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Juvenile hormone-like and anti-gonadotropic activities of Fluoromevalonate against the Egyptian cotton leaf worm *Spodoptera littoralis* Boisd. (Lepidoptera: Noctuidae)

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Abstract

The cotton leaf worm, *Spodoptera littoralis* is destructive pest of cotton and various crops all over the year in Egypt. The present study was carried out aiming to assess the effects of the anti-JH compound, Fluoromevalonate (FMev), on survival, growth, development, metamorphosis and reproductive potential of this pest. Four doses: 100, 50, 25 and 5 µg/larva had been topically applied (once) onto newly moulted 5th (penultimate) instar larvae and newly moulted 6th (last) instar larvae. FMev exhibited a weak toxicity against larvae, pupae and adults. LD_{50} values were estimated in 42.03 and 629.20 µg/larva, after treatment of 5th and 6th larval instars, respectively. FMev inhibited the larval growth when applied onto 5th instar larvae but promoted it after treatment of 6th instar larvae. The larval was remarkably shortened, but the pupal duration was slightly or remarkably prolonged, depending on the treated larval instar. FMev failed to exhibit anti-JH activity but a JH-like activity against this insect. The pupation rate was regressed. Treatment of 6th instar larvae with FMev resulted in the production of morphologically abnormal pupae, at the higher three doses. FMev exhibited a blocking effect on the adult emergence. FMev exhibited potent anti-gonadotropic activity against *S. littoralis*, since complete sterilization was recorded.

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Introduction

The cotton leaf worm, *Spodoptera littoralis* Boisd. has been considered as destructive phytophagous lepidopterous pest of cotton and various vegetable and field crops all over the year in Egypt (Hosny *et al.*, 1986; Shonouda and Osman, 2000; El-Khawas and Abd El-Gawad, 2002; Adham *et al.*, 2009) as well as tropical and temperate zones of the old world (Magd El-din and El-Gengaihi, 2000). To control the attacks of *S. littoralis*, several types of conventional insecticides have been used over the past 40 years (Casida and Quistad, 1998). The intensive use of broad-spectrum insecticides against *S. littoralis* has led the development of resistance against many registered pesticides making their control even more difficult (Ishaaya *et al.*, 1995; Smagghe *et al.*, 1999; Miles and Lysandrou, 2002; Aydin and Gurkan, 2006; Davies *et al.*, 2007, Mosallanejad and Smagghe, 2009). As a result of improper and excessive uses, also, these insecticides usually exhibit several adverse impacts on the human health and beneficial animals as well as cause serious toxicological problems to the environmental systems because these chemicals have a long half-life and retention in the environment for long periods (Van Der Gaag, 2000; Costa *et al.*, 2008; Relyea, 2009; Tiryaki and Temur, 2010; Damalas and Eleftherohorinos, 2011; Chowański *et al.*, 2014).

Therefore, eco-friendly insecticides have received global attention in recent years as alternative for the conventional insecticides. These alternative compounds are characterized by lower toxicity to non-target organisms than conventional insecticides and they are effective at low concentrations (Attathom, 2002; Gade and Goldsworthy, 2003). Also, they are biodegradable into harmless compounds, which allows for avoiding the problems of environmental pollution (Tiryaki and Temur, 2010; Walkowiak *et al.*, 2015; Li *et al.*, 2017). At present, the use of insect juvenile hormone analogues (JHAs) or insect growth regulators (IGRs), in general, is considered as the possible alternative agents of conventional insecticides for controlling this pest (Raslan, 2002). IGRs are regarded as a 'third generation of insecticides' or biorational pesticides because they differ in their mode of action from other insecticides and have low toxicity to non-target organisms (Zhou *et al.*, 2003). Because of their desirable characteristics, such as low toxicity, less environmental pollution, high selectivity, and low impact on natural enemies and people, IGRs are used to control various insect pests (Wu, 2002; Cedric, 2005; Wang and Wang, 2007).

The JH is necessary for insect development throughout the immature stages (Staal, 1986). In addition, JHs play important roles in several other physiological processes, such as reproduction, diapause, behaviour, polymorphism, migration, metabolism and innate immunity (Riddiford, 1994; Gilbert *et al.*, 2000; Mitsuoka *et al.*, 2001; Tatar *et al.*, 2001a,b; Truman and Riddiford, 2007; Riddiford, 2008; Flatt *et al.*, 2008; Denlinger *et al.*, 2012; Amsalem *et al.*, 2014). Precocenes (anti-JH compounds) and their synthetic analogues received a great attention by entomologists both doing fundamental and applied work due to their twin advantage; using as a physiological probe in the former avoiding surgical allatectomy and as an effective tool in devising 'fourth generation insecticides' in the latter (Muraleedharan *et al.*, 1986; Sariaslani *et al.*, 1987; Moya *et al.*, 1997; Szczcpanik *et al.*, 2005; Singh and Kumar, 2011).

It has been demonstrated that the design of JH mimics or anti-JH agents is an effective strategy for insecticide discovery (Bede *et al.*, 2001). Compounds with anti-JH activity are considered as new representatives of IGRs lacking some disadvantages of juvenoid-type chemicals (Bowers, 1982; Staal, 1982). These anti-JH chemicals are potentially efficacious for control of the major insect pests where most of the damage is caused by larval stage (El-Ibrashy, 1982). On reproduction in adults of several insect orders, precocenes have been shown to prevent normal vitellogenic development of the oocytes or disturb the embryonic development leading to sterility (Staal, 1986; Kumar and Khan, 2004; Ringo *et al.*, 2005; Amiri *et al.*, 2010).

Fluoromevalonate

FMev (tetrahydro-4-fluoromethyl-4-hydroxy-2H-pyran-2-one) was known for its hypocholesteremic activity in mammals (Nave *et al.*, 1985). As reported by Sánchez *et al.* (2015), FMev is a competitive inhibitor of mevalonate diphosphate decarboxylase and exhibited inhibitory effect on cholesterol biosynthesis, cell proliferation and cell cycle progression in human leukaemic HL-60 and MOLT-4 cells. FMev was reported to exhibit anti-JH activity against several species of different families in Lepidoptera, such as *Manduca sexta*, *Samia cynthia*, *Phryganidia californica*, *Galleria mellonella*, *Spodoptera exigua*, and *Heliothis virescens* (Quistad *et al.*, 1981; Farag and Varjas, 1983; Balamani and Nair, 1989). Edwards *et al.* (1985) reported that FMev exhibited anti-JH activity against the American cockroach *Periplaneta americana* (Blattodea: Blattidae) through the inhibition of JH III biosynthesis in CA. The present study was carried out aiming to assess the effects of FMev on survival, growth, development, metamorphosis and reproductive potential of the dangerous insect pest *S. littoralis*.

