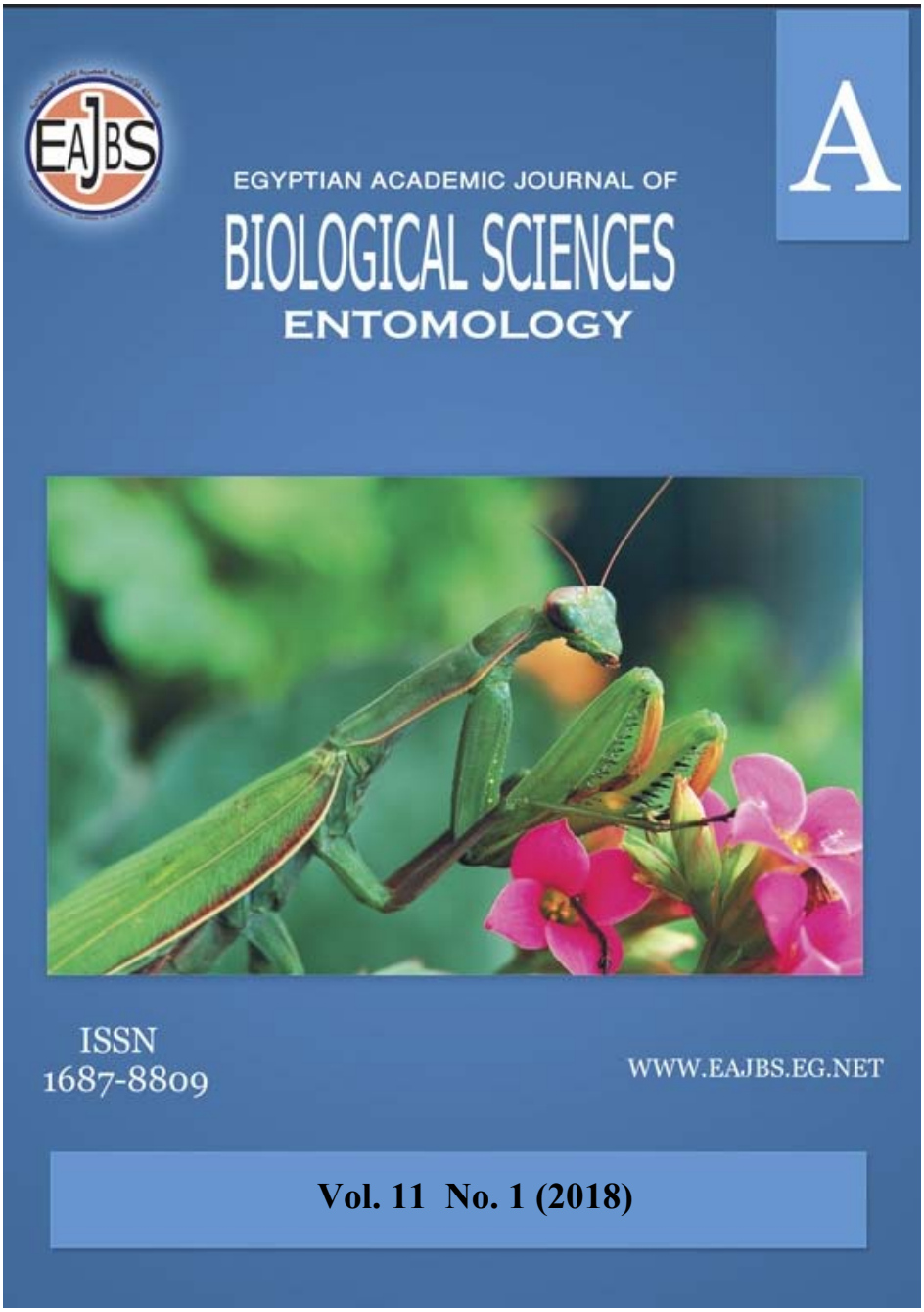

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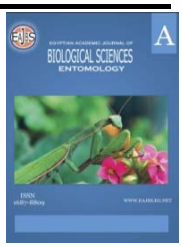

