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Investigating the Toxicity of Some Pharmaceutical Compounds on The 3rd Larvae of The *Culex pipiens molestus* Forskal

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Abstract

THE 3rd-INSTAR *Culex pipiens molestus* Forskal larvae were used in this study to evaluate the toxicity of different concentrations of some drugs (niclosamide, isoniazid, piperazine, sulfasalazine, and 4-amino antipyrine). The mosquito mortality percentages were calculated using a gradient concentration of the examined medicines to estimate the acute toxicity testing. A concentration of 15 ppm of niclosamide on the 4th day of the experiment had a deadly impact on a mosquito's third instar larvae, resulting in a 100% death rate. The LC_{50} value of the niclosamide solution was found to be 23.11. On the 2nd day of treatment, however, 140 ppm of isoniazid resulted in 100% larval mortality. The LC_{50} value of the isoniazid solution was found to be 206.16. Practically all of the treated larvae were killed by the 300 ppm dosage of piperazine on the 3rd day of the treatment. The LC_{50} value of the piperazine solution was found to be 504.38. A concentration of 400 ppm of sulfasalazine on the 5th day of the experiment had a deadly impact resulting in a 100% death rate on mosquito's larvae. The LC_{50} value of the sulfasalazine solution was found to be 626.59. During the 3rd day of the study, a concentration of 2000 ppm of 4-aminoantipyrine caused 100% fatality in the larvae. The LC_{50} value of the 4-aminoantipyrine solution was found to be 3656.57. The effect of drug solutions as an inhibitor of egg-laying was that the concentrations used to kill third-instar larvae of mosquitoes had an effect of preventing egg-laying by 100% at all concentrations except for the niclosamide solution, which gave an egg-laying prevention percentage of 54.2, 43.4, 26.0, and 12.4 for concentrations 15, 12, 9, and 7 ppm, respectively. The concentrations used in the experiment to kill the third instar of mosquitoes were reduced to reach the concentrations at which female mosquitoes could lay eggs.

Keywords: Culex, Drugs, Larvae, Mosquitoes, Toxicity

Introduction

Increasing levels of globalization, human mobility, and climate change have caused invasive species to spread ecologically. These invasive species, which include arthropods, spread fatal diseases that might spark epidemics or pandemics [1]. Mosquitoes are flying, blood-sucking insects that act as carriers by ingesting hazardous causative agents into their bodies and transmitting those to their prey by biting them [2]. Malaria, a disease produced by the Plasmodium parasite that kills over a million people a year, is one of the most fatal infections carried by female mosquitoes of Anopheles. They also transmit the nematode worms that cause elephantiasis, a disease that doesn't kill people but causes psychological suffering and incapacity. In addition, they diffuse the virus, causing dengue fever, one of the most common and significant viral illnesses now carried by mosquitoes. According to the indicators, both the total number of Infection cases and nations where the illness is endemic are rising greatly [3,4].

Even though traditional chemical pesticides have been used to manage pests for nearly a century, there is still a risk because of the residues of pesticides within food chains, especially since some of them are difficult to break down. Not to mention the numerous negative impacts these chemicals have on wildlife, humans, pets, and the environment [5,6]. Insecticides, larvicides, and habitat modification are used to control mosquitoes. Safe larvicides for use on humans were required in this case [7].

As a result of all these obstacles, many researchers are beginning to look for novel substances that can be useful, secure, and not harmful to humans or beneficial to wild animals. In the first quarter of the 20th century, mosquito control was primarily focused on source reduction,

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which also included petroleum oils, as well as environmental management [8]. Utilizing insect repellent and pesticides to control adult and larval mosquitoes was one of the most effective ways to reduce mosquito bites [9].

Numerous chemical elements included in plant oils are known to have insecticidal properties. It has been found that numerous plants' alkaloids, terpenoids, steroids, phenolics, and essential oils work well as insecticides [10].