Materials and methods

Experimental insect

A sample of Egyptian cotton leafworm, *Spodoptera littoralis* Boisd. (Lepidoptera: Noctuidae) pupae was kindly obtained from the culture of susceptible strain maintained for several generations in Plant Protection Research Institute, Agricultural Research Center, Doqqi, Giza, Egypt. In Department of Zoology and Entomology, Faculty of Science, Al-Azhar University, Cairo, a culture was raised under laboratory controlled conditions ($27\pm2^{\circ}$C, $65\pm5\%$ R.H., photoperiod 14h L and 10h D). Rearing procedure was carried out according to Ghoneim (1985) and improved by Bakr *et al.* (2010). Larvae were provided daily with fresh castor bean leaves *Ricinus communis*. The emerged adults were provided with cotton pieces soaked in 10% honey solution as a food source. Moths were allowed to lay eggs on *Oleander* branches. The egg patches were collected daily, and transferred into Petri dishes for another generation.

Fluoromevalonate (FMev) administration

FMev (tetrahydro-4-fluoromethyl-4-hydroxy-2H-pyran-2-one) was kindly provided by Dr. Heba Hassan, Prof. at Plant Protection Research Institute, Agricultural Research Center, Doqqi, Giza, Egypt. Molecular formula: $C_6H_9FO_3$ FMev was diluted in acetone to prepare four doses: 100, 50, 25 and 5 µg/larva. Each dose was topically applied (once) onto the thoracic sterna of newly moulted 5th (penultimate) and newly moulted 6th (last) instar larvae by Hamilton microapplicator (NHN 737). Groups of 20 healthy larvae were used as replicates for each dose. Control larvae had been topically applied only with 1µl acetone. All treated and control larvae were kept individually under the previously mentioned laboratory controlled conditions. All larvae were provided with fresh castor bean leaves every day, during the feeding period. Starting from the day after treatment all treated and control insects were observed daily to record all criteria of study.

Criteria of study

Insecticidal activity, growth, development and metamorphosis

Mortality in larvae, pupae and adults were determined in %. LD_{50} values were calculated using the total mortality by Microsoft office Exel, 2007, according to Finny (1971).

Coefficient of growth was calculated according to El-Ibrashy and Aref (1985) as follows: maximal body weight (mg)/ duration (in days) for each larva.

Developmental duration

Dempster's equation (1957) was used for calculating the developmental duration (in mean days±SD) and Richard's equation (1957) was used for calculating the developmental rate.

Pupation rate was expressed in % of the developed pupae. Adult emergence was determined in %. *Precocious metamorphosis* was determined in % of precocious pupation. *Impaired morphogenesis* was determined in % of deformed larvae, pupae and adults.

Reproduction parameters

After pupal stage of control and treated larvae, the emerged adult females of *S. littoralis* were daily collected and released in plastic jars (3L) provided with sterilized cotton pieces, soaked in 10% honey solution, for feeding, as well as suitable *Oleander* branches as an oviposition site. The treated adult females were coupled with normal adult males (1:2) of the same age, at least 3 replicates, obtained from the main culture. The eggs were collected daily, and carefully transferred to Petri dishes to count eggs.

Oviposition efficiency

Oviposition efficiency could be detected by the oviposition rate as follows:

Number of laid eggs per ♀/reproductive lifetime (in days) x 100.

Reproductive capacity

Fecundity

The laid eggs were counted for calculating the number of eggs per female.

Fertility

The hatchability was usually expressed in hatching percentage of laid eggs.

Sterility index

It was calculated according to Toppozada *et al.* (1966) as follows:

Sterility Index = 100 − [(a b / A B) × 100]

Where: a: mean number of eggs laid per female in the treatment. b: percentage of hatching in the treatment.

A: mean number of eggs laid per female in the controls. B: percentage of hatching in the controls.

Incubation period

The laid eggs were kept in Petri dishes under the same laboratory controlled conditions, as previously mentioned. Just after the oviposition, eggs were observed until hatching for recording the incubation period (in mean days±SD).

Statistical analysis of data

Data obtained were analyzed by the Student's *t*-distribution, and refined by Bessel correction (Moroney, 1956) for the test significance of difference between means.

Results and discussion

Affected survival of S. littoralis by FMev

After topical application of FMev (once) onto the newly moulted 5th (penultimate) instar larvae, toxicity of the tested compound was expressed in mortality among larvae, pupae and adults. According to data of Table (1), different mortality %s were recorded among the treated 5th instar larvae.

The successfully moulted 6th instar larvae suffered a toxic action of FMev only at the highest dose. The pupal mortality was observed only at the higher two doses. The adult mortality was observed only at the highest dose. The same table (1) contains data of FMev toxicity after treatment of 6th instar larvae.

Table 1. Toxicity (%) of FMev on *S. littoralis*.

Dose (µg/larva)	Treatment of 0-day old 5th instar larvae						Treatment of 0-day old 6th instar larvae				
	Larval mort.		Pupal mort.	Adult mort.	Total mort.	LD$_{50}$ (µg/ larva)	Larval mort.	Pupal mort.	Adult mort.	Total mort.	LD$_{50}$ (µg/larva)
	5th instar	6th instar									
100	40.0	13.3	15.4	9.1	60.0	42.03	20.0	10.0	11.1	36.0	629.2
50	36.0	00.0	12.5	0.0	44.0		12.0	9.1	00.0	20.0	
25	60.0	00.0	00.0	0.0	60.0		00.0	00.0	00.0	00.0	
5	12.0	00.0	00.0	0.0	12.0		00.0	00.0	00.0	00.0	
Control	00.0	00.0	00.0	0.0	0.0		00.0	0.0	00.0	0.00	

Mort.: Mortality.

Depending on these data, FMev exhibited a toxic effect on larvae and pupae only with the higher two doses. Adult females were subjected to extended toxic effect of FMev only at the highest dose.

Our results were, to some extent, in agreement with those reported results of toxicity of several anti-juvenile hormone (anti-JH) compounds against different insect species.

For examples, both precocene I (PI) and precocene II (PII) exhibited larvicidal activities against several mosquito species (Saxena *et al.*, 1994; Yasyukevich and Zvantsov, 1999).

Table 2. Growth of *S. littoralis* after topical application of FMev onto 0-day old penultimate instar larvae.

