org/10.21608/javs.2022.143017.1155.

LYNN, R. C. 2008. Antiparasitic drugs. Georgis' parasitology for veterinarians, 9, 254-294.

MANSOOR, A. S. 2004. Neurobehavioral toxicity of levamisole in chicks. M.Sc. Thesis, College of Veterinary Medicine, University of mosul, Iraq.

MIDTHUN, K. M., NELSON, L. S., and LOGAN, B. K., 2021. Levamisole a toxic adulterant in illicit drug preparations: a review. Therapeutic Drug Monitoring, 43(2), 221. https://doi.org/10.1097/ftd.0000000000000851

ODO, U. U., CHRISTIAN EZEOYILI, I., AGUZIE, I. O., OLUAH, S. N., MADU, J., and NWANI, C. D., 2020. Effect of ivermectin® on biometric characteristics and organ biomarkers of African catfish Clarias gariepinus. Marine and Freshwater Behaviour and Physiology, 53(1), 17-33. https://doi.org/10.1080/10236244.2020.1734000.

OSAMA, A., FATMA, A., MOHAMED, E., HAMED, M. F., and HAMZAH, O., 2015. Studying the effect of Echinacea purpurea root on hematological, biochemical and histopathological alterations in cyclophosphamide treated Rats. Ann Vet Anim Sci, 3(2), 63-72. http://naturepub.org/navas.

OTHMAN, H. M., OTHMAN, F. M., and ALJALI, A. A., 2022. The effect of different dosages on hematological and some biochemical parameters of ivermectin after administration in goats. Libyan Journal of Basic Sciences, 17(1), 35-43. https://ljbs.omu.edu.ly/ eISSN 2707-6261.

POODA, H. S., RAYAISSE, J. B., HIEN, D. F. D. S., LEFÈVRE, T., YERBANGA, S. R., BENGALY, Z., and MOULINE, K., 2015. Administration of ivermectin to peridomestic cattle: a promising approach to target the residual transmission of human malaria. Malaria journal, 14, 1-12. https://doi.org/10.1186/s12936-015-1001-z.

QIAN, K., ZHONG, S., XIE, K., YU, D., YANG, R., and GONG, D. W., 2015. Hepatic ALT isoenzymes are elevated in gluconeogenic conditions including diabetes and suppressed by insulin at the protein level. Diabetes/metabolism research and reviews, 31(6), 562-571. https://doi.org/10.1002/dmrr.2655.

REHNI, A. K., and SINGH, T. G., 2010. Levamisole-induced reduction in seizure threshold: a possible role of nicotinic acetylcholine receptor-mediated pathway. Naunyn-Schmiedeberg's archives of pharmacology, 382, 279-285. https://doi.org/10.1007/s00210-010-0543-4.

ROMINE, N. M., MARTIN, R. J., and BEETHAM, J. K., 2014. Transcriptomic evaluation of the nicotinic acetylcholine receptor pathway in levamisole-resistant and-sensitive Oesophagostomum dentatum. Molecular and biochemical parasitology, 193(1), 66-70. https://doi.org/10.1016/j.molbiopara.2014.02.002.

SADATI, N. Y., YOUSSEFI, M. R., HOSSEINIFARD, S. M., TABARI, M. A., and GIORGI, M., 2021. Pharmacokinetics and pharmacodynamics of single and multiple-dose levamisole in belugas (Huso huso): Main focus on immunity responses. Fish and Shellfish Immunology, 114, 152-160. https://doi.org/10.1016/j.fsi.2021.04.016.

SHARMA, N., RAHAL, A., MISHRA, A., CHATURVEDI, V., GANGWAR, C., and DASS, G., 2020. Successful Management of Levamisole Toxicity in Sheep: A Case Report. http://jakraya.com/journal/pdf/27-vcsArticle_4.pdf.

SHOOP, W., and SOLL, M., 2002. Chemistry, pharmacology and safety of the macrocyclic lactones: ivermectin, abamectin and eprinomectin. In Macrocyclic lactones in antiparasitic therapy (pp. 1-29). Wallingford UK: CAB International. https://doi.org/10.1079/9780851996172.0001.

Swor, T. M., Whittenburg, J. L., and Chaffin, M. K., 2009. Ivermectin toxicosis in three adult horses. Journal of the American Veterinary Medical Association, 235(5), 558-562. https://doi.org/10.2460/javma.235.5.558.

TAWFEEK, S. E., DOMOUKY, A. M., and ABDEL-KAREEM, R. H., 2021. Protective effect of vitamin C against ivermectin induced nephrotoxicity in different age groups of male wistar rats: bio-histopathological study. Anatomy and Cell Biology, 54(4), 501-517. https://doi.org/10.5115/acb.21.124.

TRAILOVIC, S. M., and NEDELJKOVIC, J. T., 2011. Central and peripheral neurotoxic effects of ivermectin in rats. Journal of Veterinary Medical Science, 73(5), 591-599. https://doi.org/10.1292/jvms.10-0424.

VAN GENDEREN, P.J.J. 2008. Antihelminthic drugs. In Side Effects of Drugs Annual (Vol. 30, pp. 364-368). Elsevier. https://doi.org/10.1016/S0378-6080(08)00031-7.

ZOGHROBAN, H. S., ELMANSORY, B. M., ISSA, Y. A., ELTOKHY, A. K., SAFIA, H. S. A., EL MAGHRABY, G. M., and SALAMA, A.M. 2023. Novel insights on the therapeutic effect of levamisole on the chronic toxoplasmosis in mice model. Experimental Parasitology, 248, 108515. https://doi.org/10.1016/j.exppara.2023.108515

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