Piperazine possesses strong anthelmintic qualities; it is frequently utilized in medicine. As an example, piperazine citrate paralyzes muscles to efficiently control roundworms. Piperazine is also utilized as an essential linker in the insecticide industry to add various functional groups. The pharmacophore of neonicotinoid insecticides was added to N-alkyl-substituted piperazine to create neonicotinoid derivatives [11].

The goal of the present research is to inquire into the toxicity of some drugs against mosquitoes, which are easy to prepare, do not require expensive devices or solvents, and are also safe for people, pets, and the natural world, in addition to having a positive mosquito-controlling impact. This study was also conducted for the first time, according to our knowledge, against mosquitoes using pharmaceutical compounds.

Material and Methods

Establishing a culture of mosquitoes

In September 2022, mosquito egg rafts were removed from the *Culex pipiens molestus* F. culture and brought to the entomology lab at the University of Mosul College of Science. The produced egg rafts were put inside trays made of enamel, which contained two egg rafts and two liters of dechlorinated tap water. 2.25 g per tray, The diet for rabbits was provided to the larvae and put in screened cages (90× 50× 50) cm, where the adult emerged in a lab setting with a 12:12 (light: dark), (70±10) RH, and a temperature of (28±1) °C. An adult solution with 10% sugar had been given to them. There was a quail in a resting cage for 4 days of the week to receive blood feeding [12,13].

Preparation of the drug solution

Every drug solution used in the investigation was prepared using the same procedure: 0.25 g of the pure powder drug was taken, and each was dissolved in 5 ml of absolute ethanol, and the volume was completed to 10 milliliters by the same solvent (with gentle heating for niclosamide) to obtain a stock solution at 25000 ppm. Every stock solution was prepared in different concentrations:

Twenty healthy third-instar *Culex p. m.* larvae were placed in a single-use plastic mug that contained 50 milliliters of a treatment solution of 5 concentrations of niclosamide solution 5, 7, 9, 12 and 15 part per million, and 5 concentrations of isoniazide solution 100, 110, 120, 130 and 140 part per million, and 5 concentrations of piperazine solution 200, 225, 250, 275 and 300 part per million, and 5 concentrations of sulfasalazine solution 200, 250, 300, 350 and 400 part per million and 5 concentrations of 4-aminoantipyrine solution 750, 1000, 1500, 1750 and 2000 part per million utilizing three replicates for every concentration, 0.3 grams of rabbit meal, and the presence of both food and water serving as the control group, 99% ethanol alcohol was added to the control group, each according to its group : 15 ppm for the niclosamide group, 400 ppm for the sulfasalazine group etc.

It was determined what the mortality rate was. To determine the importance of the variations in the results, Abbott's equation was utilized to correct the percentage of larval mortality [14] and estimate the LC_{50} slope values with the LDP line.

$$\text{The correct mortality rate} = \left(\frac{\mathrm{T-C}}{100-\mathrm{C}}\right) \times 100$$

[T = The death rate in the treatment]

[C = The death rate in the control group]

A total of 50 females and 50 males of the same age and physiological condition were placed in a mosquito breeding cage, and a 10% sugar solution was placed in the cage for constant feeding. A series of concentrations were prepared from the original solution mentioned in the paragraph. A specific concentration of each solution was taken and placed in white plastic cups with a capacity of (100 cm^3). The treatment was carried out in separate cages. Two cups were placed, one of which contained 50 cm of control water (containing the same amount of ethanol present in the concentration). Each test group was repeated three times. The number of eggs laid after 24 hours was calculated for both the treatment and the comparison, and then the percentage of the effect preventing egg-laying was calculated for each concentration based on the equation [15].

$$ER\ \% = \left(\frac{NC\ -NT}{NC}\right) \times 100$$

ER = [percentage of repellency that is effective]

NC = [Numbers of eggs in control]

NT = [Numbers of eggs in treatment].