Dose (µg/larva)	5th instar larvae			6th instar larvae		
	Maximal body weight (mean mg±SD)	Duration (mean days ± SD)	Coefficient of growth (mean± SD)	Maximal body weight (mean mg±SD)	Duration (mean days ± SD)	Coefficient of growth (mean± SD)
100	102.8±17.5 b	1.0±0.0 b	102.8±17.5 c	622.5±32.7 b	4.0±0.7 b	160.4±29.4 b
50	103.7±5.8 b	1.0±0.1 b	103.7±7.8 b	610.8±45.0 c	4.1±0.6 b	148.9±11.11 c
25	138.3±8.7 b	1.4±0.1 a	98.8±6.8 c	605.2±55.8 c	4.2±0.7 a	148.0±39.3 b
5	151.20±17.6 b	1.5±0.2 a	108.0±21.4 a	572.8±67.0 a	4.5±0.5 a	127.9±13.4 a
Control	119.0±38.9	1.9±0.3	110.4±19.8	513.4±123.8	4.5±0.5	108.5±29.8

Mean ± SD followed with the same letter a: insignificantly different (P >0.05), b: significantly different (P<0.05), c: highly significantly different (P<0.01).

Precocenes exhibited larvicidal effects on the Colorado potato beetle *Leptinotarsa decemlineata* (Farazmand and Chaika, 2008). A toxicological effect of PII was reported by Abdullah (2009) against larvae of the red palm weevil *Rynchophorus ferrugineus*. Also, PII exhibited larvicidal and pupicidal effects on the grey flesh fly *Parasarcophaga dux* (Nassar *et al.*, 1999); larvicidal effect on the lepidopterous pest *Pericallia ricini* (Khan and Kumar, 2000); and larvicidal effect on the Asian tiger mosquito *Aedes albopictus* (Liu and Liu, 2014). Apart from precocenes, other anti-JH compounds displayed different degrees of toxicity against some insects, such as synthesized EMD (ethyl (E)-3-methyl-2-dodecenoate) (Kuwano *et al.*, 1988) and some synthesized analogues of FMev (tetrahydro-4-fluoromethyl-4-hydroxy-2H-pyran-2-one)(Shuto *et al.*, 1988) against the mulberry silkworm *Bombyx mori*.

Table 3. Growth of *S. littoralis* after topical application of FMev onto 0-day old last instar larvae.

Dose (µg/larva)	Maximal body weight (mean mg±SD)	Duration (mean days±SD)	Coefficient of growth (mean±SD)
100	338.7±98.0 a	2.8±0.8 c	118.9±18.9 c
50	745.9±128.2 c	4.1±0.3 a	189.3±35.2 c
25	349.8±78.2 b	4.3±0.6 a	088.2±23.7 b
5	334.7±33.1 a	4.2±0.4 a	081.6±12.6 a
Control	295.6±31.8	4.2±0.4	074.1±9.5

a, b, c: see footnote of Table (2).

The larval deaths of *S. littoralis*, in the present study, may be attributed to the prevention of moulting larvae to swallow volumes of air for splitting the old cuticle and expand the new one during ecdysis (Linton *et al.*, 1997). Also, these larval deaths may be due to the prevented feeding and continuous starvation of the insect (Ghoneim *et al.*, 2000). The pupal deaths can be directly related to the hormonal activity of the tested anti-JH compound or may be to other causes, such as suffocation, bleeding and desiccation due to imperfect exuvation, failure of vital homeostatic mechanisms, *etc.* (Smagghe and Degheele, 1994). The adult mortalities can be explained by the retention and distribution of FMev in the insect body as a result of direct and rapid transport *via* the haemolymph to other tissues, and/or by lower detoxification capacity of adults against the tested compound (Osman *et al.*, 1984).In the current study, LD_{50} values were estimated in 42.03 and 629.20 µg/larva, after treatment of 5th and

6th instar larvae, respectively. Thus, the 5th instar larvae were more sensitive to FMev than 6th instar larvae. However, LD_{50} (or LC_{50}) value of a compound depends on several factors, such as susceptibility of the insect and its treated stage or instar, lethal potency of the tested compound and its concentration levels, method and time of treatment, as well as the experimental conditions. For examples, LD_{50} of PII against the red cotton stainer *Dysdercus koenigii* had been found to be 85.46 and 82.37 mgl^{-1} against 4th and 5th instar nymphs, respectively (Banerjee *et al.*, 2008).

Table 4. Development and metamorphosis of *S. littoralis* after topical application of FMev onto 0-day old penultimate instar larvae.

Dose (µg/larva)	Precocious pupation (%)	Pupation rate (%)	Pupal Duration (mean days±SD)	Pupal Develop.	Abnormal pupae (%)	Adult emergence (%)
100	0	43.5	7.7±3.1 a	13.00	0	50.0
50	0	48.5	7.9±2.8 a	12.80	0	66.6
25	0	69.5	7.5±3.3 a	13.33	0	100
5	0	100	7.5±3.1 a	13.33	0	100
Control	0	100	7.3±1.9	14.70	0	100

a: See footnote of Table (2). Pupal develop.: Pupal developmental rate.

After treatment of 4th instar larvae of *A. albopictus* with PI and PII, LC_{50} values were estimated in 41.63 and 43.55 µg/ml, respectively (Liu and Liu, 2014). LC_{50} values of PII and PI against the booklice *Liposcelis bostrychophila* were calculated in 30.4 and 64.0µg/cm² , respectively (Lu *et al.*, 2014). LC_{50} of PI against the cat flea *Ctenocephalides felis* was estimated in 10.97 ppm (Rust and Hemsarth, 2017). LC_{50} values of the anti-JH agent Pitavastatin against the tobacco hornworm *Manduca sexta* and the viviparous cockroach *Diploptera punctata* were estimated in 5.23, and 395.2 µM, respectively (Li *et al.*, 2017).

Table 5. Development and metamorphosis of *S. littoralis* after topical application of FMev onto 0-day old last instar larvae.

Dose (µg/larva)	Larval-pupal inter. (%)	Pupation rate (%)	Pupal Duration (mean days±SD)	Pupal Develop.	Abnormal pupae (%)	Adult emergence (%)
100	20	90.0	7.50±3.5 a	13.33	50	11.5
50	10	95.5	7.39±1.4 a	13.53	10	45.5
25	00	100	8.00±0.8 c	11.95	05	50.1
5	00	100	8.44±0.7 c	11.85	00	53.5
Control	00	100	7.35±1.1	13.61	00	100

a, b, c: See footnote of Table (2). Larval-pupal inter.: Larval-pupal intermediates. Pupal develop.: see footnote of Table (4).

