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Assessment of some metal-organic frameworks on the biological activities of *Culex pipiens* (Diptera: Culicidae)

Omnia M.H.M. Kamel* Reda M. Abdelhameed

Department of Applied Organic Chemistry, Industrial Chemistry Research Institute, National Research Center, Cairo,12622, Egypt.

Abstract

In Egypt, *Culex pipiens* (Diptera: Culicidae), has been investigated and declared as a vector of several human diseases. Here, safe, eco-friendly, and high-potency alternate insecticides were used. For this purpose, metal-organic frameworks (MOFs) with different metal centers (Iron, cobalt, manganese and nickel) were synthesized as they were used as anti-mosquitoes. MOFs with different concentrations to give mortality between 20 – 90% for the third larval instar were used. Also, sub-lethal concentration was investigated its effect on some biological activities (life cycle disorder, fecundity, sterility index, and egg-hatchability). The highest value of LC_{50} and LC_{95} were 110.55 & 389.48 ppm for Co-MOFs and the lowest value of LC_{50} and LC_{95} were 42.64 & 241.33 ppm for Fe-MOFs after 48hrs. The reproductive potency was affected as a result of the applied Fe-MOFs and Mn-MOFs. The damage that occurred from Fe-MOFs was more than that happened from Mn-MOFs; the sterility index was 100% and 75.2% for Fe-MOFs and Mn-MOFs respectively.

Keywords: MOFs, Mosquitoes control, Acute and latent effects, *Culex pipiens*

1. Introduction

Mosquitoes are well known for their importance to public health because they can lead to serious health issues and are thought to be the world's deadliest killer, killing an estimated 750000 people per year [1]. According to El-Zayyat et al. [2], *Culex pipiens* (Diptera: Culicidae) has been identified as a disease vector in Egypt. *Wuchereria bancrofti* is recognized for transmitting human lymphatic filariasis [3], Japanese encephalitis [4], Rift valley fever virus [5], and West Nile virus [6,7]. In Egypt, *Cx. pipiens* was identified as the filarial vector [8,9]. Also, the previous work reached the same results in many governorates [10,11] .

Chemical insecticides are still used as the first weapon against mosquitoes to stop diseases spread out. But these insecticides produce big problems associated with human health, arise resistance to insecticides and increasing hazards to environment [12,13]. Recently, there has been a lot of study interest in the use of novel insecticides made of nanoparticles made using different synthesis methods. With a focus on mosquitoes and ticks, numerous studies have been carried out to test their toxicity against a variety of arthropod pests and vectors. [14-16]. Metal-organic frameworks (MOFs) are a type of crystalline material consisting of metal ions or clusters linked by organic ligands. Due to their high surface area, tunable pore sizes, and chemical stability, MOFs have attracted significant attention for various applications, such as gas storage [17], water treatment [18], light emission [19-21], drug delivery [22], cancer therapy [23], and optical imaging [23]. MOFs are also becoming very popular among interested biologists, namely, in their in vivo biological activity, biocompatibility, and cytotoxicity [24]. From the previous, the authors try to innovate eco-friendly compounds for using against mosquitoes to decrease the spreading of mosquitoes which act as a vector to many human diseases.

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*Corresponding author e-mail: dromniakamel@yahoo.com; (Omnia M.H.M. Kamel).

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2. Materials & Methods

2.1. Chemicals and materials

All chemicals (1, 3, 5-benzenetricarboxylic acid (H_3-BTC, 99%), *N, N*-dimethylformamide (DMF, 99.9%), ethanol (99.9 %), methanol (99%), Ferrous chloride ($FeCl_2$, 99.9%), Nickel chloride ($NiCl_2$, 99%) , manganese chloride ($MnCl_2$, 99%) and cobalt chloride ($CoCl_2$, 99%) were purchased from Aldrich Company (Burlington, Massachusetts, United States).