Results and Discussion

Table 1 demonstrates the effect of niclosamide solution on *Culex p. m.* larvae in their third instar. The 15 and 12 ppm concentrations had the highest effect on the larval mortality rate at 45 and 35%, respectively, after one day of treatment, while 18.3 and 8.3% of mosquito larvae were killed by a

concentration of 9 and 7 ppm, respectively; however, the 5 ppm concentration didn't cause any deaths. During the fourth day of the experiment, a 100% mortality rate was obtained at a con. of 15 ppm. On the seventh day, 12 ppm resulted in a 100% mortality rate, while on the fifth day, 9 ppm produced a 44.1% mortality rate. However, compared to the control group, which reported a death rate of 0%, the concentration of 7 ppm resulted in a reduced percentage of mortality (22%) on the fifth day of the treatment. The LC_{50} value of the niclosamide solution was found to be 23.11.

Table (2) demonstrates the isoniazid solution's efficacy against *Culex pipiens molestus* F. larvae in their third instar. According to Table 2, the 140 ppm concentration had the greatest effect on larval mortality on the first day of the experiment, with a mortality rate of 55.0. Subsequently, the concentration of 130 ppm resulted in 25.0% of deaths. On the second day of the experiment, however, a 100% fatality rate was caused by a 140 ppm concentration. 86.6% of the larvae had been killed by the 130 ppm concentration on the experiment's fourth day. After that, on the experiment's third day, the concentrations of 120 and 110 ppm caused 63.3 and 36.6% of fatalities, respectively, in contrast to the 0.0% death rate reported for the control group. The LC_{50} value of the isoniazid solution was found to be 206.16.

Table 3 indicates the activity of the piperazine solution against the 3rd instar larvae of *Culex p. m.* The results in the table indicate that the 300 ppm con. had the greatest influence on the death of larvae on the first day of the experimental period (71.6). That was followed by concentrations of 275, 250, 225, and 200 ppm, which caused the deaths of 45, 26.6, 18.3, and 13.3%, respectively. The rate of deaths was 100% for the concentration of 300 ppm, whereas the percentage of deaths for the concentration of 275 ppm was 76.2% in contrast to the control group, which recorded a death rate of 0% on the third day of the experimental period, while the con. 200 ppm produced a lower percentage of fatalities (22%). The concentration of 275 ppm gave a fatality rate of 100% on the experiment's seventh day, whereas the concentrations of 250, 225, and 200 ppm gave a 70.1, 49, and 36.8% mortality rate, respectively, in contrast to the group in control, which noted a 0% death rate on the seventh day of the experiment. The LC_{50} value of the piperazine solution was found to be 504.38.

The activity of the sulfasalazine solution against *Culex pipiens molestus* F. larvae in their third instar is shown in Table 4. The 400 and 350 ppm concentrations had the biggest effect on the on the mortality of larvae after just one day of treatment, with respective rates of 39 and 25.4%. These concentrations were followed by the 300 ppm concentration, which only killed 10.1% of the larvae; however, the 250 and 200 ppm concentrations did not cause any deaths. While the concentration of 400 ppm caused a 100% death rate on the experiment's fifth day, The con. of 350 ppm killed 96.4% of the larvae. Following that, concentrations of 300, 250, and 200 ppm caused 63.8, 32.7, and 10.3% of deaths, respectively, in contrast to the control group, which reported a death rate of 0% on the sixth day of the experiment. The LC_{50} value of the sulfasalazine solution was found to be 626.59.

The activity of a 4-aminoantipyrine solution against third-instar *Culex pipiens molestus* F. larvae is shown in Table 5. According to the results in this table, the 2000 ppm concentration had the greatest impact on the experiment's first day's larval mortality, which was 32.2%. Following that, concentrations of 1750, 1500, 1000, and 750 ppm resulted in 20.3, 15.2, 8.5, and 3.4% of deaths, respectively. The death rate was 100% for the con. of 2000 ppm on the experiment's third day, 69.5, 41.1, 21.4, and 12.5 percent for the concentrations of 1750, 1500, 1000, and 750 ppm, respectively, on the experiment's sixth day. These are in comparison with the control group, which experienced a death rate of 0% on the sixth day of the experiment. The LC_{50} value of the 4-aminoantipyrine solution was found to be 3656.57.