Growth disturbance in S. littoralis by FMev
After topical application of FMev doses onto the newly moulted 5th instar larvae, data of the maximal body weight (max. wt), duration and coefficient of growth (CG) of the treated larvae and the successfully moulted 6th instar larvae were assorted in Table (2). After topical application of FMev onto the newly moulted last instar larvae, data of max. wt and CG were summarized in Table (3).

Depending on the present results FMev exerted strong inhibitory action on the growth of treated 5th instar larvae whose coefficient of growth (CG) was considerably regressed. However, FMev exerted a diverse action on the maximal body weight (max. wt), after treatment of 5th instar larvae, since max. wt was significantly decreased at the higher two doses (100 and 50 µg/larva) but remarkably increased at the lower two doses (25 and 5 µg/larva).

The present results were, to a great extent, in agreement with the very few studies examining the effects of anti-JH compounds on the growth of larvae in insects. Among these few studies, Roberto *et al.* (1998) recorded remarkable inhibition of growth after treatment of last instar larvae of the mealworm beetle *Tenebrio molitor* with several chromene derivatives. PI and PII exhibited growth-inhibiting activities against the mosquito species *Aedes aegypti, Anopheles sacharovi* and *An. stephensi* (Saxena *et al.*, 1994; Yasyukevich and Zvantsov, 1999). After feeding of caterpillars of the tobacco hornworm *Manduca sexta* on a treated diet with HMG-CoA reductase inhibitors, Fluvastatin, Lovastatin or Pitavastatin, the growth rate of treated larvae was significantly slow (Li *et al.*, 2017).

Table 6. Reproductive potential of *S. littoralis* as influenced by FMev after topical application of sublethal doses onto 0-day old penultimate instar larvae.

Dose (μg/larva)	Oviposition Rate (%)	Fecundity (mean eggs±SD)	Hatchability (%)	Sterility index (%)	Incubation period (mean days±SD)
100	75	135.5±30.5 c	00.0	100	---
50	85	336.5±32.1 c	00.0	100	---
25	90	338.7±32.5 c	00.0	100	---
5	90	208.5±98.1 c	00.0	100	---
Control	100	943.3±85.5	98.8	---	3.5±0.5

a, b, c: see footnote of Table (2).

To understand the growth inhibition of *S. littoralis*, in the current study, FMev might affect the tissues and cells undergoing mitosis (Nasiruddin and Mordue, 1994). Also, FMev might exert an inhibitory action on the haemolymph and fat body protein contents, as suggested by Lange *et al.* (1983) for locusts after treatment with precocenes. On the contrary, treatment of 6th instar larvae with FMev, in the present study, promoted the larvae to attain increasing max.wt and enhanced their CG. This promoting action of FMev on the larval growth cannot be interpreted right now!!

Disrupted development and metamorphosis of S. littoralis by FMev
Affected development durations
After topical application of FMev onto 5th instar larvae, data of affected larval duration were assorted in Table (2). In view of these data, duration of the treated larvae was conspicuously shortened, especially at the higher two doses. As obviously shown in Table (3), topical application of FMev onto last instar larvae resulted in shortened larval duration, especially at the higher two doses. Data of Table (4) exiguously revealed a slight prolongation of the pupal duration after topical application of the higher two doses of FMev onto 5th instar larvae. Moreover, considerable prolongation of the pupal duration was easily observed in Table (5) after topical application of FMev onto the last instar larvae with the lower two doses.

Results of the current investigation disagreed with many reported results of prolonged larval duration after treatment with various anti-JH compounds. For examples, Bowers and Aldrich (1980) recorded a prolongation of 5th nymphal instar in the milkweed bug *Oncopeltus fasciatus* after treatment with PI. Treatment of the 4th instar nymphs of the desert locust *Schistocerca gregaria* with PII resulted in prolongation of the duration of both 4th and 5th nymphal instars (Eid *et al.*, 1982). Farag and Varjas (1983) recorded a prolongation in the larval duration after topical application of FMev onto the three latter instars of fall webworm *Hyphantria cunea*.

Treatment of 6th instar larvae of the lawn armyworm *Spodoptera mauritia* with PII resulted in prolongation of duration in last larval instar (Mathai and Nair, 1983, 1984).

Table 7. Reproductive potential of *S. littoralis* as influenced by FMev after topical application of sublethal doses onto 0-day old last instar larvae.

Dose (µg/larva)	Oviposition Rate (%)	Fecundity (mean eggs±SD)	Hatchability (%)	Sterility index (%)	Incubation period (mean days±SD)
100	58.3	098.2±18.0 d	00.0	100	---
50	70.0	283.8±33.2 c	00.0	100	---
25	81.5	602.8±149.4 c	00.0	100	---
5	83.8	104.6±18.9 d	00.0	100	---
Control	100	1259.2±120.3	98.3	---	3.5±0.4

a, b, c: See footnote of Table (2). d: very highly significantly different (P<0.001).

The nymphal period of the grasshopper *Aiolopus thalassinus* was prolonged after topical application of PIII onto 5th instar nymphs (Osman, 1988). Treatment of the tobacco cutworm *Spodoptera litura* larvae with PI, PII or ethoxyprecocene (a synthetic analog of P II) resulted in prolongation of larval period (Srivastava and Kumar, 1997, 1999). After treatment of 4th instar nymphs of *D. koenigii* with PII, duration of the successfully moulted 5th instar nymphs was prolonged (Banerjee *et al.*, 2008). Apart from precocenes, prolongation of the larval period in *H. cunea* was recorded after treatment with FMev (Farag and Varjas, 1983). Similar results of prolonged larval duration were reported in *B. mori* by KK-22 (phenylimidazoles) (Kuwano and Eto, 1983; Asano *et al.*, 1984). After treatment of 4th instar larvae of *B. mori* with the synthesized 3-(2-methyl-l-phenyl-l-propenyl) pyridine, the larval period was prolonged (Yoshida *et al.*, 2000).