Comparative Modelling, Toxicological and Biochemical Studies of Imidacloprid and Thiamethoxam Insecticides on the House Fly, *Musca domestica* L. (Diptera: Muscidae)

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ABSTRACT

Neonicotinoid baits are recently replacing anticholinesterase baits for adult house fly (*Musca domestica* L.) control. Recently, imidacloprid (IMI) and thiamethoxam (THIA) are widely used for the control of this pest. In this study both compounds were docked to elucidate their interactions with acetylcholine binding protein (AChBP). The feeding technique was used to evaluate the toxicity of tested insecticides to adult house flies. Bioassay experiments showed that the THIA was more toxic to adult house flies than IMI with LC_{50} values 7.27 and 21.08 ppm; respectively. The biochemical activities of acetylcholinesterase, ATPase, cytochrome P-450 and carboxylesterase were increased by insecticides treatment, while, the total protein content was reduced.

INTRODUCTION

The use of insecticides is very important for the control of house fly (*Musca domestica* L.), in spite of their ability to develop resistance to these insecticides with long term exposure. The resistance development rates are low to insecticides applied as baits than those which are applied as sprays Khan *et al.* (2013). Neonicotinoids baits are widely spread in recent years and replaced the conventional insecticide baits used for the house flies management Kristensen and Jespersen (2008).

THIA and IMI are synthetic derivatives of nicotine; they exert their selective, specific and irreversible toxic effects by interaction with nicotinic acetylcholine receptors (nAChR) of the insect nervous system. THIA is the second generation of neonicotinoids and belongs to thianicotinyl subclass while, IMI is the first generation and belongs to chloronicotinyls subclass Shi *et al.* (2011). THIA and IMI provide excellent effect against a broad range of insects with sucking and chewing habits Jeschke and Nauen (2008) such as leaf miners as well as some lepidopterous species, aphids, Colorado potato beetle, whiteflies, fleas, beetles, wireworms, rice hoppers and thrips Abdallah *et al.* (2016). They are also extensively used in control of insect

pests of public health and agricultural importance Li *et al.* (2012). The study of ligand-bound and ligand -free structures of acetylcholine binding protein (AChBP) allowed gaining deep insights into the structure of the active site and its relation to function Selvam *et al.* (2015). Therefore, the docking studies are important to clear the insecticide- enzyme interactions and their effect on toxicity.

For these previously mentioned reasons, this study focused on these two neonicotinoids to perform a modelling study to deeply demonstrate their binding mode and how they complex with nAChR. Also, this study aimed to evaluate their experimental potency to adult house flies compared to the theoretical efficacy expected by docking interactions. The biochemical measurements are used to understand the physiological and biochemical defence mechanisms of house flies against the tested insecticides.

MATERIALS AND METHODS

Molecular Docking Study:

The chemical and three-dimensional (3D) structures of insect nAChR were studied. The 3D-structure of nAChR was obtained from Protein Data Bank (http://www.pdb.org/). The crystal structure of the acetylcholine binding protein of the great bond snail, *Lymnaea stagnalis* (Ls-AChBP) in complex with IMI (PDB: 2ZJU) Ihara *et al.* (2008) was used for the molecular docking studies because there is still no crystal structure of nAChR of house fly and *Ls*-AChBP has high homology to the extracellular domain of insect nAChR. Actually, *Ls*-AChBP has been used to study the interaction between compounds with nAChR.

Molecular modelling studies occurred by discovery studio 2.5 modules [Accelrys Inc., San Diego, CA (2009)] program in order to investigate the binding mode of tested insecticides and evaluate their binding affinities with the specified binding sites; using what is called CDOKER protocol Wen *et al.* (2012) .