2.2. Fe-MOF Synthesis

Fe-MOF was synthesized as follows: $FeCl_2$ (1 g, 3.38 mmol) and 1, 3, 5-benzenetricarboxylic acid (1 g, 5.5 mmol) was dissolved in 10 mL DMF at room temperature. The obtained mixture was locked and heated at 110 ° C for 24 h. The product was filtered and washed with dimethylformamide to eliminate uncreated organic molecules, then washed again with methanol to exchange dimethylformamide. The final product was dried in an oven at 80 °C for 4 hours and then stored under vacuum until used.

2.3. Synthesis of Co-MOF

Co-MOF was synthesized as follows: $CoCl_2$ (1 g, 3.38 mmol) and 1, 3, 5-benzenetricarboxylic acid (1 g, 5.5 mmol) was dissolved in 10 mL DMF at room temperature. The obtained mixture was locked and heated at 110 ° C for 24 h. The following steps were mentioned before in preparation of Fe-MOF.

2.4. Synthesis of Mn-MOF

Mn-MOF was synthesized as follow: $MnCl_2$ (1 g, 3.38 mmol) and 1, 3, 5-benzenetricarboxylic acid (1 g, 5.5 mmol) was dissolved in 10 mL DMF at room temperature. The obtained mixture was locked and heated at 110 ° C for 24 h. The final material was reached as previously illustrated in synthesis for Fe-MOF.

2.5. Synthesis of Ni-MOF

Also, the synthesis of Ni-MOF was stated before but with the exchange of the salt used by $NiCl_2$ (1 g, 3.38 mmol) and all steps like the previous.

2.6. Characterization of materials

High-resolution scanning electron microscopy (HRSEM Quanta FEG 250 with field emission gun, FEI Company - Netherlands) was used to examine the morphological structures of MOFs. An energy dispersive X-ray spectroscopy (EDX) analysis unit (EDAX AME-TEK analyzer) coupled to the same microscope was used to record the elemental analysis. Cu K X-radiation at 40 kV, 50 mA, and = 1.5406) at room temperature, where diffraction data were collected in steps of 2° ranging from 4° to 50° with a step size of 0.02° and scanning rate of 1 s, allowed X-ray diffraction (XRD) to be detected for samples.

2.7. Tested mosquitoes

2.7.1. *Culex pipiens* culture

Culex pipiens larvae were intake from Medical Entomology Institute then start rearing colonies and maintained at the laboratory in Research and Training Center – Ain Shams University. The colony was reared as mentioned before by Abdel-Haleem et al., [25].

2.7.2. Larvicidal activity

Four substances were evaluated at various concentrations. The mortality data were collected after 24 and 48 hours, and the LC50 & LC95 were determined using the probit analysis [26]. The Briggs [27], equation was used to compute the percentage of larval mortality. Larval mortality% is calculated as A-B/A x100, where A and B are the numbers of tested larvae and pupae, respectively. Calculations were made on the timespan from the start of the first instar of larvae and the start of pupation. El-Sheikh (2002) estimated the pupation rate. The number of pupae (A) and the number of examined larvae (B) are used to calculate the percent of pupation (A/B x 100). Calculating the amount of time between the beginning of pupation and the beginning of the pupal stage allowed researchers to establish the duration of the pupal stage. The number of adults that emerged (A) divided by the number of pupae that were examined (B) yields the percentage of adult emergence (A/B100). El-Sheikh [28], cites the following equation as the one used to construct the Growth index. The growth index is calculated as follows: growth index = a/b, where a is the proportion of adult emergence and b is the mean development in days.

2.7.3. Reproductive potential of resulted females treated by MOFs:

2.7.3.1. Fecundity

As stated by WHO [29], protocol the fecundity of female mosquitoes can be calculated after the application of selected compounds according to their potency at sub-lethal concentrations (LC_{25}). The egg raft which lay by each female was counted. Estimation of fecundity will do by comparing the number of eggs laid from treated emerged females with the control one.

2.7.3.2. Hatchability percent of egg

The hatchability of eggs was evaluated as two groups (hatched and unhatched) as stated by Hassan *et al.* [30]. Further investigation was carried out using a dissecting microscope; the eggs can classify as unhatched eggs (embryonated and unembryonated) [31]. The hatchability percent was calculated according to the equation stated by **El-Sheikh** [28]. The percent of hatching eggs= A/B×100, where (A) is the whole number of hatched eggs and (B) is the total number of eggs laid.