The results of the research demonstrated that when exposure time and solution concentration increased, the percentage of deaths also increased. Recently, there have been many studies suggesting antifungal, antibacterial, and anthelmintic agents as alternative chemicals to insecticides. Pesticides—especially those that are organosynthetic—bring many benefits to human health and are important to crop protection. The present study has similarities to those carried out by [16], who indicated some of the compounds have promising insecticidal properties, especially new piperazine-containing heterocyclic mono-, di-, and tri-amide derivatives, which could be employed as novel insecticidal leading structures for further study (e.g., against diamondback moth, LC_{50}: 0.00220.0081 mg/L). The current research has similarities to those carried out by [17]. The findings demonstrated that at 1.5 ppb of ivermectin, the larvae of *Culex quinquefasciatus* died at a rate of 73.38% due to paralysis. This explanation accords with previous published work [18], which found that mosquitoes are more toxic to erythromycin (ER) than amoxicillin (AM); their respective LC_{50} values are 60.2 and 107.6 µg L-1. ER has a relative toxicity of 0.95, and AM has a relative toxicity of 1.7.

Table 6 shows the effect of drug solutions as an inhibitor of egg-laying. The concentrations used to kill third-instar larvae of mosquitoes had an effect of preventing egg-laying by 100% at all

concentrations except for the niclosamide solution, which gave an egg-laying prevention percentage of 54.2, 43.4, 26.0, and 12.4 for concentrations 15, 12, 9, and 7 ppm, respectively. The concentrations used in the experiment to kill the third instar of mosquitoes were reduced to reach the concentrations at which female mosquitoes could lay eggs. Sulfasalazine, piperazine, and isoniazid have an 82.2, 80, and 75% inhibitory effect on egg laying at concentrations of 25, 50, and 200 ppm, respectively. The average number of eggs laid is 18.3, 20, and 30, respectively, while the percent effective repellence is -0.69, -0.66, and -0.61, respectively.

The results of this study agree with those of [19], that aspirin, an inhibitor of cyclooxygenase, was injected into *Aedes albopictus* shortly after blood-feeding, and this injection dramatically and dose-dependently decreased egg formation at choriogenesis. Furthermore, giving aspirin orally to *Anopheles albopictus* and *An. gambiae* also reduced the number of eggs they produced. The current research has similarities to those carried out by [17], who found that at 1.5 ppb of ivermectin the substance stored in the fat body was mobilized and fewer eggs were produced in the adult stage in the *Culex quinquefasciatus*. [20] Founding studies on prostaglandin E2 (PGE2) as a crucial but supplementary modulator of oogenesis in the *Aedes albopictus* mosquito, which transmits human illness. After blood-feeding (BF), the injection of aspirin, an inhibitor of cyclooxygenase (COX), prevented nurse cells from dumping into an egg that was developing, therefore inhibiting oogenesis.

Fig. 1 shows the phenotypic deformities of the *Culex p.* stages that appeared when treated with the drug solutions used in the current study. There were states of abnormal growth of the larvae, such as case B), which represents larvae suffering from atrophy and blackening of the abdominal area, which appeared in the solutions of niclosamide, piperazine, and isoniazid. Case C) suffers from deformation of the head area, merging with the chest area, and fusion of the abdominal rings that appeared in the solutions of piperazine and sulfasalazine compared to the control larval state A). As for pupae, state E) suffers from blackening, and state F) is in an intermediate state between pupa and adult. compared to the control pupa state D). State H represents an adult's inability to shed body appendages from the molting skin compared to the control adult state G). These drugs affect the physiological processes of the insect during its metamorphosis, which may be the reason for their impact on mosquito larvae. This mode of action is similar to that of insect growth regulators. As an alternative, there can be an unbalanced release of ecdysone, or juvenile hormone, between stimulation and inhibition. These drugs can interfere with the hormones created by the endocrine glands, hindering the insect's growth and finally leading to its fatality. His investigation's abnormalities are similar to the impact that growth regulators have on the larvae of mosquitoes, according to other studies [21-23].