The 2ZJU PDB file was downloaded that image the IMI cocrystallized with the AChBP. The enzyme was prepared for docking and the cocrystallized molecules were removed. The active binding site was characterized and selected. The tested molecules were drawn and underwent energy minimization then docked in the active site of enzymes using CDOCKER protocol. The binding orientations and interactions of resulted conformations were examined and these conformations were compared.

Insecticidal Assay:

Insects:

A laboratory susceptible strain of house fly pupae were obtained from the Research Institute for Medical Entomology in Dokki, Giza, Egypt and colonized in entomology department laboratory. Adults were provided with powdered milk mixed with distilled water 1:1 in cotton pads in separate Petri dishes for feeding and as breeding media. The larval diet was a mixture of wheat bran, yeast, sugar and powder milk (40:10:3:3, by weight), respectively according to Bell *et al.* (2010) and Shah *et al.* (2015) with some modifications, and maintained under controlled conditions of 27 ± 2 °C and 60–70% relative humidity and 14:10 light: dark photoperiod Abbas *et al.* (2014).

Insecticides:

Commercial formulation of imidacloprid is (Pest 20% WP, El helb Co.) and thiamethoxam is (Actara 25% WG, Novartis Co.).

Insecticidel Bioassay Test:

Feeding application method was used to compare the toxicities of insecticides

to adult house flies. Serial dilutions of different insecticide concentrations were made. Two-day old adults were used in insecticide bioassays. Six concentrations of tested insecticides in distilled water were added to (10%) sugar solution. Six ml. of each concentration was added to small plastic cups containing cotton pad and used for bioassay test according to procedure described by Kristensen and Jespersen (2008) with some modifications. Then they were anesthetized by chilling and 20 flies transferred to each replicate. Each concentration has three replicates. Mortality was recorded 48 hours post treatments. The recorded mortalities were averaged to establish a regression lines using log probit scales (probit analysis Finney (1971) program) representing concentrations versus percentage of mortality.

Biochemical Assay:

Preparation of Samples for Biochemical Assay:

After the detection of the LC_{50} values using the adult house flies. The insects were homogenized in distilled water (50 mg /1 ml) using chilled glass Teflon grinder. The homogenate was centrifuged at 8000 r.p.m. for 15 min. in a refrigerated centrifuge.

Protein Assay:

Total proteins were determined by the method of Bradford (I976) depending on coommasie brilliant blue G-250 reagent (CBB).

Acetylcholinesterase (AChE) Activity Assay:

AChE activity was detected according to the method described by Simpson *et al.* (1964) by using the substrate, acetylcholine bromide (AChBr).

ATPase Activity Assay:

The total enzyme activity of the ATPase was measured according to Amaral *et al.* (2001). The main idea of this method is measuring the amount inorganic phosphate resulted from hydrolysis of ATP by ATPase.

Cytochrome P-450 Monooxegenase Activity Assay :

For determination of the cytochrome P-450 monooxygenase activity, the p-nitroanisole o-demethylation was assayed according to Hansen and Hodgson (1971) method with slight modifications.

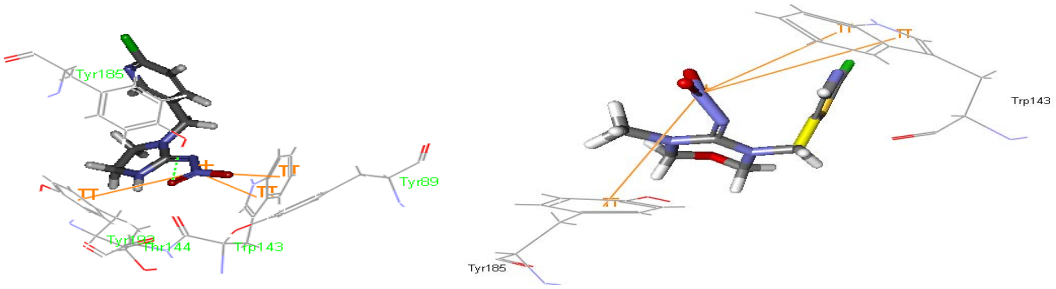
Carboxylesterase Activity Assay:

Carboxylesterase activity was measured according to Simpson *et al.* (1964) method, using methyl n- butyrate (MeB) as substrate.