2.7.3.3. Sterility index (SI)

The equation developed by Toppozada et al. [32], was used to calculate the sterility percentage. The percentage of sterility is calculated as follows: 100 - [ab/Ab]100, where (a) is the number of eggs laid by each treatment-group female and (b) is the proportion of hatched eggs. The numbers in (A) and (B) reflect the proportion of hatched eggs in the control group and the number of eggs laid by each control female, respectively.

2.8. SEM study for treated mosquito larva

Scanning for larvae treated by selected two (the most potent) compounds with sub-lethal concentration. Third larval instar was fixed in 2.5% glutaraldehyde, post-fixed in osmium tetraoxide, dehydrated, critical point dried, ion sputtered gold, and examined using an SEM (QUANTA FEG 250). Observations were made on the whole body (especially the head and the siphon region) to investigate the deformation that occurred as the results of treatment.

2.9. Statistical analysis:

Biological data were expressed as mean ±SE and SD by Microsoft Excel. The mortality data were analyzed to estimate LC50, LC95, and slope with standard error values using multiple linear regressions [26].

3. Results and Discussion

3.1. Characterization of MOFs

Figure 1 displays the PXRD patterns of Ni-MOFs and Mn-MOFs. The sharpness of the peaks is proof the purity of the network, which are quite consistent with previously published work. The XRD pattern of Ni-MOFs and Mn-MOFs showed diffraction peaks at 2ɵ=6.7°, 9.4°, 11.6°, 13.4°, 17.4°, 19.1°, 20.1°, 25.9°, 29.4°, 35.3° and 39.2. The as-prepared sample's five major XRD peaks are consistent with the known structure of Ni-MOFs and Mn-MOFs, and the synthesized Ni-MOFs and Mn-MOFs sample exhibits distinct diffraction peaks, indicating strong crystallinity.

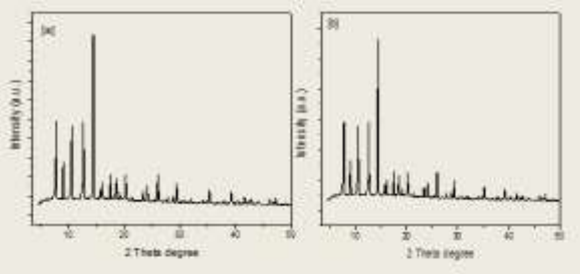

Figure 1. PXRD of Ni-MOF (a) and Mn-MOF (b)

Through the use of field emission SEM, the morphology of Ni-BTC was identified. Figure 2a displays SEM pictures of the MOF crystals. The MOF crystals are discovered to have well-regulated 0.5–0.8 µm particle sizes. Additionally, EDS spectra showed Nickel, oxygen and carbon (figure 2b). The shape and nanostructure of Mn-MOFs as measured by FE-SEM were shown in Figure 2c. The Mn-MOFs nanoparticles were found to be relatively consistent in size, with an average diameter of 310 nm. Additionally EDS spectra showed manganese, oxygen and carbon (figure 2d).

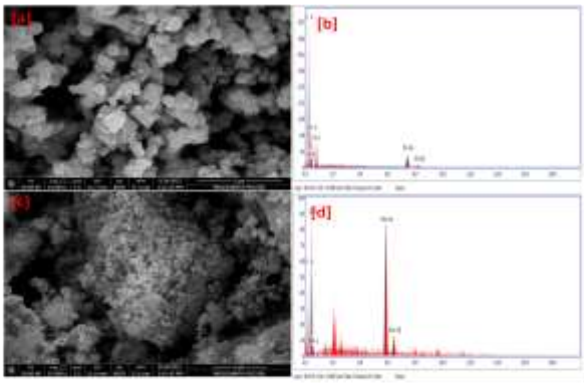

Figure 2. SEM of Ni-MOF (a) and Mn-MOF (c) and EDX of Ni-MOF (b) and Mn-MOF (d)