On the other hand, our results were in accordance with those reported results of shortened larval duration after treatment with some anti-JH compounds, such as *P. dux* after treatment of the 3rd instar larvae with PII (Nassar *et al.*, 1999); the flesh fly *Sarcophaga ruficornis* after treatment of the last instar larvae with PI, PII or PIII (Srivastava and Kumar, 1996); the house fly *Musca domestica* after treatment of the larvae with PII (Gaur and Kumar, 2009);

B. mori after treatment of the 3rd and 4th instars with the imidazole compound SSP-11 (Kiuchi *et al.*, 1985).

To explicate the shortened larval duration of *S. littoralis*, in the current investigation, it may be due to the response of these treated larvae for avoiding the adverse action of FMev, as a xenobiotic agent. On the other hand, the prolongation of pupal period in *S. littoralis*, in the present study, indicated a retarding action of FMev on the development as expressed in regression of the developmental rate. This prolongation in the pupal duration may be attributed to the indirect interference of this compound with the neuroendocrine organs responsible for the synthesis and release of tropic hormones, like prothoracicotropic hormone (PTTH) (Subrahmanyam *et al.*, 1989). Also, the recorded prolongation of pupal stage may be attributed to a disturbing action of FMev on the persistence of JH in the haemolymph where it is only in the absence of JH that ecdysone could be activated and lead to the formation of the next stage (Bowers, 1982; Kuwano *et al.*, 1988). In addition, FMev may exhibit a delaying effect on the pupal transformation into adults (Linton *et al.*, 1997). In particular, the final step of chitin biosynthesis pathway was inhibited by FMev and the precursor was not converted into chitin leading to a prolongation of developmental duration (Djeghader *et al.*, 2014).
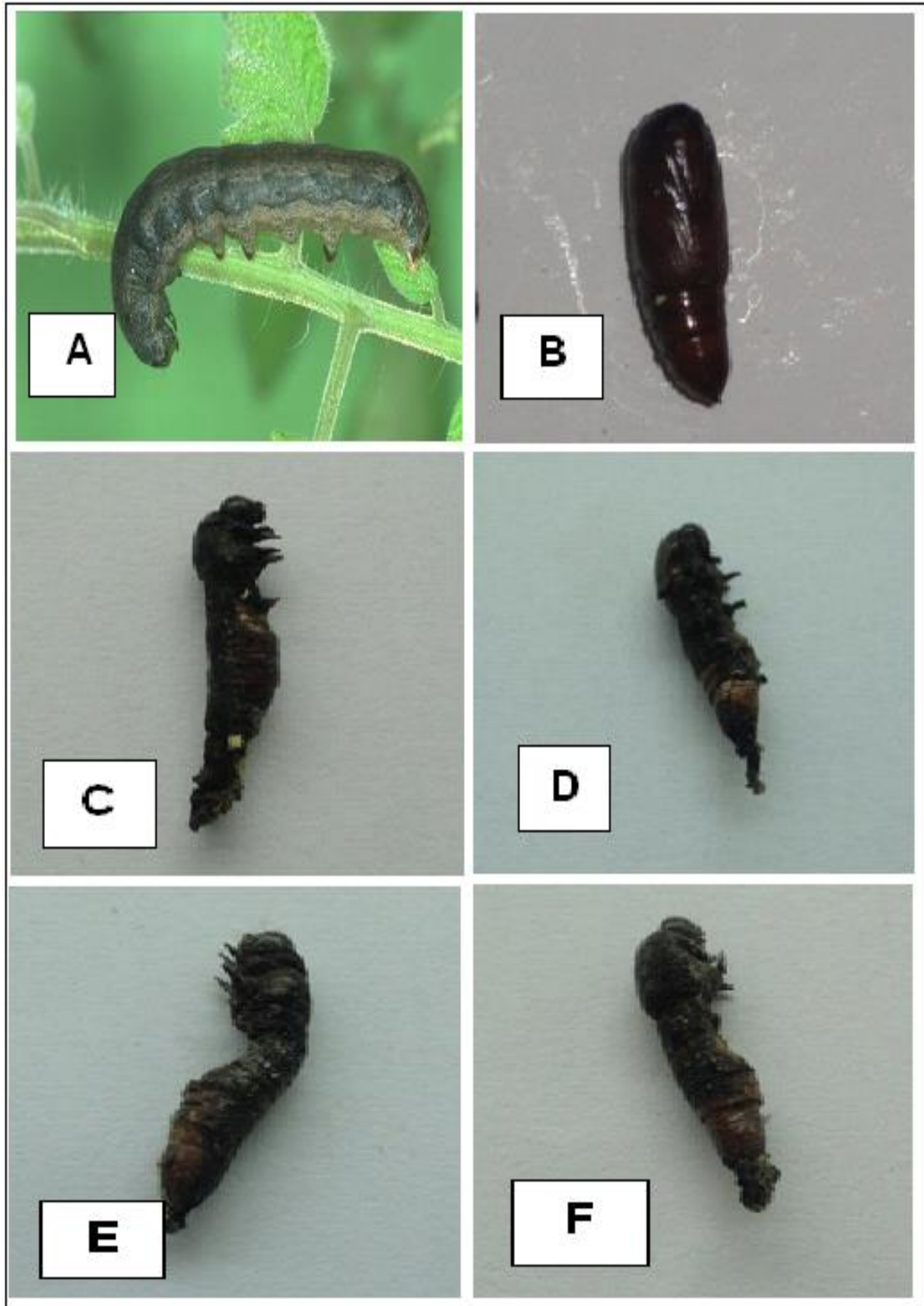
Fig. 1. Larval-pupal intermediates of *S. littoralis* as features of disturbed metamorphosis program after treatment of last instar larvae with the higher two doses of FMev. (A): Normal last instar larva. (B): Normal pupa. (C, D, E & F): Various larval-pupal intermediates.

Impaired metamorphosis and morphogenesis
Disturbance of metamorphosis

Just a look at the data arranged in Table (4), FMev failed to induce precocious pupation in *S. littoralis* after treatment of the penultimate instar larvae. Thus, FMev did not show an anti-JH activity against this insect. On the other hand, data of Table (5) revealed that FMev exhibited a JH-like activity or an allatotropic effect on the treated last instar larvae, since non-viable larval-pupal intermediates were produced at the higher two doses (20 and 10% intermediates, at 100 and 50 µg/larva, respectively, Fig. 1). These mosaic creatures were unusual and perished after formation.

In the current study, failure of FMev to induce the precocious pupation in *S. littoralis* contradictory to some reported results of precocious pupation or precocious metamorphosis in several lepidopterous species as a response to the tested compound, FMev, such as *M. sexta*, *Samia cynthia*, *Phryganidia californica*, *Galleria mellonella*, *Spodoptera exigua*, *S. littoralis* and *Heliothis virescens* (Quistad *et al.*, 1981; Farag and Varjas, 1983). Also, the 3rd instar larvae of *M. sexta*, treated with FMev, exhibited visible symptoms of JH deficiency follow the moult to 4th instar, such as production of premature pupae (Edwards *et al.*, 1983). Edwards *et al.* (1985) reported anti-JH activity for FMev against the American cockroach *Periplaneta americana via* the inhibition of JH III biosynthesis. Apart from FMev, different anti-JH compounds induced precocious metamorphosis in various insects, such as PII against the flesh fly *Neobellieria bullata* (Darvas *et. al.*, 1990), PII against the lepidopterous pest *Pericallia ricini* (Khan and Kumar, 2000) and a synthesized 3-pyridine derivative against *B. mori* (Yoshida *et al.*, 2000).