RESULTS

Modeling Studies:

Docking of IMI and THIA illustrated in fig. (1). IMI showed one hydrogen bond made via bonding of (O) of nitromethylene of imidazolidine ring with Tyr185, in addition to double π- π bonds with Trp143 and one with Tyr192 occurred, with docking interaction energy = 20. While THIA presented three π- π interactions, one between nitromethylene group with Tyr185 and the other two π- π bonds with Trp143, and exhibited docking energy = 21.12.



(a) **(b)**

Fig. (1): showing the (a) imidacloprid and (b) thiamethoxam docked to (*Ls*-AChBP).

Toxicological studies

The LC_{50} values of IMI and THIA were 21.08 and 7.27 ppm; respectively. The toxicity index of IMI (34.5%) was estimated basing on LC_{50} value of THIA (100%). The relative potency of THIA was 2.9 in relative to IMI (1.00) therefore; the toxicity of THIA to adult house flies was approximately three times higher than IMI as presented in Table (1) and graphically in fig. (2) and (3). The previously mentioned data revealed that the THIA showed higher toxicity to adult house flies than IMI. The slope values of IMI and THIA were 3.82 and 3.08 which indicated that the population used in bioassay had somewhat the same homogeneous response to the tested insecticides.

Table (1): Toxicity of imidacloprid and thiamethoxam to adult house fly.

Insecticides (ppm.)	**Imidacloprid**	**Thiamethoxam**
LC_5 (*F.l. at 95%)	7.83(6.26-9.79)	2.12(1.63-2.75)
LC_{50} (*F.l. at 95%)	21.08(19.02-23.37)	7.27(6.50-8.12)
LC_{95} (*F.l. at 95%)	56.72(47.39 -67.99)	24.83(19.76-31.39)
Slope ± SE	3.82 ± 0.11	3.08 ± 0.07
Toxicity index	34.5	100
Relative potency	1.00	2.9

* Fiducial Limits

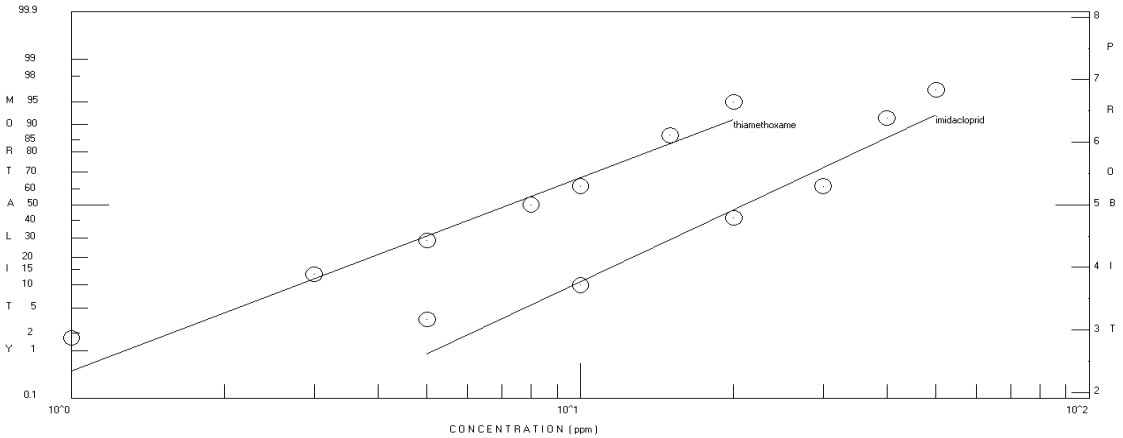


Fig. (2) show toxicity regression lines of imidacloprid and thiamethoxam bioassay against adult house fly.