X-ray diffraction patterns of Co-MOFs are displayed in Figure 3a. The diffraction peaks were showed at 2ɵ= 17.51°, 18.71°, 27.11°, and 35.51°, which correspond to the (220), (111), (002), and (440) planes. The XRD pattern of synthesized Fe-MOFs is depicted in Figure 3b. Peaks at 2 = 11°, 19°, 24°, 28°, and 34° are present in the pattern and are in keeping with Fe- MOF literature findings. Figure 4a displays the Co-MOFs SEM images. About 5.5 µm cubic-shaped microcrystals make up the Co-MOFs. EDX image (figure 4b) showed clearly cobalt atom besides oxygen and carbon. Figure 4c showed scanning electron microscopy photos of Fe-MOFs particles that demonstrate the tiny crystallized shape. Figure 4d showed iron, oxygen and carbon atoms in the structure of Fe-MOFs.

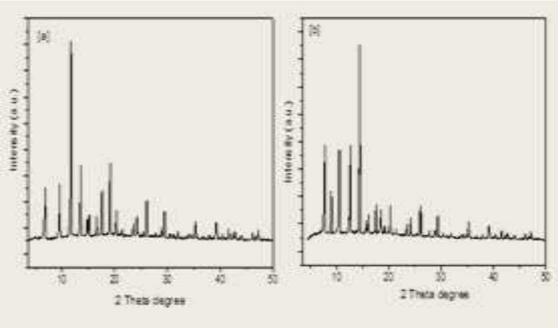

Figure 3. PXRD of Co-MOF (a) and Fe-MOF (b)

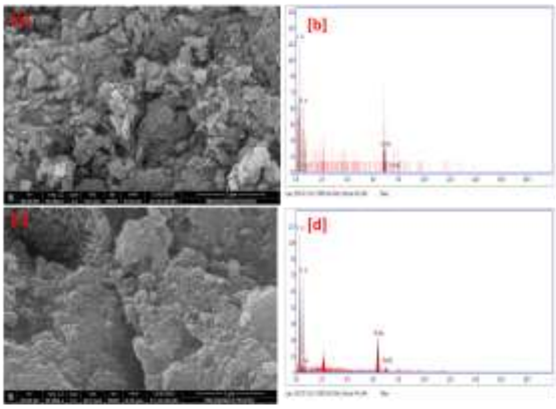

Figure 4. SEM of Co-MOF (a) and Fe-MOF (c) and EDX of Co-MOF (b) and Fe-MOF (d)

3.2. Larvicidal activity

The screening of four tested MOFs against the third larval instar was represented in Tables (1&2). The data showed a variety in potencies may be due to the difference in the metal used with the MOF base material. Figure 5 appears some kinds of mortality of larvae by application with Fe-MOFs and Mn-MOFs in comparison with control one. The figures appear stretching between the head and thorax and appear diffusion of the whole body as a result of Fe-MOFs and Mn-MOFs applications respectively; this finding may be attributed to the effect directly on the nervous system. These results agree with previous work [33-35]. The life cycle was affected by applied sub-lethal concentration; the longevity of the larval period and pupal period and the percentage of pupation and adult emergence also the longevity of the adult period were directly proportional to the concentration of tested materials. Many authors arrived at similar results but with other tested materials [34, 36-40].

Table (1): Third-instar *Cx. pipiens* larvae susceptibility to Co-MOFs and Ni-MOFs at various time points and coefficient limitations

Concentration (ppm)	Mortality percent %			
	Co-MOFs		Ni-MOFs	
	24 hrs	48 hrs	24 hrs	48 hrs
50	11.67	15	15	20
100	26.67	45	28.33	51.67
150	43.33	65	46.67	71.67
200	71.67	78.33	78.33	83.33
control	0.00	0.00	0.00	0.00
LC_{50} (ppm) (co. limit)	149.35 (128.48 – 173.66)	110.55 (96.88 – 126.14)	135.69 (117.76 – 156.37)	96.00 (83.62 – 110.19)
Lc_{95} (ppm) (co. limit)	592.98 (348.22 – 912.49)	389.48 (272.67 – 557.36)	508.17 (326.19 – 793.55)	339.80 (244.33 – 473.41)
Slope ± SE	2.85 ± 0.2	3.01 ± 0.17	2.87 ± 0.2	3.00 ± 0.17