However, the failure of FMev to induce precocious pupation or other features of precocious metamorphosis, in the present study on *S. littoralis*, was in agreement with those reported results of failure of the same compound to exhibit anti-JH activity in the non-lepidopterous species, such as those belong to orders Diptera, Coleoptera,

Heteroptera, and Orthoptera (Menn, 1985). Moreover, no precocious metamorphosis could be induced in 3rd and 4th instar larvae of the lepidopteran *Cydia pomonella* (Tortricidae)(Benz and Ren, 1986). FMev doses were topically applied once onto 1-day-old larvae of the gypsy moth *Lymantria dispar* had no observable influence on the development. All larvae treated with FMev on day-2 developed normally, with few exception of incomplete moulting to the last instar (Fescemyer *et al.*, 1992). In addition, some of other anti-JH compounds failed to induce precocious metamorphosis, such as PI against the sunn pest *Eurygaster integriceps* (Tarrant *et al.*, 1982), PII against *S. mauritia* (Mathai and Nair, 1983), the synthesized anti-JH compound EMD or its analogues against *B. mori* (Kuwano *et al.*, 1988), the synthesized compound (S)-(+)-FMev against *B. mori* (Shuto *et al.*, 1988) and PII against *S. gregaria* (Islam, 1995).

The failure of FMev to induce precocious pupation of *S. littoralis*, in the current study, can be understood because it did not exhibit an anti-JH activity indicating the inability to affect the larval JH levels (Edwards *et al.*, 1983). Some authors (Burt *et al.*, 1978; Haunerland and Bowers, 1985; Staal, 1986) reported that the larvae of holometabolous insects-with few exceptions- are less susceptible to the action of Precocenes than hemimetabolous insects. In contrast to our finding, some holometabolous insects, such as *S. mauritia* and *S. littoralis* have been reported to be sensitive to the anti-JH activity of Precocenes (Mathai and Nair, 1984; Khafagi and Hegazi, 2001).

On the other hand, FMev exhibited a JH-like activity on the treated last instar larvae of *S. littoralis*, in the current investigation, since non-viable larval-pupal intermediates had been produced, at the higher two doses. The present finding was in corroboration with those results of JH-like activity exhibited by a number of anti-JH compounds, as expressed in the production of larval-pupal intermediates. Treatment of *S. litura* larvae with PI and PII and ethoxyprecocene (a synthetic analog of P II) resulted in formation of larval-pupal intermediates (Srivastava and Kumar, 1997, 1999).

Khafagi and Hegazi (1999) studied the latent effects of PI and PII on the wasp *Microplitis rufiventris* parasitizing on its host *S. littoralis* and recorded some larval-pupal intermediates in the wasp. Also, larval-pupal creatures were produced in *S. mauritia* after treatment with EMD (Balamani and Nair, 1989). In addition, the formation of larval-pupal intermediates was recorded in some insects as response to some precocenes (Khan and Kumar, 2000).

Fig. 2. Pupal abnormalities of *S. littoralis* after treatment of last instar larvae with the higher three doses of FMev. Normal pupa (at left) and dwarf pupa (at right). These dwarf-sized pupae failed to metamorphose into adults.

The formation of larval-pupal intermediates, in the present study, indicated a degree of disturbance in the metamorphosis program of *S. littoralis* by FMev. It can be interpreted by the impairment of hormonal regulation of pupation program (Al-Sharook *et al.*, 1991). The production of these intermediates may indicate a JH-like activity of FMev retarding the perfect larval-pupal transformation. FMev might interfere with the chitin biosynthesis and chitin synthase (Mayer *et al.*, 1988). The molt induction had lethal consequences because the induction of a rapid molt did not provide enough time for the completion of larval-pupal transformation. Thus, the insects molted to non-viable forms between stages (Tateishi *et al.*, 1993). Wilson (2004) discussed the JH action on the molecular basis and reported that the effects of JH may be due to interference with the expression or action of certain genes, particularly the *broad complex* (*br*-C) transcription factor gene, that direct

changes during metamorphosis, such as the pupal development. Therefore, JHAs or anti-JH compounds cause misexpression of *br*-C which then leads to improper expression of one or more downstream effector genes controlled by *br*-C gene products. Symptoms of impaired development like the production of larval-pupal intermediates are the end results (Nandi and Chakravarty, 2011).

Perturbation of pupation
Depending on the data arranged in Table (4), FMev exerted an inhibitory action on the pupation rate after treatment of 5th instar larvae with the higher three doses (100, 50 and 25 µg/larva). As easily seen, the inhibitory action of FMev intensified parallel to the dose level. Also, the pupation rate was regressed after treatment of last instar larvae with the higher two doses of FMev. No information is reported for the inhibitory effects of anti-JH compounds on the pupation rate in insects. However, the present result was consistent with those reported inhibitory effects of some juvenile hormone analogues (JHAs) or other insect growth regulators (IGRs) on the pupation rate in various insects, such as the diamondback moth *Plutella xylostella* by Hexaflumuron (Mahmoudvand *et al.*, 2012); *S. littoralis* by Novaluron (Ghoneim *et al.*, 2015); the lesser mulberry pyralid *Glyphodes pyloalis* by Lufenuron (Aliabadi *et al.*, 2016); the pink boll worm *Pectinophora gossypiella* (Ghoneim *et al.*, 2017a) and the olive leaf moth *Palpita unionalis* (Ghoneim *et al.*, 2017b) by Novaluron.