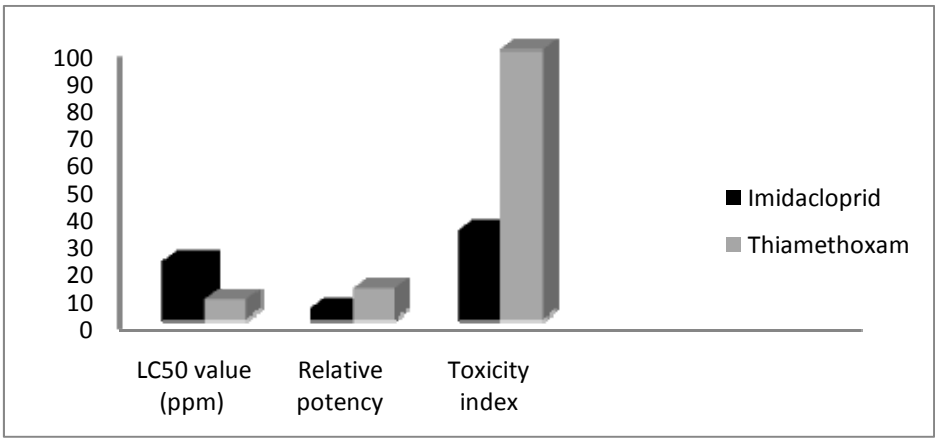


Fig. (3): show the LC_{50}, relative potency and toxicity index values of imidacloprid and thiamethoxam.

Biochemical Studies:

The sub-lethal concentration (LC_{50}) effects of the tested insecticides on total protein content and different enzymes in haemolymph of the adult house flies, 24 h after treatment were mentioned in Tables (2), and graphically illustrated in Figure (4). Results revealed that tested insecticides induced highly significant reduction in total protein contents in treated adult compared with untreated control insects at $p<0.01$ by using *Duncan`s* multiple range test Duncan. (1955). Where, THIA highly reduce the total protein than IMI with % reductions -47.38% and -32.71%, respectively.

THIA exhibited significantly higher AChE activity compared to the IMI ($p < 0.01$) with % changes 38.9% and 25.68%, respectively. The tested insecticides showed high level of ATPase activity with significant difference where, the extreme activity achieved by THIA with % increase (91.89%), while IMI presented 59.1%.

The biochemical analyses indicated that the activity of the detoxifying enzymes carboxylesterase (CarE) and cytochrome P-450 were significantly higher for IMI than of THIA. However, the activities of CarE were high than cytochrome P-450. Whereas, the lowest determined activity was observed for the detoxifying enzyme cytochrome P-450.

Table (2): Effect of imidacloprid and thiamethoxam on acetylcholinesterase, ATPase, cytochrome P-450 and carboxylesterase activities and total protein content in haemolymph of adults house fly

Enzyme	**Activity mean ± SE**		**%Change**	
	Imidacloprid	Thiamethoxam	Imidacloprid	Thiamethoxam
Acetylcholinesterase	36.57 ±0.28**b**	40.42 ±0.16**a**	25.68%	38.9%
ATPase	41.52 ± 0.37 **b**	50.084 ± 0.29**a**	59.1%	91.89%
Cytochrome P-450	75.25± 0.08 **a**	67.78 ± 0.14 **b**	19.83%	7.93%
Carboxylesterase	58.6±2.1 **a**	54.4±0.02 **b**	32.87%	23.35%
Total protein content	29.87±0.28 **a**	23.36±0.16 **b**	-32.71%	-47.38%

-Means bearing different subscripts are significantly different ($p> 0.01$) Duncan`s multiple range test.