Table (2): Fe-MOFs and Mn-MOFs sensitivity of third-instar *Cx. pipiens* larvae at various time points and coefficient limits

Concentration (ppm)	**Mortality percent %**			
	Fe-MOFs		**Mn-MOFs**	
	24 hrs	**48 hrs**	**24 hrs**	**48 hrs**
10	3.33	11.67	5	10
50	23.33	48.33	18.33	43.33
100	46.67	73.33	40	66.67
150	66.67	96.67	58.33	91.67
control	0.00	0.00	0.00	0.00
LC_{50} (ppm) **(co. limit)**	103.04 (82.38 – 129.03)	42.64 (34.57 – 52.52)	133.80 (98.20 – 182.95)	50.67 (41.08 – 62.44)
Lc_{95} (ppm) **(co. limit)**	691.48 (350.88 – 1376.03)	241.33 (166.56 – 351.95)	1324.06 (498.90 – 3579.59)	317.26 (206.44 – 391.30)
Slope ± SE	1.99 ± 0.09	2.19 ± 6.07E-02	1.65 ±7.98E-02	2.06 ± 6.09E-02

Figure 5. A: effect of Fe-MOF, B: Mn-MOF & C: Control

In endopterygota insects, plant extracts prevent the development of imaginal discs, which are the progenitors of numerous adult integumentary structures. Due to adult chitin deformation [41] or lower adult emergence % [42,43], this may be the cause. Treatment with the studied extracts resulted in a reduction in the number of eggs laid by each female Cx. pipiens mosquito and the percentage of hatching eggs. These findings complemented those of Jayarama and Pushpalatha [44]. The decline in fecundity and fertility is attributed to the inability of sperm to reach females during copulation or to partial sterility of either females or males [45]. Additionally, hormones regulate egg maturation in culicinae species. This could indicate that the Cx. pipiens' hormonal system was affected by the plant extracts used. Riddiford [46] demonstrated that juvenoids may cause female infertility in endopterygota insects when applied at a certain point of oocyte development. The extracts utilized may have a direct impact on the corpora allata, which would result in fewer germanium eggs being produced. The corpora allata may become inactive in insects 48 hours after treatment, according to Yamashita et al. [47]. The numbers of eggs laid by Bombyx mori fifth-stage larvae were decreased by 12% because of the loss of the corpora allata. Data from Tables (3-5) revealed that the reproductive potency was affected as a result of applied Fe-MOFs and Mn-MOFs. The damage that occurred from Fe-MOFs was more than that happened from Mn-MOFs; the sterility index was 100% and 75.2% for Fe-MOFs and Mn-MOFs respectively. The decline in fecundity and fertility is attributed to the inability of sperm to transfer to females during copulation or to partial sterility of either females or males [44,45]. Additionally, hormones regulate egg maturation in culicinae species. This might mean that the plant extracts utilized interfered with the Cx. pipiens' hormonal system. In endopterygota insects, Riddiford [46] showed that juvenoids may result in female sterility when used at a specific stage of oocyte development.

Table (3): Biological aspects changing of *Cx. pipiens* after treatment with Fe-MOFs

Concentration (ppm)	Larval mort. %	Mean Larval Period (days)±SD	Pupation %	Mean Pupal duration (days)±SD	Adult Emergence % (a)	Mean adult longevity (days) (b)±SD	Growth Index (a/b)
Untreated	0.0	4.6±0.7	100	1.4±0.5	100	6.5±0.8	15.38
10	11.67	4.4±0.5	86.64	1.6±0.5	90	5.5±0.5	16.36
50	48.33	4.5±0.5	70.50	1.4±0.5	61.42	5.5±0.5	11.17
100	73.33	4.9±0.8	52.67	1.6±0.6	43.51	5.3±0.5	8.21
150	96.67	5.1±0.9	27.34	2.2±0.4	23.67	4.8±0.5	4.93