Conclusions

The current study indicates the use of medicinal compounds that kill *Culex p. m.* larvae, used for the first time according to our knowledge, which have proven their acute toxicity at low concentrations. The study also proved that the concentrations used in killing the larvae all prevented egg-laying by 100% at all concentrations except for the niclosamide solution.

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Author`s contribution: All researchers participated in designing the research. The first researcher carried out the practical aspect and writing. The second researcher completed the task of supervising.

TABLE 1.The impact of niclosamide solution on *Culex p. m.* larvae in their third instar

Days	Concentration (part per million)					
	5	7	9	12	15	Control
	Percentage of deaths					
1	0.0	8.3	18.3	35.0	45.0	0.0
2	1.6	18.3	28.3	46.6	65.0	0.0
3	5	18.3	33.3	58.3	90.0	0.0
4	3.6	16.9	40.6	69.5	100	0.0
5	5	22.0	44.1	79.6	100	0.0
6	5	22.0	44.1	89.9	100	0.0
7	5	22.0	44.1	100	100	0.0

TABLE 2. The impact of isoniazid solution on *Culex p. m.* larvae in their third instar

Days	Concentration (part per million)					
	100	110	120	130	140	Control
	Percentage of deaths					
1	0.0	5.0	13.3	25.0	55.0	0.0
2	0.0	16.6	38.3	38.3	100	0.0
3	15.0	36.6	63.3	61.6	100	0.0
4	25.0	36.6	63.3	86.6	100	0.0
5	26.6	36.6	63.3	86.6	100	0.0
6	26.6	36.6	63.3	86.6	100	0.0
7	26.6	36.6	63.3	86.6	100	0.0

TABLE 3. The impact of piperazine solution on *Culex p. m.* larvae in their third instar.

Days	Concentration (part per million)					
	200	225	250	275	300	Control
	Percentage of deaths					
1	13.3	18.3	26.6	45.0	71.6	0.0
2	15.2	27.1	35.5	57.6	88.1	0.0
3	22.0	33.9	57.6	76.2	100	0.0
4	22.7	33.2	66.6	78.9	100	0.0
5	29.7	47.3	66.6	82.4	100	0.0
6	35.0	48.4	70.1	91.1	100	0.0
7	36.8	49.0	70.1	100	100	0.0

TABLE 4. The impact of sulfasalazine solution on *Culex p. m.* larvae in their third instar.

Days	Concentration (part per million)					
	200	250	300	350	400	Control
	Percentage of deaths					
1	0.0	0.0	10.1	25.4	39	0.0
2	5.0	6.8	13.6	59.3	74.5	0.0
3	11.8	18.6	32.2	76.2	88.1	0.0
4	11.8	27.1	42.3	83	94.9	0.0
5	10.3	31.0	60.2	87.9	100	0.0
6	10.3	32.7	63.8	96.4	100	0.0
7	10.3	34.4	63.8	96.4	100	0.0

TABLE 5. The impact of 4-aminoantipyrine solution on *Culex p. m.* larvae in their third instar

Days	Concentration (part per million)					
	750	1000	1500	1750	2000	Control
	Percentage of deaths					
1	3.4	8.5	15.2	20.3	32.2	0.0
2	13.6	22.0	32.2	45.7	91.4	0.0
3	15.5	24.0	34.4	53.4	100	0.0
4	14.0	22.7	42.1	70.1	100	0.0
5	14.0	22.7	42.1	70.1	100	0.0
6	12.5	21.4	41.1	69.5	100	0.0
7	12.5	21.4	41.1	69.5	100	0.0

TABLE 6. The effect of drugs solutions as an inhibitor of egg laying against female of *Culex pipiens molestus*