Deranged morphogenesis
After treatment of 5th instar larvae, FMev failed to exhibit morphogenic efficiency on the present insect, since no malformed pupae or adults had been observed. On the other hand, FMev exhibited morphogenic efficiency on pupae, after treatment of 6th instar larvae only with the higher three doses, since morphologically abnormal pupae had been observed (50, 10 and 5% abnormal pupae, at 100, 50 and 25 µg/larva, respectively, *vs.* 0% abnormality in control pupae). As clearly seen in Fig. (2), some features of the impaired pupation program appeared in dwarf-sized pupae which failed to metamorphose into adults. This result was, to a great extent, in

agreement with those reported results on the impaired morphogenesis of some insects by FMev. For examples, application of FMev on the last instar larvae of the cabbage looper moth *Trichoplusia ni* resulted in disrupted metamorphosis, such as delayed tanning and the formation of abnormal pupae (Newitt and Hammock, 1986; Sparks *et al.*, 1987). FMev induced various morphogenetic abnormalities and death before pupation in *S. mauritia* (Nair and Rajalekshmi, 1988). Also, the present result was in agreement with those reported results on the impaired morphogenesis of some insects by different anti-JH compounds. Treatment of 3rd instar larvae of *B. mori* with some terpenoid imidazole compounds led to the formation of miniature pupae after molting to 4th instar larvae (Kuwano *et al.*, 1983). Topical application of PIII onto eggs or 5th instar nymphs of *A. thalassinus* resulted in some prothetelic morphogenic disturbances (Osman, 1988). Production of abnormal puparia was recorded in *S. ruficornis* after administration of PI, PII or PIII to the last instar larvae (Srivastava and Kumar, 1996). Treatment of *S. litura* larvae with PI, PII or ethoxyprecocene (a synthetic analog of P II) resulted in the production of abnormally formed pupae (Srivastava and Kumar, 1999). Puparial malformations were observed in *P. dux* after topical application of PII onto the 3rd instar larvae (Nassar *et al.*, 1999). Treatment of *M. domestica* maggots with PII led to the formation of abnormal puparia (Gaur and Kumar, 2009). Larval treatment of *E. integriceps* with PI led to the production of some morphological abnormalities (Amiri *et. al.*, 2010).

For interpretation of the pupation rate regression and impairment of the pupation program in *S. littoralis*, as caused by FMev in the present study, FMev might exert a prohibiting action on the prothoracic gland (ecdysone-producing gland) and hence the ecdysone could not be synthesized and/or released. It is well known that the absence of ecdysone leads to failure of ecdysis. Whatever the mode of action, FMev suppressed the chitin synthesis and prevented the normal deposition of new cuticle during apolysis leading to the production of pupal deformities (Retnakaran *et al.*, 1985).

In addition, FMev might block the release of morphogenic peptides, causing alteration in both ecdysteroid and juvenoid titers (Barnby and Klocke, 1990). A suggestion of Gaur and Kumar (2010) may be appreciated. FMev might disrupt the ecdysteroid metabolism or might alternatively act directly to inhibit the release of ecdysis-triggering hormone.

Blocked adult emergence
FMev exerted a blocking action on the adult emergence after treatment of 5th instar larvae only with the higher two doses (50.0 and 66.6% adult emergence, at 100 and 50 µg/larva, respectively, *vs.* 100% emergence of control adults, Table 4). Moreover, topical application of FMev onto last instar larvae resulted in blocking of emergence, in a dose-dependent course (11.5, 45.5, 50.1 and 53.5% adult emergence, at 100, 50, 25 and 5 µg/larva, respectively, *vs.* 100% emergence of control adults, Table 5). This finding was, to a great extent, in corroboration with those scarcely reported results of the effects of anti-JH compounds on adult emergence in insects. Inhibition of adult emergence in *S. ruficornis* was recorded after larval treatment with PII (Khan and Kumar, 2005). KK-42 (a terpenoid imidazole) was reported to inhibit the adult emergence of *B. mori* when applied to the newly formed pupae (Kadono-Okuda *et al.*, 1987).

For interpretation of this result, it important to point out that the adult emergence in insects is a crucial physiological process and regulated by the eclosion hormone. The disturbance of this hormone appeared in partial or complete arresting of adults to emerge. The present result of blocked adult emergence can be interpreted by the disruptive effect of FMev on the normal metabolism of insect hormones during the development of the juveniles leading to failure of adult emergence (Trigo *et al.*, 1988). In particular, FMev may disturb the adult eclosion hormone release and/or inhibition of the neurosecretion (Al-Sharook *et al.*, 1991; Josephrajkumar *et al.*, 1999). On the molecular basis, anti-JH compounds, like FMev, might cause misexpression of certain genes, particularly the *brood* complex (*br*-C) transcription factor gene, leading to symptoms of impaired metamorphosis, like blocking of adult emergence (Wilson, 2004; Nandi and Chakravarty, 2011).

Disrupted reproductive potential of S. littoralis by FMev

Inhibited oviposition efficiency of adult females

Depending on data of Table (6), the oviposition efficiency of adult females was considerably prohibited by FMev after treatment of 5th instar larvae (75, 85, 90 and 90% oviposition, at 100, 50, 25 and 5 µg/larva, respectively, *vs.* 100% oviposition by control females). As obviously shown, the inhibitory effect of FMev on the oviposition rate was found in a dose-dependent manner. In a similar trend, the oviposition rate was regressed after treatment of 6th instar larvae with FMev (58.3, 70.0, 81.5 and 83.8% oviposition, at 100, 50, 25 and 5 µg/larva, respectively, *vs.* 100% oviposition by control females, Table 7).

These results were in accordance with some reported results of inhibited oviposition of different insect species by various IGRs (Bakr *et al.*, 2005; Al-Dali *et al.*, 2008; Al-Mekhlafi *et al.*, 2012; Ghoneim *et al.*, 2014; Hassan *et al.*, 2017; Hamadah *et al.*, 2017).

However, very few studies have examined the effects of anti-JH compounds on this important reproductive parameter. Topical application of the dose 100 µg of FMev onto the mated females (1 day after feeding) of the tick *Ornithodoros moubata* led to inhibition of the oviposition (Connat and Nepa, 1990). Exposure of the vinegar fly *Drosophila melanogaster* females to 0.14 µmol of PI resulted in remarkably regressed oviposition rate (Ringo *et al.*, 2005). Larval treatment of *E. integriceps* with PI led to decreasing egg laying rate (Amiri *et. al.*, 2010). It is known that the oviposition rate can be used as an informative indicator for the oviposition efficiency in insects (Ghoneim *et al.*, 2014).

This prohibited oviposition efficiency of *S. littoralis* can be explained as a result of the inhibition of ovarian DNA synthesis or the interference of FMev with vitellogenesis *via* certain biochemical processes. However, anti-JH compounds may exert a reverse action to that exerted by the ecdysteroid agonists which stimulate the neurosecretory cells to release a myotropic ovulation hormone (Parween *et al.*, 2001).