Table (4): Biological aspects changing of *Cx. pipiens* after treatment with Mn-MOFs

Concentration (ppm)	Larval mort. %	Mean Larval Period (days)±SD	Pupation %	Mean Pupal duration (days)±SD	Adult Emergence % (a)	Mean adult longevity (days) (b)±SD	Growth Index (a/b)
Untreated	0.0	4.6±0.7	100	1.4±0.5	100	6.5±0.8	15.38
10	10	4.0±0.4	88.48	1.4±0.5	92	5.8±0.7	15.90
50	43.33	4.1±0.8	72.35	1.6±0.5	73.43	5.8±0.6	12.66
100	66.67	4.8±0.7	53.86	1.6±0.5	59.61	6.0±0.5	9.94
150	91.67	4.5±0.6	30.67	1.8±0.4	39.54	6.0±0.8	6.59

Table (5): Effect of Fe-MOFs and Mn-MOFs on the female of *Cx. pipiens'* ability to reproduce

Tested compound	No. of Females	No. of eggs laid		No. of hatched eggs		No. of unhatched eggs					Sterility index (S.I.) %
		Total	Mean ±SE	Total	%	Total	Embryonated		Unembryonated		
							No	%	No	%	
Untreated	18	4050	225±10.2	3985	98.4	65	12	18.5	53	81.5	0.0
Fe-MOFs	6	360	60±0.6	0.0	0.0	0.0	10	16.67	40	66.67	100
Mn-MOFs	10	1043	104.3±1.2	550	52.7	493	138	28	355	72	75.2

3.3. SEM for treated mosquito larvae with MOFs

The observation from scanning by electron microscope was made mainly on siphon (Figure 6A,B,C) and head capsule (Figure 7A,B,C) which appears abnormalities in antennae (expanding) and sensor hairs on the head in both treatments, that's mean they losing their sensation and cells of antennae were enlargement trying to capture any small amount of oxygen. The head appears compact in the treatment compared to the control. The siphon appears damaged from the tip and the sensor hairs were compacted together these results agreed with the finding by [48].

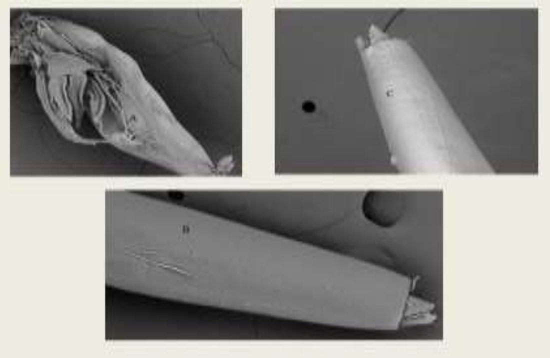

Figure 6. A: siphon of Fe-MOF, B: Mn-MOFtreated larva & C: siphon of control

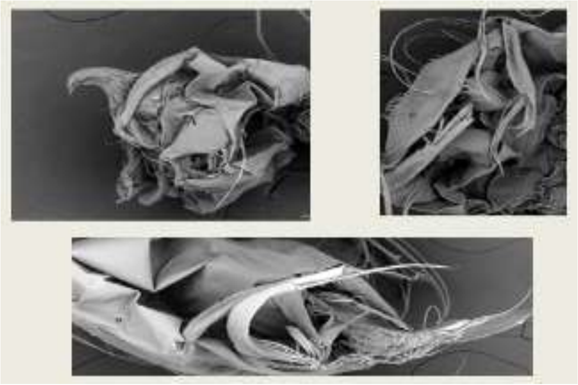

Figure 7. A: head capsule of Fe-MOF, B: Mn-MOF treated larva & C: control

4. Conclusion

MOFs with diferant metal center were synthesized and well characterized using different spectral techniques. From the present study metal-organic frameworks appear larvicide activities with different degrees against mosquito larvae according to the metal derivatives in MOFs. Also, they have a latent valuable effect on lifecycle and reproductive potency. These compounds are promising to use in integrated vector management.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

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