Drugs solutions	Concentrations (ppm)	Average number of eggs laid	Index activity oviposition (IAO)	Percent effective repellency(% ER)
Sulfasalazine	25	18.3	-0.69	82.2
	15	26.6	-0.42	60.0
	10	53.3	-0.26	41.8
	5	66.6	-0.11	20.0
Piperazine	50	20	-0.66	80.0
	40	41.6	-0.47	64.3
	20	75	-0.25	40.0
	10	95	-0.16	28.7
4-Aminoantipyrine	200	20	-0.61	75.9
	150	41.6	-0.33	50.0
	125	58.3	-0.12	22.2
	100	91.6	-0.04	8.4
Isoniazid	50	30	-0.61	75
	40	45	-0.29	45.9
	30	63.3	-0.12	21.8
	20	108.3	-0.03	7.1
Niclosamide	15	53.3	-0.37	54.2
	12	56.6	-0.27	43.4
	9	61.6	-0.14	26.0
	7	83.3	-0.09	12.4

Fig. 1. Phenotypic abnormalities that appeared in *Culex pipiens molestus* stages after treatment with drugs solutions

A)Normal larva, B) Atrophy and blackening of the abdominal area, C) Larva with a deformed head, D) Normal pupa, E) Black pupae, F) An intermediate state of the insect between pupa and adult, G) Normal adult, H) An adult is unable to shed body appendages from the molting skin.

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دراسة سمية بعض المركبات الصيدلانية على يرقات الطور الثالث للبعوض *Culex pipiens molestus* Forskal

الفت تحسين ياسين و منيف عبد مصطفى

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الخلاصة

تم استخدام يرقات الطور الثالث للبعوض *Culex pipiens molestus* Forskal في هذه الدراسة لتقييم سمية تراكيز مختلفة من بعض الأدوية (نيكلوساميد، أيزونيازيد، بيبرازين، سلفاسالازين، و4-أمينو أنتيبيرين). اذ تم حساب النسبة المئوية لموت اليرقات باستخدام تركيزات مختلفة من المحاليل الدوائية لتقدير مدى سميتها. كان للتركيز 15 ج ف م من محلول النيكلوساميد في اليوم الرابع من المعاملة تأثير قاتل ليرقات الطور الثالث للبعوض مما ادى الى نسبة قتل وصلت الى 100% وكانت قيمة LC_{50} لمحلول النيكلوساميد 23.11 ج ف م. بينما في اليوم الثاني من المعاملة ، ادى استخدام تركيز 140 ج. ف. م. من محلول الايزونيازيد الى موت يرقات الطور الثالث بنسبة 100%. في اليوم الثالث من التجربة وقد وجد أن قيمة LC_{50} لمحلول أيزونيازيد هي 206.16 ج ف م. تم قتل جميع اليرقات المعاملة بتركيز 300 جزء في المليون من محلول البيبرازين في اليوم الثالث من التجربة وقد وجد أن قيمة LC_{50} لمحلول البابيبرازين 504.38 ج ف م. كان لتركيز 400 جزء في المليون من السلفاسالازين في اليوم الخامس من التجربة تأثير مميت ليرقات الطور الثالث للبعوض أدى إلى معدل وفيات بنسبة 100٪. وقد وجد أن قيمة LC_{50} لمحلول السلفاسالازين هي 626.59 ج ف م. خلال اليوم الثالث من الدراسة، تسبب تركيز 2000 جزء في المليون من 4-أمينوأنتيبيرين في موت يرقات البعوض بنسبة 100%. وقد وجد أن قيمة LC_{50} لمحلول 4-أمينوأنتيبيرين هي 3656.57 ج ف م. وقد وجد أن لاستخدام المحاليل الدوائية في هذه الدراسة تأثير مانع لوضع البيض. إن جميع التركيزات المستخدمة في هذه الدراسة لقتل يرقات العمر الثالث للبعوض كان لها تأثير مانع لوضع البيض بنسبة 100% باستثناء محلول دواء النيكلوساميد الذي اعطى نسبة منع 54.2 ، 43.4 ، 26.0 ، 12.4 للتراكيز 15 ، 12 ، 9 ، 7 ج. ف. م. على التوالي . تم تخفيض التركيزات المستخدمة في التجربة لقتل الطور الثالث للبعوض للوصول الى التركيزات التي يمكن ان تضع انثى البعوض بيضها.

الكلمات الدالة: البعوض ، الكيولكس ، الادوية ، اليرقات ، السمية.