Reduced reproductive capacity
Fecundity

The functional compartments of reproductive capacity taken in consideration herein were fecundity (mean eggs/♀) and fertility (hatching% of laid eggs). According to the data of Table (6), FMev exerted strong suppressive effect on fecundity, in no certain trend, after treatment of 5th instar larvae with different doses. Similarly, FMev exerted drastically reducing action on fecundity after treatment of 6th instar larvae (see Table 7). These results were, to a great extent, in agreement with those reported results of fecundity inhibition in some insects and ticks after treatment with FMev, such as *Pieris brassicae* and *C. pomonella* (Benz and Ren, 1986) and the ticks *Boophilus microplus* (Connat, 1988) and *O. moubata* (Connat and Nepa, 1990). This result was, also, in agreement with those reported results of fecundity inhibition in different insects after treatment with some anti-JH compounds. For examples, topical application of PII doses of 0.125 and 0.0625 mg onto 3rd instar larvae of *P. dux* caused inhibition of the female natality (Nassar *et al.*, 1999). Exposure of 5th instar nymphs of *N. lugens* to different doses of PII resulted in fecundity reduction, in a dose-dependent manner (Pradeep and Nair, 2000). After treatment of *E. integriceps* nymphs with PI, fecundity of adult females was reduced (Amiri *et al.*, 2010). Repeated daily topical application of PI and PII onto *S. littoralis* larvae led to reduced fecundity of its parasitic wasp *M. rufiventris* (Khafagi and Hegazi, 2004). Apart from precocenes, application of the anti-JH compound H17 reduced the fecundity of *L. decemlineata* (Lehmann *et al.*, 2015). On the other hand, the present findings were inconsistent with those reported results of Precocene failure to affect the fecundity of some insects, such as the bug *Panstrongylus megistus* (Hemiptera: Reduviidae) of which males were treated with PII and ethoxyprecocene (synthesized PII analogue) but the fecundity did not differ statistically from that of the control groups (Cavalcante and Regis, 1992).

To understand the fecundity inhibition of *S. littoralis*, in the present study, it is important to point out that the JH is required for post-eclosion development of the vitellogenin-producing adult fat body. In many insects, including *S. littoralis*, JH modulates fecundity at least in part because JH is necessary to induce yolk proteins uptake into oocytes (Soller *et al.*, 1997), while ecdysone, produced from egg follicles, induces yolk protein mRNA expressed in the fat body (Bownes, 2004; Raikhel *et al.*, 2005; Schwedes and Carny, 2012). In addition, the fecundity inhibition in *S. littoralis* may be due to the interference of the tested FMev with one or more processes from the ovarian follicle development to the egg maturation. (1): FMev may cause some disorders in the ovaries, including cell death in the germarium, resorption of oocytes in the pre-vitellarium and vitellarium (Khan *et al.*, 2007; Zhou *et al.*, 2016). (2): FMev may inhibit the synthesis and metabolism of proteinaceous constituents during oogenesis (Salem *et al.*, 1997). (3): FMev may exert an inhibitory action against the function of authentic gonadotropic hormone (JH in adults) responsible for the synthesis of vitellogenins and vitellogenesis (Di Ilio *et al.*, 1999).

Fertility

With no exception, all eggs of *S. littoralis*, in the present study, failed to hatch, regardless the larval instar under treatment and FMev dose. In other words, FMev caused complete sterility in *S. littoralis* (zero fertility). Therefore, no incubation period could be measured (see Tables 6 and 7). This result exceeded some of the reported results of partially reduced fertility of some insects as a result of larval treatments with a number of anti-JH compounds. For examples, topical application of PIII onto eggs and 5th instar nymphs of *A. thalassinus* led to sterility of adult females (Osman, 1988). After treatment of *E. integriceps* nymphs with PI, the hatchability of laid eggs was reduced (Amiri *et al.*, 2010). Apart from precocenes, phenolic chromene and hydroxyethyl chromene (isolated from *Ageratum conyzoides*) were found to cause sterility in the bug *Dysdercus flavidus* (Vyas and Mulchandani, 1984; Okunade, 2002). Bowers and Aregullin (1987) isolated an anti-JH compound, polyacetylenic sulfoxide, from *Chrysanthemum coronarium* which produced sterile adults in the large milkweed bug *Oncopeltus fasciatus*.

As clearly seen in the present study, FMev caused complete sterilization in *S. littoralis*. For explicating the sterility of this pest, some suggestions can be provided herein. (1) Maturation of the insect eggs depends basically on the vitellogenins, precursor materials of these macromolecules including proteins, lipids and carbohydrates, all of which are necessarily required for the embryonic development (Soltani and Mazouni, 1992; Chapman, 1998). These materials are synthesized primarily by fat body during the immature stages (Telfer, 2009) or by the ovary *in situ* (Indrasith *et al.*, 1988). Wherever the site of their synthesis, FMev might disturb the production of these materials and/or accumulation in adult females of *S. littoralis* leading to sterility. (2) FMev might indirectly prevent the fertility *via* its disruptive effect on opening of the intracellular spaces in follicular epithelium or generally prohibited the role of the gonadotropic hormone responsible for the regulation of vitellogenin deposition into oocytes (Davey and Gordon, 1996). (3) The sterility may be due to the penetration of residual amounts of FMev in *S. littoralis* mothers into their eggs and disturbance of embryonic cuticle synthesis. So, the fully mature embryos had weakened chitinous mouth parts that were insufficiently rigid to perforate the surrounding vitellin membrane and free from the eggs (Sallam, 1999; Sammour *et al.*, 2008). (4) The sterility of *S. littoralis* may be due to dramatic lethal effect of FMev on survival of the developing embryos at certain stages. However, the exact mode of anti-gonadotropic action of FMev on *S. littoralis* is not available right now!!

Because FMev caused complete sterility in *S. littoralis*, in the current investigation, it can be analogous to allatectomy (surgical removal of corpora allata, JH-producing organs) of last instar larvae of *S. littoralis* which caused sterility (El-Ibrashy, 1971; Ghoneim, 1985).

It may be important to mention that the reproduction in insects is mainly controlled by the juvenile hormone (JH), which is also responsible for protein metabolism, and is specifically needed for egg maturation (Ghoneim *et al.*, 2014).

Effects of IGRs on the insect reproduction can be grouped into: i) reproductive behaviour, ii) oviposition, iii) egg hatchability (ovicidal and embryocidal), and iv) sterilization of adults (Mondal and Parween, 2000). On the other hand, ecdysteroids have essential functions in controlling the processes involved in insect reproduction, i.e., vitellogenesis, ovulation of matured eggs and spermatocyte growth (Wigglesworth, 1984; Hagedorn, 1985).

Conclusion

According to the obtained results in the present study, it can be concluded that FMev is a weak toxic compound against *S. littoralis*. It slightly or remarkably affected the growth and development. Although FMev was reported in the current literature as anti-JH agent, it failed to exhibit such activity against the present insect but JH-like activity. On the other hand, FMev was found potent anti-gonadotropic agent against *S. littoralis*. However, this compound should be assessed under field conditions before recommendation for use in the IPM program against this dangerous pest.

Acknowledgement

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