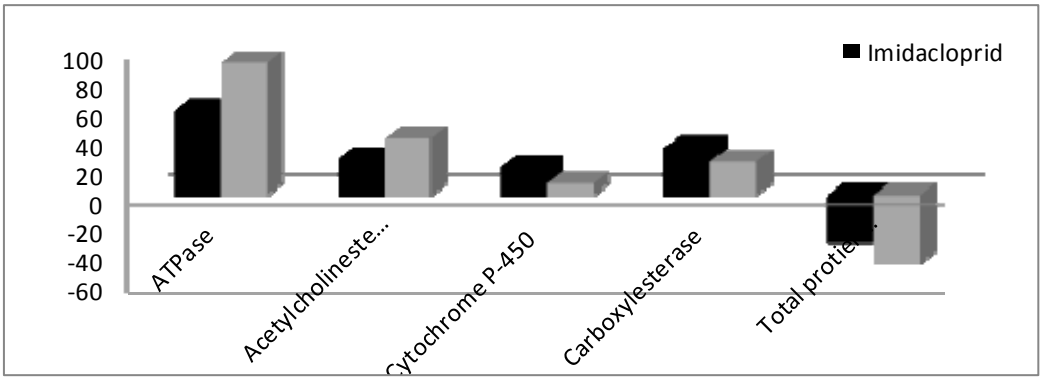


Fig. (4): Effect of imidacloprid and thiamethoxam on total protein content and activities of ATPase, acetylcholinesterase, cytochrome P-450 and carboxylesterase in haemolymph of adults house fly.

DISCUSSION

It was noticed that the expected toxicities of IMI and THIA obtained from insecticides docking to the simulating enzyme vary from the experimental toxicity results. The docking results revealed that the IMI had excellent bonding interactions than THIA, therefore, the potency of IMI expected to be higher than of THIA. In contrast to expected results, the experimental data cleared that the THIA was more effective than IMI to adult house flies. These differences in the toxicity might be due to variations in sensitivity, tolerance or a reduction in susceptibility of adult house flies because of the past chemical use conferring cross-resistance beyond natural variations.

THIA was highly toxic to house flies than IMI, and this agrees with Saeed *et al.* (2017) who stated that THIA was more effective to the susceptible population of cotton leaf hopper, *Amrasca devastans* (Distant) than IMI. Although this result disagree with Chen *et al.* (2015) who showed that IMI exhibited high toxicity to both RF75 and SS strains of *Aphis gossypii* than THIA. Additionally, the IMI-resistant strain of *A. gossypii* at the 45th generation did not develop cross-resistance to the second generation of neonicotinoid (THIA) Shi *et al.* (2011).

Modelling studies showed the mode of action of neonicotinoids via their clear interactions with AChBP. AChE was determined for the purpose of examining the response of this enzyme to neonicotinoids although there is no correlation between AChE and neonicotinoid toxicity. The treatment of adult house flies with IMI and THIA enhanced AChE activity but with different levels. THIA treatment exhibited significantly higher AChE activity compared to the IMI treatment these findings agree with Samson-Robert *et al.* (2015) who approved that the neonicotinoids are the only insecticide that cause an increase in AChE activity. In addition, increased AChE activity has also been reported in response to exposure to neonicotinoids, in both honey bees Boily *et al.* (2013).

ATPase is a group of enzymes that play an important role in intracellular functions and that are considered to be a sensitive indicator of toxicity. They hydrolyze adenosine triphosphate (ATP) into adenosine diphosphate (ADP) and inorganic phosphate (Pi). In this process, the energy released becomes available for cation transport. These enzymes, especially (Na^+/ K^+-ATPase), play a central role in whole body osmoregulation, that provide energy for the active transport of Na^+ and K^+ across the cell membrane Rabea *et al.* (2010). The Na^+/ K^+ ATPase is one of

important associated proteins that correct functioning of nAChRs, which might have strong and stable interaction with insect nAChRs. When the nAChR agonist nicotine was added, the steady state current of Na^+/K^+ ATPase increased significantly Bao *et al.* (2015). Furthermore, It is widely assumed that metabolic detoxification or metabolism resistance mechanisms to toxins in insects are high energy consumption Guedes *et al.* (2006) and Kliot *et al.* (2014). The up-regulation of the ATPase activity is indicative of an increased energy demand, most likely due to the activation of detoxification mechanisms and other defence mechanisms. Resistance of insects to botanical insecticides and other pesticides has also been associated with the increased expression of genes and proteins involved with ATPase synthesis and energy metabolism Rand *et al.* (2015). These results confirmed the results obtained in this study that showed great increase in ATPase activities in adult house flies after IMI and THIA treatments.

Detoxification is considered one of the major mechanisms of insect's physiological defence to insecticides (metabolic resistance). The major enzyme responsible for the metabolism or detoxification of toxins are the P-450s and CarEs Li *et al.* (2007).Oxidative degradation by P-450, hydrolytic degradation by CarE and target site insensitivity are major factors affecting house flies susceptibility to neonicotinoids Markussen and Kristensen (2010); and Khan *et al.* (2015). The increase of detoxification enzymes activity (CarE and P-450) by IMI than THIA could weaken house flies defence responses to THIA than IMI Chen *et al.* (2015); this similar with Kandil *et al.* (2008) they found that a high synergistic ratio obtained from mixing of THIA with esterase inhibitor reflects the role of esterases in the detoxification mechanism found in THIA resistance strain. This increase suggests that the mechanism of resistance was due to increased ester hydrolysis caused by higher levels of CarE. The expression levels of esterases were upregulated significantly in the resistant strains compared to the susceptible strains of the cotton aphid Pan *et al.* (2015).

On the other hand the P-450 apparently showed minor role in insects resistance to neonicotinoides. This result agrees with Koo *et al.* (2014) and Abdallah *et al.* (2016) who noted that no effect of P-450 in the IMI and THIA resistant strains of *A. gossypii* were found when using either synergists or a determination of the enzyme activity. In contrast, by using specific enzyme inhibitors, Zhu *et al.* (2017) demonstrated that honey bees mainly rely on P-450s for detoxifying IMI, while esterases play substantially less roles in the detoxification.

In conclusion the unique mode of action of neonicotinoids indicated that the probability of cross-resistance with other insecticides groups was not possible. In general, the low toxicity of neonicotinoids might be a result of the metabolic detoxification of esterases and P-450; so, the enhanced activities of CarE and P-450 enzymes seem to be associated with insensitivity of house flies to IMI. In addition, the mutation at an insecticidal target site and other factors such as reduced penetration of the insecticide through the cuticle might enhance in insecticides resistance.

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ARABIC SUMMARY

دراسة مقارنة للنمذجة والتأثيرات السمية والبيوكيميائية لمركبى **imidacloprid** و **thiamethoxam** على الذبابة المنزلية **(Diptera: Muscidae) *Musca domestic* L.**

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الملخص العربى

استبدلت طعوم Anticholinestrasesمؤخرا بطعوم neonicotinoid و لذلك لمقاومة الأطوار البالغة للذبابة المنزلية (*Musca domestica* L.). و قد استُخدم مؤخرا كلاً من Imidacloprid (IMI) و Thiamethoxam (THIA) على نطاق واسع لمكافحة هذة الآفة. تم ترسية كلا المركبين فى هذه الدراسة لتوضيح تفاعلاتهم مع(Acetylcholine binding protein (AChBP . تم أيضاً استخدام تقنية التغذية لتقييم سمية المبيدات محل الدراسة للاطوار البالغة للذبابة المنزلية. و قد أوضحت التجارب الأحيائية أن مركب THIA لها تأثير أكثر سمية على الأطوار البالغة من الذبابة المنزليه مقارنة ب IMI حيث كانت نسبة الجرعة المميتة للنصف ٧,٢٥ و ٢١,٠٨ على التوالى. و كذلك أوضحت الدراسة تزايد النشاط البيوكيميائى لكل من Acetylcholinesterase و ATPase، و carboxylesterase و Cytochrome P-450 بينما اختُتزل اجمالى المحتوى البروتينى.